Blandy’s Urology

Third Edition

Edited by

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I would like to dedicate this book to my family for their continued support, with a special thank you to my parents, who have always pushed me to achieve my best and taught me that knowledge, not wealth, is important. Thank you to my wife for supporting me along the journey and truly being the joy of my life and my better half.

Thank you to all my colleagues and trainees who have undertaken the effort in participating in a textbook that encompasses as much as possible and passes knowledge from one generation to the next.
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Preface

This book has been written for the urologist-in-training as well as for established urologists who would like to refresh their knowledge. The book was inspired by Professor Blandy’s original book, *Urology*; whereby his book taught many urologists and was considered the ‘go to’ book for learning about urological conditions. His original book remains a cornerstone of many urologists’ libraries and provides a great pictorial representation of many illnesses as well as basic science.

In this, the third edition, the aim is to incorporate the basic knowledge and update the information with guidelines, management, and development of current urological practices. As Prof. Blandy put it, ‘Our purpose has not been to provide a huge encyclopedia, but rather a workaday handbook to be a friendly companion in the ward and the operating theatre which will make each day more interesting and more fun’. Keeping this phrase in mind, this text encompasses a great deal of information for not only a urologist to establish safe practices, but also for urologists-in-training to prepare for their exams and understand the basic science and pathophysiology in urology.

As such, the first two editions provided the backbone of this edition. In keeping with the memory of the late Prof. Blandy, this book retains much of his world-renowned tradition and passion for teaching and inspiring future generations of urologists.

The current edition combines contributors, at the top in their fields, coupled with trainee contributions; the result is a book written by trainees, supervised by specialists, for trainees in the hope that it will give all readers as much information as the original Blandy’s *Urology*.

‘Are those who know and those who do not know alike? Only the men of understanding are mindful.’

*(Quran: Surah Al Zumar 39:9)*
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Part I
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Armaments in Urology

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1.2 Wound Healing in the Urinary Tract
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1.3 Simulation in Urology
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1.1

Principles of Urological Technology
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Abstract

Urology and technology have always been intricately related. Our specialty has been a pioneer of minimally invasive diagnostic and therapeutic approaches which have evolved in complexity and functionality. We started using endoscopes, then innovated with ample use of lasers, and have now introduced the widespread use of robotic assisted surgery. Urologists are challenged to be familiarised with a diversity of devices, which range from flexible, rigid, and semi-rigid endoscopes to a number of lasers with different wavelengths and capabilities.

Keywords  endoscopy; laparoscopy; laser; catheters; stents; guide wires

Key Points

Optics in Urology

- The introduction of the Harold Hopkins rod-lens telescope into urology has been a significant step in the evolution of endourology.
- Coherent fibre-optic bundle endoscopy enables both high-quality images and light transmission using flexible instruments for the purpose of cystoscopy as well as ureterorenoscopy.

Diathermy and Lasers in Urology

- Diathermy remains widely utilised in urology, exploiting the heat generated when an alternating current passes through a conductor.
- Laser energy is now ubiquitous in surgery and perhaps indispensable for some purposes, such as transmitting energy down a flexible endoscope.

Catheters, Stents, and Guidewires

- Basic knowledge of these commonly used technologies is required to safeguard appropriate uses of each.

1.1.1  Optics in Urology

Historically, urologists have been defined by their endoscopic skills. This continues to be the case, with advances in optical and camera technology ensuring that urologists remain at the forefront of surgical innovation.

1.1.1.1  The Rod-Lens System

The first cystoscope was introduced by Maximilian Nitze in 1876. Modifications through the first half of the twentieth century changed the device so that it was lit by a heated platinum wire at its distal end [1]. The wire was soon replaced by Edison's electric lamp. The telescope, originally made as an integral part of the instrument, was later constructed so to be removable from a separate sheath through which the instrument could be irrigated. To transmit the image, the telescope had glass lenses and prisms separated by spaces of air (Figure 1.1.1). Limitations of this design include the technical difficulties in engineering small lenses that are of high enough quality to avoid image degradation and peripheral aberration. Metal mounts required for such traditional designs would also reduce light transmission through the telescope.

Late in the 1950s, Professor Harold Hopkins was approached by James Gow, a renowned urologist from Liverpool, with the aim of improving this system. The
rod-lens telescope reverses the traditional glass-lens system, such that the telescope is, in essence, a rod of glass with air gaps within that act as the lenses (Figure 1.1.2).

Changing the main transmission medium from air to glass doubled the light which could pass through a system of given diameter. A second doubling of light transmission resulted from the omission of the metal spacers, which were no longer needed to position the lenses; the rods could be mounted without them [2].

Furthermore, the refractive surfaces of the rods were technically easier to precisely engineer so that they could be manufactured to a high degree of optical accuracy. Hopkins complemented these improvements by making use of modern glasses, sophisticated computer-aided design, and multilayer lens blooming. The latter minimised internal reflections within the system, improved light transmission, and suppressed stray images [3].

The result of these improvements has been a family of telescopes, each with good optical resolution through an angle of field of 70° or more, with the image quality of a microscope. The angle of view can be varied by incorporating a prism behind the objective lens. The traditional 30° telescope is a throwback to the days of distal illumination and is widely used, not only for cystoscopy, but laparoscopy as well (Figure 1.1.3). Rotating an angulated cystoscope around its axis during endoscopy therefore enables optimal visualisation of a spheroid structure, such as the bladder.

The rod-lens element of the telescope enables image transmission, but illumination is mediated by a separate system incorporated into the telescope design. Parallel to the rod-lens element is a noncoherent fibre-optic bundle (see below). This is not used for image transmission, but it transmits light from an external source (such as a 3000 W xenon-arc lamp) to provide the illumination required.

Problems related to the rod-lens telescope are relatively infrequent, given the precision engineering required in their manufacture and the workload required of them.

Reduced image contrast can occur as a result of a breach of fluid into the telescope system, resulting in

![Figure 1.1.1](image1.png) Diagram of conventional cystoscope. The glass lenses are held in place by metal spacers and separated by air spaces.

![Figure 1.1.2](image2.png) Rod-lens telescope, with ‘lenses’ of air, separated by ‘spaces’ of glass, with no need for metal spacers. Source: Courtesy of Professor H. H. Hopkins.

![Figure 1.1.3](image3.png) (a) Comparison between the angle of view offered by the conventional 30° ‘fore-oblique’ optic and the forward viewing 0° telescope. (b) The tetroviewing 120° telescope allows the bladder neck and anterior bladder wall to be seen clearly.
1.1 Principles of Urological Technology

internal condensation. In these circumstances, the telescope must be immediately sent away for repair or replacement because of the risk of contamination to a patient.

Poor light transmission may be the result of damage to the fibre-optic bundles within the telescope itself that transmit the external light source from the external cable connection to the distal end of the telescope. Sometimes, poor illumination is because of the fibre-optic cable that transmits light from the external light source to the telescope; this can be checked by qualitatively comparing the illumination coming directly from the external cable with the illumination from the telescope itself with light cable attached.

Blurring of the image or loss of some of the image field can be as a result of accretions accumulating on the proximal or distal end of the telescope. Chipping of the rod lens can result in partial blurring when the damage is nearer the eyepiece, but cracking or chipping can sometimes be seen more discretely with more distal telescope damage.

1.1.1.2 Fibre-optic Flexible Endoscopes

Unlike rigid endoscopes which utilise rod-lens technology, flexible endoscopes all use fibre-optic image transmission. The basis of fibre-optics is the passage of light along glass fibres by a process of total internal reflection, hence, why endoscopes can maintain adequate lighting and imagery (Figure 1.1.4). J. L. Baird [4] conceived the idea of using an array of fibres to transmit an image, but it was Hopkins who constructed the first working fibre-scope [5].

Each glass fibre consists of a light-transmitting translucent core surrounded by glass cladding with a lower refractive index. Light is transmitted through the fibre via a process called ‘total internal reflection,’ with reflection occurring at the interface between the two transparent materials. As there may be up to $10^4$ internal reflections over a 1-m length of fibres, even a small light loss at each one would cause a considerable fall-off in the efficiency of light transmission were it not for the cladding present. The cladding also protects the surface of the fibre core from damage and contamination which would otherwise interfere with internal reflection. Light losses of 50% or less over a 1-m light path can be achieved.

The glass fibre core and cladding is arranged in bundles that may be coherent or non-coherent. Coherent bundles are arranged such that the proximal position of each fibre with respect to the entry face maps precisely to the corresponding position of the fibre distally on the exit face of the flexible instrument. This enables light focusing on the distal face of the endoscope to be transmitted precisely to create an identical image at the proximal face of the endoscope.

Noncoherent fibre bundles are such that the fibres are arranged randomly, enabling light but not image transmission. In urology, flexible cystoscopes, semi-rigid ureteroscopes, and flexible ureteroscopes all utilise coherent fibre-optic technology, whereas light-transmission cables are incoherent fibre bundles. The individual fibres within endoscopes are typically smaller than for light-transmission cables, but the principles underlying both coherent and noncoherent fibre bundles are essentially identical.

1.1.2 Surgical Energy

1.1.2.1 Diathermy

Surgical diathermy utilises the principle that as a current passes through a resistor, heat is dissipated. This results in a temperature rise, and from a surgical perspective, controlled tissue cutting and coagulation [6].

An alternating current from the domestic mains causes such tissue heating, but at 50 Hz, it can also cause electrocution and ventricular arrhythmias, resulting in a potentially fatal outcome.
The underlying principle of safe diathermy (amongst other factors) is not a function necessarily of high or low voltage or current, but of the kHz range frequency at which neurophysiological conduction and axon depolarisation seem to be refractory. A low-frequency current as small as 1 mA can induce fatal cardiac arrhythmias, but at radiofrequencies (500–5000 kHz), neurophysiological conduction does not occur, and currents as high as 2 A can therefore be used for surgical diathermy.

Surgical diathermy exploits the heat generated when an alternating current passes through a conductor. When there is a large density of electrical current passing through tissue, the temperature rise can be enough to give a useful surgical effect. In monopolar diathermy, the surgeon uses a small active electrode to give a high current density and a large heating effect at the operative site at a frequency of about 200 kHz. Because the current density near the large return electrode, which completes the circuit, is small, it produces little heat. In bipolar diathermy the thermal effect occurs in tissue held between two small active electrodes and does not pass through the patient's body which is not being treated. Bipolar frequency is between 250 kHz and 1 MHz.

Nerves and muscles are stimulated by alternating current of low frequency (faradism), but this faradic effect does not occur when the frequency exceeds a certain value as neurophysiological conduction becomes refractory as such frequencies. Surgical diathermy is used for both cutting and coagulation. A pure cutting current utilises an alternating current which is constant; the root mean square of such a waveform enables energy to be delivered at a sufficient level to vaporise intracellular water with cell destruction, achieving very high current densities. For electro-coagulation, the diathermy waveform consists of bursts of alternating current between periods of rest (all still occurring at high frequency), resulting in protein denaturation (and hence thermal coagulation), without vaporisation. The dead tissue is shrunken and desiccated in situ – distortion of the walls of blood vessels, coagulation of plasma proteins, and stimulation of the clotting mechanism all act to check bleeding. Ideally, intracellular temperatures do not reach 100 °C so there should be no unwanted cutting.

1.1.2.2 Contact Diathermy

In contact diathermy, the main impedance (resistance) to current flow is at the interface between the electrode and tissue, where it is influenced by the type of tissue and its state of hydration. The impedance of fat is high compared to muscle, and contact diathermy works less efficiently on adipose tissue. As diathermy proceeds, the tissue in contact with the electrode dessicates and electrical impedance rises. Eventually, the current flow is insufficient to produce further heating and the surgical effect ceases. This limits the depth of penetration of diathermy applied to one spot. The effect of contact diathermy also depends on the size and shape of the active electrode. A ball electrode with a large surface area held in contact with tissue will tend to apply current at a relatively low density, giving a coagulating effect, but the depth of tissue coagulated is proportional to the square of the diameter of the ball. Contact cutting by point diathermy is mainly by physical disruption of tissue softened by coagulation and is usually less effective than noncontact cutting.

1.1.2.3 Noncontact Cutting

Contact with tissue is necessary in bipolar diathermy but most urological diathermy is monopolar and non-contact. For current to cross a gap between a resectoscope loop and the prostate it must be driven by a sufficient voltage to ionise the intervening medium and produce a spark. (A spark is a less sustained discharge than an ‘arc’.) Once established, a spark produces the very high temperatures needed for cutting. However, most of its energy is dissipated near the tissue surface, and little is available to give the gentler heating needed for deeper coagulation and haemostasis.

The cutting current is a continuous simple sine wave. The peak voltage provided is enough to give short, intense sparks which produce enough local heat to explode cells into steam (Figure 1.1.5). There is little coagulation and the cut is ‘pure’. For coagulation, the electrical energy must be applied more slowly so that the heat to which it is converted has time to spread below the surface of the tissue (i.e. the power supplied must be reduced).

In contact diathermy, so long as the effective voltage is sufficient to overcome the impedance of the contact interface, coagulation can be obtained by reducing the voltage of the sine wave current. Alternatively, the current density can be reduced by increasing the contact surface of the electrode.

A high voltage is essential to drive the spark in noncontact diathermy, and a different method must be used for coagulation. The total current supplied in a given time, hence the rate of heating, is reduced by applying the current in bursts. In the gap between the bursts, no current flows. Because the coagulation current is turned off most of the time, it can have large peak voltages and currents but actually deliver much less power than a continuous cutting current. Fulguration (literally flashing like lightning) is provided by a current with an interrupted waveform. This has a high peak voltage but the effective power can be the same as a cutting current with a much lower voltage peak. The resulting sparks are longer, and there is more sustained tissue heating leading to coagulation and haemostasis. The high peak voltage
Principles of Urological Technology

1.1.1

can drive current through the high impedance of desiccated tissue: thus fulguration can continue until carbonisation or charring occur.

In summary, the 'cut' current is typically a continuous sine wave, producing sparks whose heat explodes intracellular water to steam. The 'coag' current is a sine wave current supplied in bursts, which allows the sustained heating in depth needed for coagulation (Figures 1.1.5b and c). Peak voltage and mean power output can be varied by adjusting the duration of bursts of current to give a combination of cutting and coagulation; this is known as 'blended' current.

Diathermy output settings, that can be varied, are normally measured in Watts (Joules per second) and are the product of the voltage and current.

1.1.3 Dangers

1.1.3.1 Electrocutation

Diathermy machines are manufactured to national and international safety standards which minimise the risk of any part of the machine becoming live with mains current. As with any electrical device, servicing must be regular and expert.

1.1.3.2 Fire and Explosion

Ignition of alcohol-based solutions used for skin preparation is a well-recognised complication of diathermy which is still reported each year by the medical defence
societies. It occurs when the flammable fluid is allowed to pool on or under the patient. The surgeon must take care that all excess spirit is removed before using diathermy. Better still, disinfecting fluids containing alcohol should be avoided if a suitable aqueous alternative is available. Thankfully, explosive gases are rarely used in modern anaesthesia. If they are, diathermy is an unnecessary hazard and should be avoided.

### 1.1.3.3 Burns

Burns are the most common type of diathermy accident. They occur when the diathermy circuit is completed in some way other than that intended by the surgeon, usually an unauthorised flow of current to earth. Most monopolar generators are ground referenced by earthing the patient plate side of the output transformer via the metal case of the device (Figure 1.1.6). If the active electrode is touched to any earthed object, current will flow. When the system works properly, heating occurs only at the tip of the active electrode. The current passes through the patient's body and escapes safely via the return electrode. Unfortunately, this long current path offers opportunities for alternative unwanted passage of current to earth. If the patient electrode is incorrectly attached, there is a danger that the circuit might be completed by a small earthed contact point. If the current density at this point is sufficient, the patient will be burned.

Most devices monitor the attachment of the patient plate and sound an alarm when contact is inadequate. A simple method is to attach the plate by two wires through which a small current flows: if a wire breaks, the current is interrupted and the diathermy can be automatically inactivated. This checks the integrity of the connection of the plate to the diathermy machine. It does not guarantee that the plate itself is properly attached to the patient. Another safety device uses a small direct current, which by passing through the active electrode, the patient, and the patient electrode, monitors the integrity of the whole diathermy circuit. Other machines have even more sophisticated safety measures; however, it remains the surgeon's duty to ensure that an appropriate plate is used and to supervise its attachment to the patient.

Unfortunately, burns may still occur at small earthed contact points where current will flow at the expense of even a correctly attached return plate. All patient monitoring equipment should be isolated from the earth wherever this is possible. Electrocardiograph electrodes should be well gelled and of large enough area to disperse the current. Needle electrodes should never be used. As a general rule, the return pad should be sited as near to the operation area as possible so that the main current path will be distant from other potential routes that the current might take to ground.

Pressure on the footswitch of most machines leads to activation of all the active electrodes which are connected. Any devices which are not in use must not be in contact with the patient. An unused electrode should be safely stored in an insulated quiver where it will be safe if the footswitch is inadvertently activated.

The surgeon and assistants are also liable to suffer burns when using diathermy equipment because they constitute an effective alternative path to earth. Such burns are particularly likely in the practice of ‘touching’
the live electrode onto another metal instrument such as tissue forceps grasping a bleeding vessel. Surgical gloves are not effective insulation against diathermy current, especially if they are holed. The person holding the instrument, often an unfortunate assistant, may receive a small but deep and painful burn.

Bipolar diathermy is intrinsically safer than monopolar diathermy because current passes between two small electrodes on the same handpiece. Secondary currents induced by the main radiofrequency may leak to ground, but they are too small to cause trouble. Unfortunately, in most urological applications, bipolar diathermy is not as useful as monopolar diathermy.

1.1.3.4 Neuromuscular Stimulation: The ‘Obturator Twitch’

Although the high-frequency current used for surgical diathermy does not cause neuromuscular stimulation, the sparks which it induces may invoke secondary currents which can do so. The sparks make random electrical ‘noise’ in the midst of which are alternating frequencies able to induce a faradic effect. Such currents can be electronically suppressed by capacitors in the circuit. However, they may be sufficient to cause trouble in the special conditions of diathermy in the region of the ureteric orifices close to the course of the obturator nerve and the psoas muscle. The problem is seen with both ‘cut’ and ‘coag’ currents and can usually be abolished by full chemical neuromuscular blockade.

1.1.3.5 Pacemakers and Diathermy

Implanted pacemakers are not uncommon in patients who are elderly and come to urological surgery. Diathermy currents can interfere with the working of pacemakers, causing possible danger to the patient. This was more of a problem with some of the previous fixed-rate devices, which could be fooled into delivering stimulation at such a high rate that dangerous dysrhythmias could result. Modern pacemakers are designed instead to be inhibited by high-frequency interference so that the patient may receive no pacing stimulation at all while the diathermy is in use. Some demand pacemakers revert to a fixed rate of pacing, and it is essential to have a magnet available so that they can be reset if necessary.

A number of additional precautions are wise in these patients. First, if monopolar diathermy is to be used, the patient plate should be sited so that the current path does not pass through the heart or the pacemaker. Second, the heartbeat should be monitored throughout the operation. Lastly, a defibrillator should be on hand in case a dangerous dysrhythmia develops through malfunction of the pacemaker.

Precautions to avoid complications:

- Diathermy pad: over well-vascularised area, away from any prosthesis, underlying skin free from scarring or hair, 70–150 cm²
- Avoid inflammatory liquids, such as alcohol-containing skin prep
- Patient should avoid contact with any other metal (e.g. drip stand)
- Avoid touching any other instruments with diathermy
- Pacemaker/ICD
  - Is surgery necessary?
  - Check with cardiologist or pacemaker clinic. May need preoperative check or reprogramming (fixed rate/monitor only sometimes via clinical magnet) and postoperative check.
  - Ask patients to bring their card with all details.
  - Diathermy pad away from pacemaker and electrocardiogram leads, diathermy machine away from pacemaker, use bipolar diathermy if possible, continuous heart rate monitoring, defibrillator and external pacemaker to be available, short bursts of diathermy, minimise operative time.
  - Prophylactic antibiotics: avoid fluid overload.
  - Postoperative check if surgery was an emergency.

1.1.4 Urological Diathermy

Transurethral resection requires high-power monopolar diathermy currents which must be handled with great care. Typically, higher power output settings are required (e.g. 160-W cutting/60-W coagulation compared to 30–40 W for open surgery) because the use of irrigation fluid rapidly dissipates the intense heat required. There is an almost inevitable leakage of diathermy current from the loop to the metal instrument which poses a potential danger to both the surgeon and the patient. Most resectoscopes now have an all-metal design with an insulated beak so that current that travels into the instrument is free to leak from it into the urethra. This is not usually a problem because the area of contact with the urethra is sufficient to make a burn unlikely. However, if through some fault, the loop comes into direct contact with the sheath, the full diathermy output will be applied to the urethra.

A fully insulated sheath might be expected to give protection against this hazard; unfortunately, this has dangers of its own. Damage to the insulating layer will lead to unpredictable leakage into the patient or the surgeon. If the loop should break and make contact with the metal frame of the instrument, a large current could flow to ground via the surgeon’s body. Such currents are usually prevented by the return fault circuit of the machine, but small and significant currents may pass to ground during fulguration.
Conducting lubricating gels should be used with all metal resectoscopes to avoid the possibility of preferential conduction at sites where the gel is thin or absent. By contrast, petroleum jelly or mineral oil, which do not conduct electricity, must be used only with an insulated sheath because these lubricants cannot provide an alternative path between the loop and the urethra, and they always end up smearing the lens.

1.1.4.1 LigaSure Diathermy

This utilises pressure and energy to seal vessels. It is a bipolar device which allows the administration of high current and low voltage energy (180 V) and high coaptive pressure during the generation of tissue temperature under 100°C, which results in sealing of vessels up to 7 mm in diameter. Once the energy is applied, the hydrogen cross-links rupture and then renature, resulting in a vascular seal that has high tensile strength. The melted collagen and elastin in the vessels form a permanent seal.

1.1.4.2 Harmonic Scalpel

The harmonic scalpel utilises ultrasound energy to cause coagulation at lower temperatures than electrosurgical equipment (50–100°C compared with 150–400°C). Coagulation occurs by the coaptation or compression of the vessels walls followed by denaturing protein when the instruments blades vibrate at 55,500 Hz (i.e. 55,500 vibrations/s). The ultrasound transducer located in the hand piece is composed of piezoelectric crystal sandwiched under pressure amongst metal cylinders. The ultrasound generator converts ultrasonic energy into mechanical energy or the vibrations.

This comprises the utilisation of both the harmonic scalpel and the LigaSure, by simultaneously delivering ultrasonically generated frictional heat energy and electrically generated bipolar energy.

1.1.5 Lasers in Urology

LASER is an acronym for light amplification by the stimulated emission of radiation. Laser energy is now ubiquitous in surgery and perhaps indispensable for some purposes, such as transmitting energy down a flexible endoscope (e.g. holmium: YAG laser ablation of upper tract stones via a flexible ureterorenoscope).

Laser energy is light energy which, like electromagnetic radiation in general, may interact with matter to create heat and other phenomena. The characteristics of light is that it is that form of electromagnetic radiation defined by its ability to be perceived by the human eye, although infrared and ultraviolet radiations, which also interact with biological systems, are included within this definition. The wavelengths of visible light range from 400 nm (violet) to 760 nm (red) and form only a small part of the electromagnetic spectrum [7].

Laser light differs from conventional white light only in that it is:

1) Monochromatic: consisting of light waves propagating at a single frequency
2) Collimated: the photons propagate in parallel via narrow beams with little divergence, resulting in high pinpoint irradiance.
3) Coherent: the propagated waves are such that wave peaks and troughs are in phase.

Electromagnetic radiation propagates in wave form, characterised by a frequency (ν), which is inversely proportional to its wavelength (λ) and related to the speed of light as follows:

\[ C = \lambda \nu \]

where \( c \) is the velocity of light in a vacuum \( (2.99 \times 10^8 \text{ m s}^{-1}) \). ‘White light’, such as sunlight, is polychromatic with a wide distribution of wavelengths.

All types of electromagnetic radiation have mutually perpendicular coupled electric and magnetic fields which are able to interact with the electrons and nuclei of the atoms that comprise matter. The predominant interaction is that of the electric field component with the negative charge of electrons. Towards the end of the nineteenth century, it was realised that many aspects of electromagnetic radiation could be more accurately understood by regarding the radiation as comprising discrete particles or packets of energy called ‘quanta’ or photons. A key principle of quantum physics is dual wave/particle nature of matter. This is key to understanding how laser light (along with all electromagnetic radiation) has both particulate properties (in the form of photons) and waveform characteristics.

1.1.5.1 Basis of Energy Generation in LASERs

Lasers require:

1) An energy source. This is sometimes called a ‘pump source’ and may consist of an electrical flashlamp, arclamp, electrical discharge, chemical reaction, or another laser. A helium-neon (HeNE) laser typically utilises an electrical discharge, whilst a Nd:YAG laser utilises a Xenon flash lamp.

2) A gain material, or laser material. This is the medium which determines the wavelength of the laser output and the source of photons from exciting electrons in that medium. Examples of lasers in urology include KTP:YAG and Ho:YAG devices.
3) An optical resonator. A simple example would be a paired parallel mirror on either side of the gain material, one mirror being partly reflective. This enables the photons to oscillate between the mirrors within the gain material, resulting in amplification prior to light emission.

The pump source excites electrons to a higher orbital or energy level. The laws of quantum physics ‘allow’ electrons to occupy only certain discrete energy levels. When the excited electrons relax, or decay, to their ground state, they emit a photon, the energy of which is discrete and precise for the particular laser material and corresponds to the transition energy between the excited and ground state (Figure 1.1.7). This emission of a photon from the transmission from excited to ground state is called ‘stimulated emission’. The emitted photon has a precise wavelength defined by this change in the discrete energy levels, and hence the monochromatic nature of laser light. The basic construct of a laser is illustrated in Figure 1.1.8.

**Figure 1.1.7** (a) Photon emission with electron transition. (b) Photons are emitted when a particle changes from a higher to a lower energy state. (c) The impacting and emitted photon have the same wavelength and are discharged in phase; two photons emerge where only one went in.

**Figure 1.1.8** Laser construction. The active laser medium is contained between mirrors. Energy is pumped into the laser medium from a power source to propel more particles into a higher energy state. In stimulated emission, photons radiate in all directions. Only those which are parallel to the axis of the laser cavity emerge through the front mirror as the laser beam.
1.1.5 Laser Interface with Tissue

When photons from a laser interact with the surgical field, there are several potential outcomes for the incoming beam:

1) Reflection – a small percentage of the incoming laser light is reflected at the interface between the transmitting medium and the operative surface. This may cause some collateral heating but is not usually of clinical significance.

2) Scattering – this is a function of both the tissue operated on and the wavelength of laser used. Longer wavelength laser light (i.e. lower frequency) towards the red/infrared end of the spectrum tends to scatter less than shorter wavelength blue/violet light.

3) Extinction length – this is the attenuation of the laser light in tissue and is an important function of laser wavelength and an important consideration because it informs us to the depth of necrosis or tissues heating for a given laser. In general, lasers operating at shorter wavelengths (e.g. green light lasers) will have greater depth of penetration than infra-red Holmium:YAG lasers, which have an extinction length of less than 0.5 mm.

4) Absorption – this is the most important phenomenon for surgery, by which the laser light interacts with tissue or stone to create the cutting, vaporisation, or coagulation effect required by the urologist. Absorption of photons can only occur when there is a chromophore presence (i.e. a set of chemical bonds or molecules which interact with incoming photons to obliterate that photon, excite the chromophore, and enable the conversion of light into heat energy). Fortunately, human tissue consists largely of chromophores, including water and blood. Different tissues absorb different wavelengths of laser light with varying optimisation (i.e. the absorption spectra will be molecule- and tissue-specific). For example, green light (KTP:Nd:YAG operating at 512 nm) operates at one of the absorption peaks of haemoglobin. Blood is red when illuminated by conventional white light because haemoglobin molecules absorb green and blue light, reflecting predominantly red light back into our retinas. Conversely, Holmium:YAG laser light operates at the invisible infrared part of the spectrum, which is optimally absorbed by water.

1.1.5.3 Clinical Applications

Lasers in urology are used predominantly for the surgical treatment of benign prostatic enlargement (BPE) and urinary tract stone disease. Laser light can be transmitted via fibreoptic technology, enabling the transmission of energy through flexible endoscopes. Lasers that emit light efficiently absorbed by water or haemoglobin enable it to effectively cut, coagulate, and vaporise in the treatment of BPE. Table 1.1.1 summarises the lasers that are currently used in urology.

1.1.5.3.1 Lasers in the Management of Urinary Tract Stones

The Ho:YAG produces light at a wavelength of 2100 nm in a pulsed fashion. At this far infrared frequency, water is absorbed to produce localised heating and tissue or stone destruction. The energy can be varied from 0.2 to 2.8 J/pulse and the frequency from 5 to 30 Hz, giving powers of up to 100 W. The light can be transmitted along low-water-density fibres and, unlike the CO2 laser, can be carried through a flexible fibre. This makes the Ho:YAG laser ideal for stone treatment using flexible-ureteroscopy, and therefore enables minimally invasive retrograde treatment of even the most inaccessible of upper tract stones. Other ureteroscopic modalities for treating stones either require a rigid instrument (e.g. lithoclast) or are unacceptably dangerous in the modern era of clinical governance (electro-hydraulic lithotripsy).

Typical power settings for laser lithotripsy are arbitrary but are often set with the pulse frequency in Hertz (Hz) numerically 10 times the energy setting in Joules (J). Examples of settings used for laser lithotripsy via the flexible ureteroscope are from 0.6 J at 6 Hz to 1.5 J at 15 Hz. The product of these settings gives the power output in Watts ($\equiv$ J s$^{-1}$):

$$\text{Power (W)} = \text{Energy (J)} \times \text{Frequency (Hz)}$$

Laser transmission via a 200-μ fibre and flexible ureteroscope can enable stones to be potentially treated anywhere in the urinary tract. Scenarios which have now made the Ho:YAG laser an essential part of the urological armamentarium are summarised as follows:

- Minimally invasive treatment, in a single sitting, of an upper ureteric stone beyond the reach of a rigid ureteroscope.
- The scenario where lithoclast treatment of a lower or middle ureteric stone via the rigid ureteroscope transmits the stone upward, beyond the reach of conventional instrumentation. In these circumstance, one could then ‘chase’ the stone using a flexible ureteroscope and Ho:YAG laser.
- Treatment of a lower calyceal stone, resistant to extracorporeal lithotripsy (ESWL), may be carried out by manipulating the flexible ureteroscope retrogradely into the calyx and allowing disintegration using the Ho:YAG.
- Similarly, stones in calyceal diverticula can be treated by retrogradely incising the diverticulum using the flexible ureteroscope and then treating the stone with the Ho:YAG laser.
Treatment of calcium oxalate monohydrate and cystine stones. These stones are hard and may be resistant to ESWL or the lithoclast. The Ho:YAG laser is capable of destroying these stones.

1.1.5.3.2 Lasers in BPE

Despite the numerous laser procedures for BPE that have emerged and, together with their acronyms, have become obsolete over the years, the principle of laser surgery for BPE is relatively straightforward. Photons, which have both particle and wavelike properties, have intrinsic energy inversely proportional to their wavelength and can be absorbed by, for example, haemoglobin or water to create heat which results in coagulation and protein denaturation or vaporisation. All the techniques briefly described here are generally easy to learn (except for the HoLEP), have excellent haemostatic properties, utilise saline as the irrigating fluid of choice, and enable surgery to be carried out as day case or <24-hour-stay surgery.

Lasers for treating BPE were first used in the early 1990s with the visual laser ablation of the prostate (VLAP), utilising a 1064 nm Nd:YAG laser. This relatively long wavelength delivers a relatively low-energy density, resulting in protein denaturation and a subsequent coagulative necrosis, with a delayed bulking effect. The subsequent sloughing of prostatic tissue resulted in persistent irritative symptoms lasting months.

Interstitial laser coagulation (ILC) involved heating tissue by directly placing a Nd:YAG fibre directly into prostatic tissue under endoscopic guidance, and although blood loss was minimal, prolonged catheterisation, chronic dysuria, and a high reoperation rate were significant drawbacks [8].

The GreenLightTM Laser vaporises tissue by delivering much higher energy densities. This laser utilises a Nd:YAG laser, which is frequency-doubled (wavelength-halved) to 532 nm, using potassium-titanyl-phosphate (KTP) crystals. This wavelength is strongly absorbed by haemoglobin and has a low extinction length, resulting in vaporisation with a low surrounding radius of coagulation. A newer generation GreenLight XPS™ MoX™ Laser utilises a high maximum power output of 180 W, with a good safety record in patients who are anticoagulated, but long-term results pending [9].

### Table 1.1.1 Lasers used in urology.

<table>
<thead>
<tr>
<th>Laser Medium</th>
<th>Abbreviation/ Acronym</th>
<th>Wavelength (nm)</th>
<th>Procedure</th>
<th>Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmium: Yttrium-Aluminium-Garnet</td>
<td>Ho:YAG</td>
<td>2140</td>
<td>Holmium Laser lithotripsy</td>
<td>Water</td>
</tr>
<tr>
<td>Kalium titanyl phosphate: Yttrium-Aluminium-Garnet</td>
<td>KTP:Nd:YAG</td>
<td>532</td>
<td>Photoselective vaporisation of the prostate (PVP)</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>Lithium Borate: Yttrium-Aluminium-Garnet</td>
<td>LBO:Nd:YAG</td>
<td>532</td>
<td>Photoselective vaporisation of the prostate (PVP)</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>Thulium: Yttrium-Aluminium-Garnet</td>
<td>Tm:YAG</td>
<td>2013</td>
<td>Thulium laser vapoenucleation of prostate (ThuVEP)</td>
<td>Water</td>
</tr>
<tr>
<td>Diode Lasers</td>
<td></td>
<td>830, 940, 980, 1318, 1470</td>
<td>Interstitial laser coagulation of prostate (ILP)</td>
<td>Water and haemoglobin</td>
</tr>
<tr>
<td>Dye Laser</td>
<td></td>
<td>405</td>
<td>5-Aminolevulinic Acid (ALA) mediated Photodynamic Therapy (PDT)</td>
<td>Haemoglobin</td>
</tr>
</tbody>
</table>
The Holmium: Yttrium-Aluminium-Garnet (Ho:YAG) laser produces a pulsed wavelength of 2140 nm. This is strongly absorbed by water, enabling precise prostatic tissue vaporisation and hence cutting, with minimal charring and a very short extinction depth. The technique of Ho:YAG enucleation (HoLEP) is different from other laser techniques in that the prostatic adenoma is enucleated in the plane between the adenoma and false surgical capsule, with the lobes subsequently removed with a tissue morcellator. It seems that this technique, whilst taking longer to learn and may also utilise more theatre time than a standard transurethral resection of the prostate (TURP), seems to have long-term results at least as good as TURP [10].

1.1.6 Catheters

Urinary catheters are the most used technology in urology for not only therapeutic means, but also diagnostics. It has been in use since 3000 BCE. The word ‘catheter’ is derived from the Greek ‘to let down’ or ‘send down’.

Catheters are classified base on a number of factors collectively:

- Size: the outer diameters measure by ‘French’ or ‘Charriere’ gauge, which refers to the outer circumference in millimetres. Newborn catheters: 4–6 Fr; Infants: 6–8 Fr; Children: 10–12 Fr; Adolescents and adults: 10–34 Fr. The Fr is 3 times the diameter in millimetres (i.e. a 1 Fr has an external diameter of 1/3 mm, therefore the diameter of a catheter in millimeters can be calculated by dividing the Fr by 3) [11].
- Channels: 1-, 2-, or 3-way catheters; (one-way catheters are the in and out intermittent self-catheterising catheters)
- Balloon size: 3–30 ml
- Tip design: Foley and Coude are the more commonly used types (Figure 1.1.9)
- Materials: Polytetrafluoroethylene (PTFE)-coated, latex-coated, complete silicone, or polyvinyl chloride.
- Length of required use: short term (e.g. PTFE coated which can be left for 28 days), long term (e.g. latex-coated and silicone catheters which can be left for three months).
- Others types of catheters such as polyvinylpyrrolidone (PVP) and salt coated create a self-lubricating aqueous layer good for intermittent catheterizations.
- Colour coded (Table 1.1.2).

1.1.6.1 Indications
- Relief of obstruction
- Irrigation of bladder
- Drainage to allow healing (low bladder pressure)
- Empty bladder prior to abdominal or pelvic surgery
- Monitoring of urine output
- Delivery of bladder instillations
- Identification of bladder neck perioperatively
- Incontinence
- Urodynamics

1.1.6.2 Complications of Catheters

1) Localised trauma: Creation of false passages if prostate is enlarged causing difficulty to insert the catheter. This can cause a self-limiting bleed, but

Table 1.1.2 Colour coding for different catheter sizes.

<table>
<thead>
<tr>
<th>Fr</th>
<th>Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Black</td>
</tr>
<tr>
<td>12</td>
<td>White</td>
</tr>
<tr>
<td>14</td>
<td>Green</td>
</tr>
<tr>
<td>16</td>
<td>Orange</td>
</tr>
<tr>
<td>18</td>
<td>Red</td>
</tr>
<tr>
<td>20</td>
<td>Yellow</td>
</tr>
<tr>
<td>22</td>
<td>Violet</td>
</tr>
<tr>
<td>24</td>
<td>Blue</td>
</tr>
</tbody>
</table>

Figure 1.1.9 (a) Side open, (b) Whistle tip, (c) Coude tip, (d) Mallecot, (e) Mushroom tip, (f) Foley.
occasionally the bleeding might need cystodiathermy to control. Strictures (50% of strictures are instrumentally caused) and traumatic hypospadias.

2) Urinary tract infections (UTIs): Asymptomatic bacteriuria invariable occurs in all catheterized patients and is time associated at a rate of about 3–10 % day⁻¹ and reaching 50% by day 10, and nearly 100% by day 28. Nearly 80% of hospital-acquired UTIs are catheter related. The mechanism behind catheter-related infections is the biofilm produced by bacteria. A biofilm is an aggregate of microorganisms in which cells adhere to each other on a surface such as a stent or catheter. These cells are embedded within a self-produced matrix of extracellular polymeric substance (EPS). This substance or slime is composed of material such as proteins, polysaccharides, and DNA. Produced by many types of bacteria, more commonly Staphylococcus aureus and Proteus spp. Protozoa and fungal infections can also produce biofilms.

Biofilm formation (Figure 1.1.10):

1) Initial attachment through weak, reversible adhesion via van der Waals forces.
2) Irreversible attachment anchors themselves more permanently using cell adhesion structures such as pilus.
3) Maturation I and II provides more diverse adhesion sites; build the matrix. Once colonisation has begun, the biofilm grows through a combination of cell division and recruitment.
4) Dispersion enables biofilms to spread and colonise new surfaces including tissue such as the bladder, ureter, or renal calyces’ walls. Enzymes that degrade the biofilm extracellular matrix, such as dispersin B and deoxyribonuclease, may play a role.

The EPS matrix protects the cells within it and facilitates communication amongst them through biochemical signals. Some biofilms contain water channels that help distribute nutrients and signalling molecules. This environment results in increased resistance to antibiotics because the dense extracellular matrix and the outer layer of cells protect the interior of the community. One factor in bacterial persistence is the ability of bacteria to grow within biofilms.

1.1.6.2.1 Treatment

Management of recurrent UTIs is difficult in these patients, but essentially regular bladder washouts, reduced frequency of catheter change, and increased fluid intake are the key points. Regular or prophylactic antibiotics work invariably and should be given if the patients are symptomatic.

1) Encrustation and stones (25% at five years) and repeated blockages and bypassing: this is based on similar principles of infected stone formation. The urine needs to be alkalinize to pH >7.2, presence of urease-producing bacteria which hydrolyses urea to ammonia and carbon dioxide (Figure 1.1.11). The high-urinary pH with ammonia leads to crystallisation of magnesium, calcium, and ammonium phosphate (i.e. triple phosphate). Urease-producing bacteria: Staphylococcus, Proteus, Klebsiella, Pseudomonas, Providencia, and Ureaplasma urealyticum.

$$\text{(a)}$$

$${\text{H}}_{2}\text{N} \xrightarrow{\text{Urease}} (\text{NH}_4)^2\text{CO}_3 \xrightarrow{} \text{NH}_4^+ + \text{HCO}_3^-$$

$${\text{H}}_2\text{N} + \text{H}_2\text{O} \rightarrow 2\text{NH}_4^+ + 2\text{OH}^- \text{ (decreases pH to >7.2)}$$

Figure 1.1.10 The five stages of biofilm development. Stage 1, initial attachment; stage 2, irreversible attachment; stage 3, maturation I; stage 4, maturation II; ND stage 5, dispersion.

Figure 1.1.11 (a and b) Urease-producing bacteria hydrolysis of urea. $2\text{NH}_3 + \text{H}_2\text{O} \rightarrow 2\text{NH}_4^+ + 2\text{OH}^- \text{ (decreases pH to >7.2)}$
Treatment is similar to recurrent UTIs in addition to acidification of urine and ensuring no encrustations or stones are left behind. For catheter bypassing not related to encrustations, bladder spasms could be the cause and are alleviated with anticholinergics.

2) Failure of balloon to deflate: can be the result of mechanical failure, encrustations around the balloon, or inexperience.

Steps to remove catheter:
- a) Experienced doctor or nurse to attempt to deflate balloon.
- b) Inflating balloon with air or water to dislodge obstruction.
- c) Leaving 10-ml syringe firmly attached for one hour to slowly aspirate fluid from balloon.
- d) Overinflate balloon to burst it carefully because this can cause injury to the bladder.
- e) Cut end of catheter just beyond the valve might cause expulsion of the balloon fluid.
- f) In patients who are female, insert needle alongside your finger into vagina and advance through anterior vaginal wall.
- g) In patient who are male, suprapubic needle with ultrasound guidance.
- h) Pass ureteroscope alongside catheter and burst balloon with guidewire or laser fibre.

3) Allergic reaction to the catheter material, especially if latex-coated.

4) Malignancy: recurrent inflammation and irritation to the bladder can cause squamous cell carcinoma. Seen rarely in the early years 0.5% at five years, increasing to 8% over 20 years.

1.1.7 Stents

These are commonly used in endourology to bypass an obstructed drainage system or postoperatively. Drainage is thought to be around the stent; however, in complete ureteric obstruction, drainage through the stent can take place.

Classified by:
- Length: 18–30 cm long with either 1, 2, or neither end coiling.
- Size: 4.8–8 Fr.
- Material: polyurethane, polyethylene, silicone, metallic, and Memokath stents (thermos-expandable stents used in malignancy cause ureteric obstruction).
- Coating: PTFE coated or hydrogel coated.

Characteristics of an ‘ideal’ stent [12]:
- Good memory and does not migrate.
- Excellent flow characteristics.
- Radio-opaque.
- Biologically inert.

- Resists biofilm formation, encrustation, and infection.
- Made of a flexible material with high tensile strength.
- Easy to insert, remove, or exchange.
- Inexpensive to buy.

There is no stent that has all these features.

Indications for use in general urology:
- Electively: protection of an anastomosis, overcoming extrinsic compression, prior to chemotherapy to optimise renal function, or preoperatively to aid identification of the ureter.
- Emergency: relief of obstruction and in management of ureteric trauma.

In endourology:
- Absolute: Ureteric injury/perforation, single kidney, transplanted kidney, or high risk of residual stone obstruction.
- Relative: Oedematous ureter, long-standing impacted stone, preoperative obstruction with renal failure, balloon dilatation, ureteric cancer treatment, or biopsy.

How they work:
- Drainage is largely around the outside of the stent.
- Reflux is through the centre.
- Stones only pass very slowly alongside stent.
- Upper tract motility is reduced.
- Stents do cause partial obstruction.

1.1.7.1 Complications

Similar to catheter complications. In addition to pain and discomfort, which can be as bad as a renal stone passage, treatment is with anticholinergics, α-blockers, analgesics, or a combination of those. Furthermore, stents left in situ after stones surgery will encrust rapidly and should not be left for more than two to three weeks because can cause complete obstruction. Haematuria is common, and patients must be warned; otherwise patients will return to seek medical advice for the alarming symptom. Lost stents, migrated stents, and stent kinking causing obstruction can happen.

1.1.8 Guidewires

Guidewires are commonly used in endourology, and safe practice dictates leaving a ‘safety’ guidewire in situ while endoscopically operating on the upper tracts. Guidewires can also be used to aid catheterisation of the bladder, especially if multiple false passages have been created. A flexible cystoscopy leads the right path, a guidewire is left in the bladder, and a catheter railroaded over the guide wire.

Classified by:
- Length: guidewires are usually 150 cm in length.
- Size: 2.5 Fr (0.032 inches)–2.9 Fr (0.038 inches).
Material and coating [12]: stainless steel core with PTFE coating (standard guide wires) or Nitonol (nickel-titanium alloy) core with hydrophilic polymer coating (just the tip: Sensor guide wires; whole guide wire: Terumo guide wires) these become slippery when wet, Nitonol with PTFE coating, or stainless steel with hydrophilic polymer coating.

References

1.2 Wound Healing in the Urinary Tract

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Abstract

Wound healing is a dynamic process that demonstrates the body’s ability to respond to change in its protective integrity and maintain homeostasis by swiftly responding to this change. Wounds, either surgically or trauma induced, are a form of cellular injury that leads to a tissue response. This response is a complex process which involves the removal of necrotic tissue and induction of repair. When tissue injury occurs, the damaged blood vessels hemorrhage into the defect, platelets aggregate, and a thrombus forms. This process allows the interaction with the complement system, and inflammatory cells are attracted to the site of injury by chemotactic factors. Platelets play an essential role in this response as they release two important factors. These factors are platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β); they are powerful chemotactic factors for inflammatory cells such as macrophages, which then migrate into the wound to phagocytose necrotic tissue and fibrin. PDGF induces the cells to change from the resting phase in G0–G1. Epidermal growth factor (EGF) and insulin-like growth factor (IGF) act to induce cell progression from G1 phase to DNA synthesis. Capillary proliferation is stimulated with angiogenic growth factors such as vascular endothelial growth factor (VEGF). The defect is repaired by capillary hyperplasia, myofibroblasts, and epithelial cells.

Nutrients and hormones play a vital role in the wound-healing process, as insulin, thyroid hormones, glucose, amino acids, and vitamin C. The deficiency in nutrients or vitamins or the presence of infection or poor local circulation may lead to delay in wound healing.

Keywords wound healing; surgical incisions; inflammatory response; effect of urine; suture materials

Key Points

- Wound healing is a dynamic process that manifests the concept of homeostasis as the body responds to trauma and induces healing.
- Inflammation is the cornerstone of the healing process.
- The urinary tract has unique characteristics in managing wound healing.
- Urine may interfere with wound healing and lead to:
  1) Delayed healing.
  2) Necrosis of the wound.
  3) Contracture.

1.2.1 Introduction

Throughout history, wound healing has been a subject of interest in all the civilizations. Since the time of ancient Egyptians, 1600 BCE, the Edwin Smith surgical papyrus described the different types of wounds. The Ebers Papyrus, 1550 BCE, described the use of different materials that can be applied to the wounds (e.g. honey, grease, and lint to absorb wound discharges). Warriors and gladiators of the Roman Empire suffered a large number of injuries, and Galen, who was appointed as a physician to the gladiators, described that maintenance of moisture in the wound promoted healing.
For many centuries, wound healing and pathology has evolved, but the risk of infection was always a major concern. At the beginning of the nineteenth century, Semmelweis, the Hungarian obstetrician (1818–1865) found that sepsis after childbirth was much lower if the medical students attending the birth washed their hands with soap and hypochlorite. Louis Pasteur (1822–1895) proved that germs are introduced to the wounds from the environment. In 1865, Joseph Lister, who was a professor of surgery in Glasgow, read Pasteur’s work and started using carboxic acid (phenol) on wounds. This has vastly reduced the rate of infection, and he then used phenol for hand washing and sterilising instruments and sprayed carboxic acid in the theatre to limit infection. This reduced the rate of infection from 50% to 15.

Gradually, the type of dressings being used evolved to encompass a wide array of customised dressings that allow variable degrees of permeability, absorbency, and antiseptic properties. Currently, wound management involves the application and manipulation of growth factors, cytokines, and bioengineered tissue [1].

1.2.2 Wound-Healing Process

The cell is a dynamic entity that maintains homeostasis despite continuous changes in the environment. When the changes are severe, cellular injury will occur. There are various mechanism of cellular injury: physical, chemical, and biological. In surgery, these three mechanisms may occur simultaneously or sequentially. A surgical incision is a form of physical injury or trauma to the tissue that may result in another form of tissue insult, such as hypoxia and predisposition to infection as a result of the breach of protective barriers. The response to injury also depends on various factors, such as, the nutritional status of the patient, blood supply to the injured area, and immunity. Previous radiation or chemotherapy may preclude an adequate response of the tissue to heal.

The response to cellular injury whether pathological as in trauma or physiological as in surgery is the same, and that is the process of inflammation. The inflammatory response is a sequential reaction to cellular injury. The mechanism of inflammation is basically the same regardless of the insulting agent. The response depends on the extent and the severity of injury and on the patient’s individual response. The inflammatory response can be divided into a vascular response, cellular response, formation of exudate, and healing [2].

1.2.3 Vascular Response

After cellular injury, arterioles in the area briefly undergo transient vasoconstriction. Histamine and other chemicals are released by the injured cells leading to vasodilation. This vasodilation results in hyperaemia, which raises filtration pressure. Vasodilation and chemical mediators cause endothelial cell retraction, which increases capillary permeability that facilitates the movement of fluid from capillaries into tissue spaces, inflammatory exudate.

Exudate is composed of serous fluid that contains plasma proteins, primarily albumin, exerting an oncotic pressure that draws more fluid leading to tissue oedema. The products of the injured cells activates the plasma protein, fibrinogen, to form fibrin. Fibrin strengthens the blood clot formed by platelets. The function of the clot is to trap bacteria and prevent their spread and to serve as a framework for the healing process.

1.2.4 Cellular Response

As more fluid is lost, the blood viscosity increases, and the blood flowing through the capillaries of the injured tissue slow down. Neutrophils and monocytes move to the inner surface of the capillaries by the process of margination and then by diapedesis, which is movement by an amoeboid fashion through the capillary wall to the site of injury. Chemotaxis is the directional migration of white blood cells (WBCs) along a concentration gradient of chemotactic factors, which are substances that attract leukocytes to the site of inflammation. Chemotaxis is the mechanism for ensuring accumulation of neutrophils and monocytes at the focus of injury.

Neutrophils arrive first at the site of injury, usually within 6–12 hours; they phagocytise damaged cells, foreign material, and bacteria. To maintain the supply for the inflammatory process, the bone marrow releases more neutrophils into the circulation, and these result in an elevated WBC count. Occasionally, the demand for neutrophils increases to the extent that the bone marrow releases immature forms of neutrophils, called ‘bands’ or ‘segmented neutrophils,’ into circulation. Increased numbers of band neutrophils in the circulation is called a ‘shift to the left,’ which is commonly found in patients with acute bacterial infections. Neutrophils have a short life span of 24–48 hours. Dead neutrophils and cellular and bacterial debris accumulate and form pus.

Monocytes are also phagocytic cells that migrate from circulating blood. They are attached to the site by chemotactic factors such as mononuclear attractant protein-1 (MCP-1), fibrinopeptides, and macrophage inflammatory proteins and usually arrive at the site within three to seven days after the onset of inflammation. Monocytes transform into macrophages after arrival at the tissue spaces and phagocytose the inflammatory debris. The role of the macrophages is to clear the debris in the injured tissue before healing can occur. Macrophages have a longer life span, and as they multiply, they remain
1.2.6 Different Methods of Making Surgical Incisions

in the injured tissue for weeks; they are instrumental in the healing process. Macrophages accumulate and fuse to form multinucleated giant cells that can engulf large particles that are too large for single macrophages. Giant cells are encapsulated by collagen and form a granuloma. This process has been classically described when tuberculosis bacillus infects the lung. As the bacillus is encapsulated, a chronic state of inflammation ensues. As the granuloma forms, the process will continue, and this cavity will contain necrotic tissue.

Each cellular component has a different role in the inflammatory process. Basophils and eosinophils have a more selective role. During an allergic reaction, eosinophils, which constitute up to 5% of the WBCs, are released in large quantities and they target organisms that are too large to be engulfed. Their mode of killing involves secreting toxic substances (e.g. reactive O2 compounds), major basic protein, which is toxic to parasites, and several enzymes. Eosinophils also release inflammatory mediators (e.g. prostaglandins, leukotrienes, platelet-activating factor, and many cytokines).

Basophils share several characteristics with mast cells. When these cells encounter specific antigens, they undergo cellular degranulation and release preformed inflammatory mediators, such as platelet-activating factor and histamine. They also synthesise new mediators such as leukotrienes, prostaglandins, and thromboxanes. Connective tissue mast cells contain chymase, tryptase, and heparin. Through the release of these mediators, mast cells play an important role in generating a protective acute inflammatory response. The main role of lymphocytes that arrive later at the injury site is humoral and cell-mediated immunity.

The complement system plays a major role in the mediation of the inflammatory response. It contributes to increasing the vascular permeability, and enhancing phagocytosis, chemotaxis, and cellular lysis. When the complement system is activated, it works in a sequential order, which is C1, C4, C2, C3, C5, C6, C7, C8, and C9. These numbers reflect the order of their discovery. The activation of the complement system is through the fixation of the component Cl to the antigen–antibody complex, which is the primary pathway. The complement is fixed by immunoglobulins IgG and IgM. When each complex is activated, it acts on the next component, hence, creating a cascade effect. In the alternative pathway; C3 is activated without prior antigen–antibody fixation [3].

1.2.5 Urinary Tract Healing

The healing process in the urinary tract after surgical intervention is slightly unique from other tissues because of the presence of urine. Due to the various surgical approaches in urological surgery, the technique involved, the location of the procedure, and the organ operated on, all contribute to the outcome of this process.

The common notion of dividing the urinary tract during surgery, which is applied in open surgery, involves division and suture of tissue. The tissue edges are bonded with fibrin, which will stimulate the growth of capillaries to form granulation tissue which will be gradually replaced by fibrous tissue, which matures to form a scar in the course of few weeks to months as a result of the remodelling process. The peculiarities of each procedure, technique, and organ involved affect the healing process. These unusual features will be discussed in the next section.

1.2.6 Different Methods of Making Surgical Incisions

In urology, there are a myriad procedures that are performed through endoscopic and minimally invasive approaches. Endoscopic surgery has replaced many conventional procedures that required open surgery and the use of the scalpel. The use of endoscopes that gradually became smaller, more robust, and provide multichannel apparatus that allows the surgeon to perform many procedures like biopsy, resection, removal of foreign body, and stone fragmentation. To provide a safe surgical environment, good visibility is essential, and hence, haemostasis and techniques for haemostasis have also evolved. Such devices include diathermy, laser technology [1], and the ‘ultrasonic scalpel’ [2]. To achieve ideal haemostasis, the application of thermal devices to the resected tissue will lead to a degree of tissue damage. This creates nonviable tissue that leads to more wound induration, and as the tissue has lost part of its blood supply, the sloughed tissue left behind acts as a foreign body and increases the risk of infection [3, 4].

A skin incision heals through a conventional process of granulation tissue formation which is gradually covered with an advancing film of epithelial cells that conglomerate from the wound edges by mitotic activity to close the defect [5]. In the urothelium, the process is different because this type of tissue has abundant mitoses in every layer.

The notion that all tissue defects healed the same way was defied as an unexpected finding that was reported by Brauer [6] but was largely ignored until confirmed nearly 30 years later by Johnson and McMinn [7], who found that healing in the biliary tree, the salivary ducts, and the urinary tract followed a different pattern to that of skin or intestinal mucosa. After endoscopic resection of bladder pathology, the defect is filled with the usual granulation tissue and gradually over this layer, a film of urothelium rapidly spreads because of the abundant mitotic activity in the cells that grow from the edge of the wound. This is
in contrast to the skin and bowel pattern of healing because the mitotic activity in these tissues are found some distance away from the wound edge (Figure 1.2.1).

This inwardly growing thin film of urothelium becomes thicker and eventually takes on the features of normal urothelial tissue. The agility and rapidity of urothelial growth has two important implications: (i) any cavity (such as a urinoma) which is in communication with the urinary tract may be relined with urothelium, and (ii) the regeneration of the urothelium is so rapid and effective that it can cover over and bury little islands of the original damaged urothelium.

### 1.2.7 Von Brunn’s Nests and Metaplasia

More than 100 years ago, Von Brunn [8] described how these buried islands of urothelium would form cysts or ‘nests.’ More than a decade later, Giani [9], while studying the healing of transitional epithelium in dogs, observed every stage between burying of fragments of epithelium, the development of von Brunn’s nests, and the formation of full-blown cystitis cystica and was able to create similar nests by implanting the vesical epithelium.

Similar epithelial growths caused by healing may occur in the skin where they give rise to innocent implantation dermoids [10]. In the urinary tract, they are peculiarly dangerous. The little nests become progressively thicker until they actually form columnar epithelium (Figure 1.2.1). In other mammals, patches of columnar mucosa are considered normal, but in humans, they are potentially malignant and are followed by the development of adenocarcinoma [11–14].

### 1.2.8 Squamous Metaplasia

Conditions that lead to recurrent inflammation and healing as a result of chronic irritation or infection can lead to the formation of squamous metaplasia (e.g. because of a calculus, bilharziasis, or a long-term indwelling catheter). The transitional urothelium changes into stratified squamous epithelium, which forms keratin and comes to resemble the skin, and in the presence of urine, changes into a characteristic white plaque – leucoplakia – which is a precursor for neoplasia. It must be distinguished from the innocent ‘vaginal metaplasia’, which is a normal feature of the trigone. The risk of malignant transformation probably varies from one site to another.

### 1.2.9 Heterotopic Ossification

The urothelium presents an interesting entity because a graft of urothelium placed in contact with almost any type of connective tissue may induce the formation of heterotopic bone, which is most likely to develop in the

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Figure 1.2.1 (a–d) A nest of cells may become buried under the healing urothelium.
vicinity of a foreign body such as a nonabsorbable suture but may be found whenever urothelium grows in an unusual site or is used as a graft (e.g. around the track of a chronic urinary fistula or around a urinoma or pseudocyst).

### 1.2.10 Regeneration of Smooth Muscle in the Urinary Tract

For quite some time, it has been considered that smooth muscle could regenerate across a gap in the bladder or the ureter. This was the basis for the intubated ureterotomy of Davis [15], in which a stricture in the ureter was incised and a splint was left in for six weeks and which then became surrounded by fibrous tissue, lined with a film of urothelium, and finally enclosed in smooth muscle. The same principle was considered and lay behind the idea that the bladder could regenerate after cystectomy, especially if a mould of plastic was left for it to grow over [16]. Today, it is believed that muscle does not truly regenerate but spreads in from the cut margin of the urethra [17].

### 1.2.11 Particular Effects of Urine

#### 1.2.11.1 The Presence of Urine Modifies the Normal Process of Healing in the Urinary Tract

1) Prolongation of the healing process. The remodelling phase continued to the tenth day for the dermis and until the twelfth day for the urethra. It is suggested that the possible reason for the prolonged urethral wound healing is because of urine extravasation through the urethra into the surrounding tissues.

2) Necrosis: Urine may interfere with the healing process and may lead to tissue necrosis. An example of this manifestation is the loss of skin and subcutaneous tissue that can follow extravasation of urine after injury to the perineal urethra when the skin of the penis, scrotum, and lower abdomen may be affected and tissue damage may take place and lead to necrosis and slough formation. Also this is evident in cases of chronic urinary incontinence, when skin excoriation is noticed. The process by which urine affects the skin or tissue is not entirely clear, but it could be multifactorial as the duration of exposure, the pre-existing skin condition, the nutritional status of the individual, and factors in the composition of urine itself (e.g. hyperosmolarity, alkaline, or acidic pH) and secondary infection. The subcutaneous injection of almost any fluid that is markedly hypertonic, acid, or alkaline is well known to give rise to pain and inflammation, and in practice even if infection is not present at first, because the tissue is damaged by inflammation, infection may inevitably follow.

The extravasation of urine, for example, after cystectomy may lead to necrosis of the momentum and delay the healing process at the anastomotic sites. It may also lead to tissue breakdown and formation of fistulas (e.g. enterocutaneous fistulas).

3) Contracture: The effect of urine by causing contracture formation on scar tissue is an important issue. All scars contract to some extent, and contracture in scars which cross joints is a common problem that may affect joint mobility. In the urinary tract, as the healing process continues through tissue remodelling, the sites of anastomosis could be affected by stricture formation. Urine exacerbates the tendency for scars to contract. When urine is diverted from the site of an injury to the urethra, the formation of a stricture may be prevented. Taking this notion into consideration, surgical technique can have an impact on this process so as to avoid the effect of scar tissue and stricture formation; however, considerable ingenuity in planning the anastomotic technique in the urinary tract is essential. The anastomosis can be designed in the form of a long elliptical shape so that even after healing and scar-tissue formation, the lumen would still be adequate for maintaining drainage (Figure 1.2.2).

Figure 1.2.2 To avoid stenosis, all anastomoses in the urinary tract are designed as an ellipse so that there will still be an adequate lumen even after contracture has taken place.
1.2 Wound Healing in the Urinary Tract

1.2.12 Suture Materials, Splints, Meshes, and Films

1.2.12.1 Suture Materials

There are different types of suture material and are classified into absorbable or non-absorbable and multifilament or braided (multifilament) (Table 1.2.1). Commonly used absorbable sutures are synthetic, whereas the non-absorbable can be natural or synthetic.

The absorbable sutures are broken down by phagocytes and are hydrolysed with no remaining material and vary depending on the length of time it takes the body to absorb the material: 30–40 days, 50–70 days, or >100 days (Table 1.2.1). Nonabsorbable sutures will remain for a long time in the wound, and although they will eventually break up, residual foreign matter will remain in the tissue (e.g. Ethibond and Prolene). This remaining material may harbour microorganisms which may hinder phagocytosis or the action of antimicrobials and lead to wound infections or chronic infection, or they may get calcified.

There is a risk of sinus formation when nonabsorbable sutures are used during infection; hence, they are avoided in infection-related procedures such as a nephrectomy of pyonephrosis.

When nonabsorbable sutures are chosen during surgery, one must bear in mind that monofilament sutures have the advantage over braided or twisted ones because they have a smaller surface area and no interstices which may harbour bacteria. This may reduce the risk of infection, although it cannot be eliminated entirely.

In the urinary tract, if a nonabsorbable suture is exposed to urine, it is almost inevitable that stones will form. There is also risk of stone formation even if absorbable sutures are used; however, it is significantly less than with nonabsorbable sutures [18, 19]. Even the most inert of metals (e.g. haemostatic clips) can cause stones to form [20]. Sutures placed right outside the urinary tract may, in the course of time, work their way like a cheese wire through living tissue until they come to lie within the urinary tract.

The tendency to form calculi does not seem to be related to the amount of histological reaction generated in the tissues. Even the most histologically inert materials (e.g. polyurethane, silicone, and hydrogels used for manufacturing double-J stents) may be affected by encrustation and stone formation with deleterious consequences.

1.2.12.2 Synthetic Absorbable Suture Materials

The synthetic absorbable suture material made of polyglycolic acid (PGA) or polyglactin (a copolymer of glycolide and lactide) provokes less inflammatory response. The breakdown of these sutures is a result of chemical

<table>
<thead>
<tr>
<th>Material</th>
<th>Absorption time (days, strength retention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbable multifilament</td>
<td></td>
</tr>
<tr>
<td>Vicryl</td>
<td>Polyglycolic acid polymer 56–70 (75% at 2 weeks, 50% at 3 weeks, and 25% at 4 weeks)</td>
</tr>
<tr>
<td>Vicryl rapide</td>
<td>Polyglycolic acid polymer 30–40 (75% at 2 weeks, 50% at 3 weeks, and 25% at 4 weeks)</td>
</tr>
<tr>
<td>Absorbable monofilament</td>
<td></td>
</tr>
<tr>
<td>Monocryl</td>
<td>Poliglecaprone 90–120 (60% to 70% at 1 week 30% to –40% at 2 weeks)</td>
</tr>
<tr>
<td>PDS</td>
<td>Polydioxanone 18–240 (3.0 : 80% at 2 weeks, 70% at 4 weeks, 60% at 6 weeks; 4.0 : 60% at 2 weeks, 40% at 4 weeks, 35% at 6 weeks)</td>
</tr>
<tr>
<td>Synthetic nonabsorbable multisilament</td>
<td></td>
</tr>
<tr>
<td>Ethibond</td>
<td>Polyester</td>
</tr>
<tr>
<td>Mersilene</td>
<td>Polyester/Dacron</td>
</tr>
<tr>
<td>Nurolon</td>
<td>Nylon</td>
</tr>
<tr>
<td>Synthetic nonabsorbable monofilament</td>
<td></td>
</tr>
<tr>
<td>Ethilon</td>
<td>Nylon</td>
</tr>
<tr>
<td>Prolene</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Pronova</td>
<td>Polyvinylidene fluoride</td>
</tr>
<tr>
<td>Natural nonabsorbable multisilament</td>
<td></td>
</tr>
<tr>
<td>Perma-hand (silk)</td>
<td>Stainless steel (metallic)</td>
</tr>
<tr>
<td>Natural nonabsorbable monofilament</td>
<td></td>
</tr>
</tbody>
</table>
hydrolysis rather than biological phagocytosis. These sutures are relatively strong for their size and maintain their tensile strength long after the healing process and the tissue has reached its maximum tensile strength.

When absorbable sutures are used in the urinary tract, they have two possible disadvantages: (i) The suture may take a considerable period of time to hydrolyse and as it is in contact with urine, there is a chance that a stone may form; and (ii) urine may accelerate the hydrolysis of the suture material, especially in the presence of a *Proteus* infection [21, 22].

### 1.2.12.3 Meshes

Meshes are frequently used in urology to treat stress urinary incontinence and pelvic floor prolapse. It can be classified into synthetic or biological meshes. Synthetic meshes can be absorbable or non-absorbable. Absorbable mesh is made of polyglactin (Vicryl) or polyglycolic (Dixon). Nonabsorbable mesh is made of polypropylene and mostly used in urological procedures because of their durability and strength.

The most important characteristic of synthetic mesh is pore size [23]. Synthetic meshes are classified according to their pore size into macroporous (>75 μm) and microporous (<10 μm) (Table 1.2.2). Macroporous mesh allows immune cells to travel through mesh structure and reduce risk of infection. It also incorporates well into the host tissue by promoting higher ratio of type I/III collagen [24].

A mesh originally used to support bladder neck is placed outside the urinary tract; however, it may migrate through the tissues into the urinary bladder causing chronic pain, urinary tract infection, and overactive bladder syndrome.

Biological meshes are primarily made of organic material of human, bovine, or porcine in origin such as dermis or pericardium. Biological mesh is treated to acellular extracellular matrix composed mainly of collagen with additional elastin and laminin. Growth factors within the mesh attract fibroblast. The three-dimensional architecture and porosity of the mesh allow structural cells to enter the mesh and adhere to it. The mesh eventually degrades and is replaced with a collagen scaffold of the host tissue in a process called ‘remodelling’ [25].

### 1.2.12.4 Injectable Agents

Injectable agents are used to treat stress urinary incontinence and vesicoureteric reflux. Polytetrafluoroethylene (PTFE, or Teflon) was first introduced in 1973 [26]. More recently, various agents have been used as a bulking agent. Injectable bulking agents can be classified into biological or synthetic. The most commonly used biological agents are collagen. Synthetic agents that are currently in use include hyaluronic acid dextranomer (Deflux) and polyacrylamide hydrogel (Bulkamid). The ideal injectable agent should be easy to prepare and inject, biocompatible, non-immunogenic, non-carcinogenic, and does not contract with time [27]. Glutaraldehyde cross-linked (GAX) collagen bulking agent has been demonstrated to be safe and efficacious in the short and intermediate term [28]. After injection, it attracts host immune cells and fibroblasts and encourages neovascularisation. Ultimately, the remodelling process results in the replacement of the injected collagen with the patient’s own type I and III collagen [29].

<table>
<thead>
<tr>
<th>Mesh type</th>
<th>Characteristics</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Macroporous prostheses (pores &gt;75 μm)</td>
<td>Prolene</td>
</tr>
<tr>
<td>Type II</td>
<td>Microporous prostheses (pores &lt;10 μm)</td>
<td>Gore-Tex</td>
</tr>
<tr>
<td>Type III</td>
<td>Macroporous prostheses with microporous components</td>
<td>Teflon</td>
</tr>
<tr>
<td>Type IV</td>
<td>Submicronic pore size</td>
<td>Silastic</td>
</tr>
</tbody>
</table>

**Expert Opinion**

- The urinary tract has unique characteristics because of the presence of urine and during surgical procedures; attention to this fact is essential as urinary diversion could be essential to allow wound healing in some situations.
- Surgery is a controlled induced trauma, and various elements of the procedure could either enhance or affect wound healing and recovery.
- During surgery, attention to good aseptic technique, haemostasis, judicious use of electrocautery, and good tissue approximation could enhance recovery and healing.
- In elective major procedures, such as cystectomy and urinary diversion and radical and partial nephrectomy, enhancing the patient’s physiological status through advice on smoking cessation, weight loss, exercise and good nutrition, and good control of diabetes and hypertension may lead to a favourable and enhanced postoperative course and recovery.
- Wound healing occurs in stages, and understanding the intricacy of each stage and how trauma or surgery may affect this process may help in better management of wounds.
1.2 Wound Healing in the Urinary Tract

References

1.3 Simulation in Urology

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Abstract

Surgical simulation can be traced as far back as ancient India, where the first notion of using cadavers and synthetic models for practice prior to surgery spawned. In modern surgical practice, the advancements in science and technology have led to the introduction of new surgical technologies as well as more challenging surgical procedures for a more complex patient population. Limitations in surgeons’ working hours and increased emphasis on utilising costly resources more efficiently have posed challenges to surgical educators. Fundamentally and most importantly, simulation training provides a platform for safe surgical education without compromising patient safety. Simulation has the potential to provide a time-efficient, cost-effective, and safe method of training. Furthermore simulated scenarios provide a means to develop nontechnical, safe, and effective teamwork skills that have been shown to influence patient outcomes. As such, there is growing interest in establishing simulation curriculums and assessment methodology with associated integration within urology training programmes to aid in the acquisition of both technical and nontechnical skills required for safe, modern urological practice.

Keywords simulation training; virtual-reality simulation

Key Points

This section covers the following topics:

- History of simulation
- Simulation modalities
- Simulation in urology

1.3.1 Introduction

The traditional Halsted model of surgical training, ‘see one, do one, teach one’, has become increasingly difficult to implement. The introduction of new surgical technologies has been accompanied by more challenging surgical procedures for a more complex patient population. In addition, reduction in working hours, fear of litigation, outcome reporting, and pressures to utilise costly operating room (OR) resources more efficiently have led to significant changes in the curricula for surgical training.

Recognising modern changes to surgical practice, surgical simulation has evolved over the last two decades as an education tool that seeks to bridge the gap between the initial phases of a procedural learning curve and the OR. The aim of simulation is to aid the acquisition of specific skills and improve both competence and confidence. Simulation training provides a safe environment for repetitive practice of different surgical skills free from risk of harm to patients and a means of providing trainees with immediate feedback and the opportunity to train to a predetermined expert proficiency. This is exemplified by the theory of ‘deliberate practice’ [1], which dictates that to achieve ‘expertise’, multiple repetitions of a skill and the provision of constructive feedback to ensure the skill is being learned correctly is required. Surgical simulation provides the trainee with an opportunity to repeatedly perform a specific skill, or set of
1.3 Simulation in Urology

Skills, in a low-risk environment away from patients, thus allowing for a safe environment where mistakes can occur. The trainee is then able to learn how to correct mistakes, problem solve, and develop the confidence to deal with complications when they occur in real-world settings without it being experienced for the first time. Furthermore, simulation allows the trainer to provide timely and constructive formative or summative feedback based on trainee performance, ensuring acquisition of competency.

1.3.2 History of Simulation in Medicine

Surgical simulation has been around long before complex, high-fidelity, virtual-reality devices were developed. Traditional basic surgical skill training was done on oranges to practise suturing skills or on a table leg for surgical knots. Currently, synthetic models have greatly improved in look, feel, and tactile behaviours, and many medical device companies now produce a range of general and specialist surgical skills models from high-fidelity materials. However, the earliest contribution to the field of surgical simulation was by the ancient Indian surgeon, Sushruta Samhita [2]. He advocated the use of cadavers and synthetic models for practice prior to surgery. He taught technical skills using experimental models that included probing on worm-eaten wood and incising vegetables, such as watermelons and cucumbers. The first modern skills ‘simulator’ was produced in 1928 when Edwin Link created a pilot trainer, which allowed trainee pilots to learn important aeronautical manoeuvres whilst remaining on the ground, making learning to fly cheaper, safer, and more accessible. By the end of World War II in 1945, there were 6271 Link Trainer simulators in circulation [3]. One of the earliest examples of medical simulation was a foetal and human pelvis bone model used by Madame du Coudray to train midwives in eighteenth-century France [4]. In 1960, the first medical simulator, a resuscitation training manikin was developed when a girl drowned in the River Seine in Paris. This model, initially created by the toy maker Asmund S. Laerdal, has now become the Resusci Anne, which is still widely used today by first aid and life support courses to teach mouth to mouth resuscitation and airway and breathing assessments. In the 1960s, Abrahamson and Denson developed the Sim One, resuscitation trainer. This could simulate breathing, heart rate, pulses, and blood pressure and had eyes and a mouth that could open and close. Further developments in high-fidelity simulators had to wait until the 1980s. The Comprehensive Anaesthetic Simulation Environment (CASE) and the Gainesville Anaesthetic Simulator (GAS) utilised concepts developed by the aviation industry to teach anaesthetic crisis management using team-based simulated scenarios. Modern high-fidelity training focuses on the technical and nontechnical skills (NTS) required to make a safe, effective surgeon and also add a realistic environment for simulations.

In 1989, the US computer scientist Jaron Lanier took the concept of virtual, describing something that appeared to exist without actually existing, and combined it with the term ‘reality,’ meaning something that is observable and measurable as opposed to the imaginary or delusional [5]. Virtual-reality (VR) surgical simulators began to grow in the 1990s beginning with lower limb reconstruction simulator (Delph et al.) to the late 1990s where a range of operations could be catered for by this technology. Evidence for its safety and effectiveness began to emerge; in particular, Seymour et al. showed that trainees could significantly reduce their procedure times to perform a cholecystectomy by 29% and were five times less likely to injure the gallbladder after using a VR trainer [6]. In 2004, the US Food and Drug Administration approved the introduction of the VR carotid stent procedure into their training programme. For the first time, trainees had to prove themselves on a competency-based task to be allowed to perform a human procedure [7]. With the development of web-based simulations, such teaching modalities are becoming cheaper and more accessible. However, the future of surgical education does not solely lie with one form of simulation, but in the combination of different modalities integrated into the curriculum.

1.3.3 Simulation Modalities

Surgical simulator training can be separated into four broad categories: physical (mechanical) simulators, animal, cadaveric, and virtual reality (VR). Physical simulator models range from part task trainers (e.g. laparoscopic box trainers) to procedure-specific trainers (e.g. ureteroscopy trainers). These are often more suitable to novice or intermediate trainees. Because of the lack of clinical variability and the inability to provide individualised proficiency-based variations in complexity, inanimate surgical simulation models often decrease in utility for advanced-level training. Animal and cadaveric surgical training has more significant cost and ethical and legislative implications; however, this is offset by providing improved contextual fidelity and opportunities to practise a whole procedure. To maximise this finite resource, it is paramount that animal-model training forms part of a well-designed, comprehensive curriculum with clear learning objectives.

VR simulators have been the mainstay of training in aviation and nuclear industries for decades, being utilised for teaching, evaluation, certification, and recertification purposes. Tasks are performed on a computer-based
platform and artificially generated virtual environment. Improvements in computer processing have led to more realistic and sensitive VR simulators, which are now capable of providing statistical feedback on the surgeon’s performance, a quality that is not shared by mechanical or cadaveric simulator trainers. This feature also eliminates the need for expert faculty present during the entirety of training and promotes a self-directed learning environment. The improvements in modern software allow for clinical variations to be built into the simulator, improving the training content delivered. VR simulators have been validated as a training tool with shown educational impact and content, context, and construct validity [8]. The main challenge to programme directors has been justifying the steep costs because little data currently shows any cost effectiveness.

Simulation training also encompasses simulated clinical scenarios such as mock OR team-training sessions. These high-fidelity facilities are used in the development and assessment of crisis management skills and non-technical skills (NTS) training such as leadership, management, and communication. With the majority of surgical errors as a result of poor communication [9], increasing attention has been directed towards simulated OR facilities to improve pre-, intra-, and postoperative communication between the surgical multidisciplinary team.

1.3.4 Simulation in Urology

Urology remains at the forefront of surgical innovation, particularly in the field of minimally invasive surgery, which includes endoscopy, laparoscopy, and robotics. As the nature of practice is changing, so are the definitions and requirements of competency [10]. Fundamental to this change in practice is patient safety, which must not be compromised. A competent urologist must have a plethora of attributes to practice in the modern surgical environment including excellent technical, team-working, communication, leadership, and decision-making skills. Urology has embraced simulation training, both in its development and application.

1.3.5 Endourology Simulation

Over the last few decades, the applications of endoscopic techniques have expanded. The development of ureterorenoscopy (URS) and percutaneous nephrolithotomy (PCNL), superseding open stone surgery, and novel bladder outflow obstruction (BOO) techniques challenging the gold standard transurethral resection of the prostate (TURP), such as Holium enucleation and Green light laser, are growing. This has necessitated the concomitant need for training and qualification in the established and newer techniques. In response to this demand, there have been a range of endourological simulators focusing on core procedures, including ureteroscopony, URS, transurethral resection of a bladder tumour (TURBT), TURP, and percutaneous access (Table 1.3.1). The most extensively studied models are the URO Mentor (Simbionix); a computer-based VR model offering semi-rigid and flexible ureteroscopy and URS modules and the Uro-Scopic trainer (Limbs & Things, Bristol UK), a high-fidelity bench model permitting use of real OR instruments in ureteroscopy and URS. Three prospective randomised controlled trials have supported these two ureteroscopy simulators in terms of face, content, and construct validity, with training on the URO Mentor showing improvements in surgical performance in the OR [11–14]. There are only two available simulators for TURBT training, with few validation studies. This may be related to difficulties in developing simulators that can encompass the variation of tumours in patients. Eight TURP, nine URS, eight ureteroscopy, and nine percutaneous access models have been developed. Universities have developed the majority of these, in particular the TURP and percutaneous access models, while ureteroscopy simulation has received greater interest from the industry.

Limitations in endourological-simulator validity studies relate to small participant numbers and the use of time as the objective parameter to assess competency. Although time is an easy parameter to measure, it is not necessarily a sign of competency, and more focus is required to objectively measure outcomes and the various steps within a procedure. For example, TURP parameters should include volume of prostate resected, blood loss, and associated injuries such as ureteric orifice or sphincter damage. With the majority of endourological simulator literature in the form of descriptive texts as opposed to validity studies, coupled with the lack of randomised controlled studies, none of the urology training models described and researched can be said to have proven validity for use in specialty training. There is also a lack in the development and research of simulation devices that focus on novel bladder outflow obstruction procedures such as Green Light Laser and Holium Enucleation.

1.3.6 Laparoscopy Simulation

There are two laparoscopic urology simulators that have undergone validation studies: Procedieus MIST VR (Mentice) and the LAP mentor (Symbionix) (Table 1.3.2). Currently these platforms have only been developed and researched for training in laparoscopic nephrectomy (LN). Wijn et al. assessed the construct validity of the LN VR simulator (Mentice, Gothenburg, Sweden) [15].
Table 1.3.1 Endourology simulators and there validation.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Simulator type</th>
<th>Description of simulator</th>
<th>Face, content, and construct validity demonstrated</th>
<th>Evidence of skills transfer to the OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethrocystoscopy</td>
<td>VR</td>
<td>URO Mentor (Symbionix)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>URO trainer</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>George Washington University Medical Center, Washington, DC, US Storz</td>
<td>Content only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bench</td>
<td>Limbs &amp; Things</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Organic: pumpkin, green pepper</td>
<td>Southern Illinois University School of Medicine, Springfield, IL, US</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal, porcine liver in pumpkin</td>
<td>Southern Illinois University School of Medicine, Springfield, IL, US</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Ureterorenoscopy</td>
<td>VR</td>
<td>URO Mentor (Symbionix)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Bench</td>
<td>Limbs and things</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mediskills</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>University Toronto model</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal, porcine kidney</td>
<td>Klinikum Coburg, Germany</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human, uterus</td>
<td>University Medical Center, Shreveport, LA, US</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>TURP</td>
<td>VR</td>
<td>Pelvic vision</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Bench</td>
<td>Limbs &amp; Things</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal, canine cadaver</td>
<td>University of California, CA, US</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>TURBT</td>
<td>VR</td>
<td>URO Mentor (Symbionix)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bench</td>
<td>Limbs and things</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PCNL</td>
<td>VR</td>
<td>PERC mentor (Symbionix)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bench</td>
<td>Limbs and things</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mediskills</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>University Hospital of Tours, Tours, France</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A total of 21 novice, 32 intermediate, and 10 experienced urologists performed the same retroperitoneal task on the LN VR three times each. In regard to outcomes, including time, blood loss, path length (distance of displacement of all instruments in m), and total score, the LN VR simulator could not distinguish between intermediate and experienced participants. Wijn et al. concluded that the simulator did not have sufficient construct validity. Brewin et al. evaluated the face, content, and construct validity of the Procedicus MIST™ nephrectomy simulator [16]. Face validity was established by eight expert laparoscopic surgeons, who believed that the simulator was a good training tool. Content validity was established by the experts, who rated the simulator as above average for realism. Construct validity was verified after performance results were analysed. Experts completed nephrectomy simulation significantly faster than novices with fewer errors and less haemorrhage and tool travel (Mann–Whitney U test p < 0.05).

The European Association of Urology (EAU) has also recognised the importance of simulation training in overcoming the initial learning curve in laparoscopic surgery and consequently developed the programme for laparoscopic urological skills (PLUS). The PLUS examination offers quality criteria and time criteria for the completion of basic laparoscopic tasks including peg transfer, cutting a circle, single knot tying, clip and cut, and needle guidance. This programme has been proven for face, content, and construct validity by a cohort of laparoscopic experts, intermediates, and novices in the Netherlands [17]. As a result, PLUS has been implemented at a national level in the Netherlands as a basic laparoscopy examination. The EAU have extended the programme further by developing the European Basic Laparoscopic Urology Skills Course [18], a combination of theory and practical assessments that aim to provide a basic level of laparoscopic competency prior to embarking on live training. Full validation is still awaited.
Similar to endoscopic simulators, there is a lack of prospective randomised controlled trials investigating the translational benefit of laparoscopic simulators to the OR. The majority of laparoscopic simulation research has focussed on LN procedures. With the expanding role of laparoscopic partial nephrectomy, pyeloplasty, cystectomy, and prostatectomy, future laparoscopic simulation development and research must keep pace.

### 1.3.7 Robotic Surgery Simulation

Since its first application in 2000 by Binder and Kramer, the uptake of robotic surgery has been rapid. This ever‐evolving surgical technique has cemented itself as the gold standard for the removal of the prostate gland. There are six commercially available robotic simulators all of which are VR platforms (Table 1.3.3): Robotic Surgical Simulator (RoSS™), SimSurgery Educational Platform (SEP), ProMIS, Mimic dV‐Trainer (MdVT), Surgical SIM RSS, and the da Vinci® Skills Simulator™ (dVSS) (Figure 1.3.1). The biomechanics lab at the University of Nebraska at Omaha have also developed their own VR simulator. These platforms aim to establish the basic principles of robotic operative techniques, namely, endowrist manipulation, camera and clutching, needle control and driving, energy, and dissection control. In terms of validation, all of the simulators except RoSS have demonstrated face, content, and construct validity, but the numbers in these studies remain small. Educational impact has been shown in studies and in all commercially available simulators except SEP. Evidence of criterion validity, such as predictive or concurrent validity, is sparse. Other parameters, such as inter‐rater and inter‐item reliability, feasibility, acceptability, and cost effectiveness of the simulation platforms were not evaluated by any of the studies. Similarly no group has validated the use of animal models and freshly frozen cadavers and structured skills training based on observation for robotic surgery. There is a distinct lack of comparative studies between the different simulators. The current body of evidence does not identify any one simulator being more effective in training the next generation of robotic surgeons than another. Each platform has the capability to train and assess a range of different robotic skills fundamental to the technique. Unlike the dVSS, the MdVT and RoSS platforms have user interfaces that are similar to, but not exact duplicates of, the dVSS console used in clinical practice. The ProMIS simulator enables virtual and physical reality to be used together and has been investigated in the laparoscopic setting previously. A randomised control trial by Feifer et al. represents the highest level of evidence for any of the simulators currently available [19]. Their study showed that the use of ProMIS and LapSim simulators in conjunction with each other could improve robotic console performance. Interestingly, the LapSim group showed no improvement, and it was therefore not clear what contribution LapSim had on the overall improvement seen when both simulators were used in conjunction. Despite SEP’s level of validation, its biggest disadvantage lies in the fact that the images are not three dimensional (3D), a fundamental concept pertaining to robotic compared with laparoscopic surgery. Further studies or perhaps even hardware upgrades to convert the two‐dimensional (2D) simulator into a 3D platform are therefore warranted.

The majority of robotic surgical simulators focus on prostatectomy training. There is an ever‐growing role for robotic cystectomy, radical nephrectomy, and partial nephrectomy. As such, current simulators will require software updates, and in future simulator, developers will need to consider these advances in their designs.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Simulator type</th>
<th>Description of simulator</th>
<th>Face, content, and construct validity demonstrated</th>
<th>Evidence of skills transfer to the OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic surgery: generic skills and prostatectomy</td>
<td>VR</td>
<td>dV-trainer (Mimic)</td>
<td>Yes</td>
<td>Tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dVSS (Intuitive Surgical)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RoSS (simulated surgical systems)</td>
<td>Face and Content</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SEP (Sim Surgery)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ProMIS (CAE healthcare)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgical SIM RSS (METI)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Partial Nephrectomy</td>
<td>Bench</td>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

VR, virtual reality.
Nontechnical Skills Simulation

NTS can be classified into cognitive factors (e.g. decision making, situational awareness), social factors (e.g. communication, teamwork, leadership), and personal resource factors (e.g. ability to cope with stress and fatigue) [20]. These NTS and related behaviours specifically affect performance in the OR. Studies have also developed validated scoring systems such as The Oxford Non-Technical Skills score (NOTECHS) and Non-technical Skills for Surgeons (NOTSS) (Table 1.3.4) that can be used for research, to provide feedback during training, and to provide an educational framework to describe these skills to surgeons [21, 22]. Research in medicine and other safety critical industries (e.g. aviation, nuclear power, and military) has shown that training can improve NTS and team performance in the workplace. Several strategies have been used to improve NTS, but in surgery, as in other industries, simulation-based team training has emerged as one of the best ways to achieve this.

Team-based training typically uses high-fidelity simulated environments to represent clinical scenarios. Simulated OR scenarios can be developed by combining a high-fidelity human patient manikin with a part-task surgical trainer in a simulated OR environment (Figure 1.3.2). Modern manikins can reproduce realistic patient physiology, while a part-task surgical simulator simulates a technical aspect of the procedure. Careful attention to scenario design, training as a multidisciplinary team, and use of video feedback can help maximise learning in these contexts. However the post-scenario debriefing has consistently been identified as the most important aspect of the learning experience [23].

Figure 1.3.1 Virtual reality robotic simulators. (a) SEP, (b) RoSS, (c) ProMIS, (d) MdVT, (e) dVSS.
A skilled facilitator can provide feedback, encourage learners to analyse specific behaviours and NTS, create a safe learning environment, and help learners to apply their knowledge to work-based settings [20].

Recognising the value of simulation and the fact that the majority of errors in surgery are the result of deficiencies in NTS, the SIMULATE programme has been developed in the United Kingdom [24]. It is a team-based simulation training programme in addition to workplace training. The programme provides training in both technical and NTS. Technical skills including TURP, TURBT, rigid and flexible URS, PCNL, laparoscopy, and robotics are taught using a combination of bench top and virtual reality simulators, whereas NTS are developed using an interactive human patient mannequin in a high-fidelity simulation environment. Trainees are provided with colleague support appropriate to the scenario (e.g. anaesthetist and nurse), and a video relay to the debriefing room allows full observation and feedback by an experienced faculty. The aim is to create an environment which is realistic enough for the surgical team to participate in the simulation and promote realistic team behaviours that can be discussed and analysed in debriefing sessions. NTS training has also been adopted by the Australasian College of Surgeons, the American College of Surgeons Association of Programme Directors in Surgery (ACS-APSD), and the Team Strategies and Tools to Enhance Performance and Patient Safety (team STEPS) [25, 26]. Further strengthening the argument to integrate such high-fidelity NTS training within urology curricula are the results of several well-designed studies by Lee et al. and Gettman et al. which have supported this type of NTS training in urology [27, 28].

### Table 1.3.4 Operating theatre team NOTECHS assessment tool.

<table>
<thead>
<tr>
<th>Leadership and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leadership</td>
</tr>
<tr>
<td>Involves or reflects on suggestions; visible; accessible; inspire; motivates; coaches</td>
</tr>
<tr>
<td>Maintenance of standards</td>
</tr>
<tr>
<td>Subscribes to standards; monitors compliance to standards; intervenes if deviation; deviates with team approval; demonstrates desire to achieve high standards</td>
</tr>
<tr>
<td>Planning and preparation</td>
</tr>
<tr>
<td>Team participation in planning; plan is shared; understanding confirmed; projects; changes in consultation</td>
</tr>
<tr>
<td>Workload management</td>
</tr>
<tr>
<td>Distributes tasks; monitors; reviews; tasks are prioritised; allots adequate time; responds to stress</td>
</tr>
<tr>
<td>Authority and assertiveness</td>
</tr>
<tr>
<td>Advocates position; values team input; takes control; persistent; appropriate assertiveness</td>
</tr>
<tr>
<td>Teamwork and cooperation</td>
</tr>
<tr>
<td>Relax; supportive; open; inclusive; polite; friendly; use of humour; does not compete</td>
</tr>
<tr>
<td>Support of others</td>
</tr>
<tr>
<td>Helps others; offers assistance; gives feedback</td>
</tr>
<tr>
<td>Understanding team needs</td>
</tr>
<tr>
<td>Listens to others; recognises ability of team; condition of others considered; gives personal feedback</td>
</tr>
<tr>
<td>Conflict solving</td>
</tr>
<tr>
<td>Keeps calm in conflicts; suggests conflict solutions; concentrates on what is right</td>
</tr>
<tr>
<td>Problem solving and decision making</td>
</tr>
<tr>
<td>Definition and diagnosis</td>
</tr>
<tr>
<td>Uses all resources; analytical decision making; reviews factors with team</td>
</tr>
<tr>
<td>Option generation</td>
</tr>
<tr>
<td>Suggests alternative options; asks for options; reviews outcomes; confirms options</td>
</tr>
<tr>
<td>Risk assessment</td>
</tr>
<tr>
<td>Estimates risks; considers risk in terms of team capabilities; estimates patient outcome</td>
</tr>
<tr>
<td>Outcome review</td>
</tr>
<tr>
<td>Reviews outcomes; reviews new options; objective, constructive, and timely reviews; makes time for review; seeks feedback from others; conducts post-treatment review</td>
</tr>
<tr>
<td>Situation awareness</td>
</tr>
<tr>
<td>Notice</td>
</tr>
<tr>
<td>Considers all team elements; asks for or shares information; aware of available of resources; encourages vigilance; checks and reports changes in team; requests reports; updates</td>
</tr>
<tr>
<td>Understand</td>
</tr>
<tr>
<td>Knows capabilities; cross-checks above; shares mental models; speaks up when unsure; updates other team members; discusses team constraints</td>
</tr>
<tr>
<td>Think ahead</td>
</tr>
<tr>
<td>Identifies future problems; discusses contingencies; anticipates requirements</td>
</tr>
<tr>
<td>Below standard = 1</td>
</tr>
<tr>
<td>Behaviour directly compromises patient safety and effective teamwork</td>
</tr>
<tr>
<td>Basic standard = 2</td>
</tr>
<tr>
<td>Behaviour in other conditions could directly compromise patient safety and effective teamwork</td>
</tr>
<tr>
<td>Standard = 3</td>
</tr>
<tr>
<td>Behaviour maintains an effective level of patient safety and teamwork</td>
</tr>
<tr>
<td>Excellent = 4</td>
</tr>
<tr>
<td>Behaviour enhances patient safety and teamwork; a model for all other teams</td>
</tr>
</tbody>
</table>

NOTECHS, Nontechnical Skills.
1.3.9 Simulation Training Curriculums

A well-structured performance-based curriculum with well-defined end points and benchmark criteria remains the holy grail of simulation training. A number of barriers exist to developing such an ideal, namely cost, agreement on choice of simulator, and types of procedures requiring simulation training. Furthermore, integration of simulation programmes into training curriculum vary across different regions with each institution developing its own curriculum content and design. Much of the education literature supports the need to create a national standardised curriculum with proficiency-based strategies [29, 30]. It has been suggested that surgeons acquire technical skills through a series of steps, beginning with cognitive orientation, followed by repetition, and then demonstration of autonomy with that skill. A validated simulation programme can be used to support and implement such a proficiency-based curriculum because it has built-in objective measures of assessment from which proficiency levels can be derived [29]. The work by Aggarwal et al. has shown this through the design of a proficiency-based curriculum for basic laparoscopic skills acquisition [30]. Performance criteria were preset by pooling the scores of expert surgeons on the simulator. Thus benchmark proficiency criteria were defined for endpoints for each task such as time taken, number of errors, and path lengths. This created the basis of proficiency-based curriculum with clearly defined endpoints. Progression along the curriculum could be charted by passing set performance criteria so proficiency can be defined and competency ensured through end-of-module examinations. This curriculum has set the blueprint for ongoing research into the most effective simulation curriculum. Such performance-based simulated criteria has led to effective skills acquisition and improved operating theatre performance. For example, proficiency-based simulator training in laparoscopic suturing and knot tying improved performance in the operating room [31, 32]. Furthermore, a proficiency-based simulator curriculum ensures uniform skills acquisition by ensuring all trainees reach a set level of competency.

1.3.10 Assessment of Trainees

Before surgical simulation-based training methods can be used to assess the competency of surgeons, they must undergo initial testing across a variety of validity and reliability parameters (Table 1.3.5). This would include the assessment of face validity, which examines the realism of the simulator or simulated scenario; construct validity which differentiates novice from experienced operators; context validity examines whether the device can teach what is supposed to teach; concurrent validity is the extent to which the results of the test correlate with the gold standard known to measure the same domain; and predictive validity is the extent to which an assessment will predict future performance [33]. Reliability relates to the reproducibility of an assessment and is linked to the assessment’s validity. It allows educators to quantify the amount of random error in the
measured data, facilitating valid interpretations and the usage of trainee assessment scores. Correlation coefficients such as Cronbach’s alpha coefficients are used to demonstrate internal consistency with reliability scores of at least 0.90 for high-stake assessments such as certification examinations [34].

As well as validity and reliability evidence, the application of simulation-based tools for assessment rely on establishing credible, defensible, and acceptable standards. Standards are categorised as either norm-based standards, which determine competency relative to the performance of a well-defined group (e.g. laparoscopic expert surgeons) or criterion-based standards, which determine competency based on a predetermined absolute level of performance. Criterion-based standards are preferred to assess competency because they imply a certain level of mastery of a skill [35].

### 1.3.11 Future of Simulation

One of the challenges for surgical educators is deciding which of the simulators to integrate into urological curriculums. With the rapid developments in technology, new simulators are constantly being developed, making research and validation of these tools challenging. Additionally more than one simulator exists for a given procedure, with a lack of comparative studies adding to the difficulties faced by programme directors. Often such decisions are based on results of research on older simulators, which have a better evidence base and on expert judgement. Compounding matters is that there are no universally accepted criteria on how to exactly validate a simulator, leading to methodological variations between studies, with a real need for a consensus regarding validation methodologies. Importantly the VR TURP trainer and the VR Uromentor (Symbionix) have been shown to improve surgical performance in the OR. Further studies with the aim of identifying this relationship are required. Although such studies are essential, they are intensive, time consuming, and pose numerous ethical conundrums. Showing this translation requires a large number of patients and training sessions and are therefore highly resource intensive. Ethical issues relate to patient consent. Patients want the best possible treatment and may withhold consent if participation entails a relative increase in their risk of complications. As such, these studies are best performed in well-organised, multicentre settings with approval from local ethics committees.

The ideal simulation programme would have a mix of high- and low-fidelity simulators to match various learning requirements. However, in reality, very few centres can afford the high-fidelity VR simulators. One suggestion has been to develop a hub-and-spoke service model where a larger, centralised simulation centre with better investments and a larger repertoire of simulators can liaise with peripheral centres to share resources [36].

---

**Table 1.3.5 Definitions of terms related to competence, training and assessment.**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face validity</td>
<td>Relates to realism of simulator. Does simulator represent what it is supposed to represent?</td>
</tr>
<tr>
<td>Concurrent validity</td>
<td>Degree to which simulator, as assessment tool, correlates with gold standard.</td>
</tr>
<tr>
<td>Construct validity</td>
<td>Refers to demonstrating difference in task performance based on experience level. Construct validity accounts for variance in test performance.</td>
</tr>
<tr>
<td>Content validity</td>
<td>Judgement of suitability of simulator as teaching modality involving formal evaluation by experts in subject matter of training device. This answers the question of whether a simulator can realistically teach what it is supposed to teach.</td>
</tr>
<tr>
<td>Predictive validity</td>
<td>Ability of test to predict future performance in operating theatre.</td>
</tr>
</tbody>
</table>

**Expert Opinion**

The focus of healthcare education has now changed. Simulation in urology must not be used as a stand-alone tool for education but rather integrated into a comprehensive curriculum, in which knowledge can be attained alongside technical skills. Organising such a large-scale training programme requires directives from national organisations to ensure that a structured, standardised approach is used for urological training. This process has been initiated and will continue over the coming decades. Integration and dissemination at a local level requires committees of surgeons with special expertise to assess trainee competence. It is essential that competence be defined in accordance with proficiency levels. Emphasis must be placed on the importance of research in education to identify where trainees begin on the learning curve and how rapidly they plateau. The future of urology depends on novel training tools to match highly sophisticated operating techniques.
References

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Principles of Medical Statistics

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Abstract

A basic knowledge of statistics is an essential skill for medical practitioners. Definitions and worked examples of key statistical concepts are provided, including descriptive summary statistics, hypothesis testing, statistical comparison tests, and correlation. Measures of diagnostic accuracy tests and elements of study design, including sample size and randomisation, are also presented.

Keywords summary statistics; confidence intervals; significance tests; correlation; diagnostic tests; study design; systematic reviews

Key Points

- This chapter will cover basic knowledge required to understand the statistics used in medical research.
- Definitions of confidence intervals, significance tests, correlation and relationships between variables, and diagnostic tests.
- Study designs and different types of studies and reviews.

2.1 Introduction

Statistics and statistical methodology have a central role to play in many areas of the medical world, from research to evidence-based medicine to published papers in medical journals. It is therefore essential that medical practitioners have a basic understanding of statistical concepts, issues, and techniques. This chapter explains basic statistical principles and covers summary statistics, significance tests, and the design of studies. Examples from the field of urology illustrate each statistical point.

2.2 Descriptive Statistics

Data can be summarised in various ways. The most appropriate statistics depend on the type of data and the distribution of values.

2.2.1 Qualitative or Categorical Data

For categorical data, such as presence or absence of disease or stage of disease (mild, moderate, or severe), data are summarised by the number of subjects in each category.
and the percentage in each category. Example 2.1 emphasises the need to look at both the actual numbers as well as the percentages when interpreting categorical data.

**Example 2.1**

<table>
<thead>
<tr>
<th>% (no.) with severe symptoms</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>45% (49/109)</td>
<td>43% (47/110)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>22% (17/76)</td>
<td>39% (38/98)</td>
</tr>
</tbody>
</table>

Looking at the percentages alone, it seems that the effect of Treatment A is better than Treatment B (the percentage with severe symptoms post-treatment is lower).

However, when looking at the associated numbers, it is clear that the comparison of treatments is more complicated (post-treatment information is missing for several patients: 30% of those having Treatment A, and 11% of those having Treatment B).

The low percentage of Treatment A patients with severe symptoms has to be weighed against the possibility of 30% of patients withdrawing from the study because of severe side effects.

We define rate as the number of events (e.g. cases of disease) per unit of population during a particular period of time. Table 2.1 includes the definition of two specific rates, ‘incidence’ and ‘prevalence’.

**Table 2.1 Summary statistics: Definitions.**

<table>
<thead>
<tr>
<th><strong>Incidence rate</strong></th>
<th>The number of new cases of disease developing during a particular time period. For example, the annual rate of newly diagnosed cases per 10,000 population.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence rate</strong></td>
<td>The number of cases of disease that exist at a particular point in time.</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>Sum of all the observations divided by the total number of observations.</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>The middle value (the 50th percentile) when data are ordered from the smallest to the largest.</td>
</tr>
<tr>
<td><strong>Variance</strong></td>
<td>The sum of the squares of the difference between each observation and the mean, divided by the total number of observations minus one.</td>
</tr>
<tr>
<td><strong>Standard deviation</strong></td>
<td>The square root of the variance.</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>The interval defined by the minimum and maximum values.</td>
</tr>
<tr>
<td><strong>Interquartile range</strong></td>
<td>The interval defined by the 25th and 75th percentiles.</td>
</tr>
</tbody>
</table>

**2.2.2 Quantitative or Numerical Data**

For quantitative data (numerical data such as length of stay or systolic blood pressure), there is a greater selection of appropriate summary statistics.

Example 2.2 shows data from a cohort of patients undergoing a surgical procedure.

**Example 2.2**

<table>
<thead>
<tr>
<th>Blood loss (ml); mean (SD)</th>
<th>50 (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating time (min); median (range)</td>
<td>100 (75–520)</td>
</tr>
</tbody>
</table>

Data for blood loss is summarised by a mean value and a standard deviation (SD).

Data for operating time is summarised by a median value and range.

There are a number of different summary statistics available, and they are shown in Table 2.1.

You may ask, ‘Why are different summary statistics used?’ The answer is that the appropriate summary statistics to choose depend on how the data are distributed.

If data are normally distributed, then the appropriate summary statistics are the mean, the standard deviation (SD), or the variance. [Note the variance is the square of the SD].

If data are not normally distributed, then the appropriate summary statistics are the median, the range, or the interquartile range. The latter is the 25th to the 75th percentile (i.e. when the data are ordered from the smallest to the largest, the lower value of the interquartile range is the ‘quarter’ point, and the higher value is the ‘three-quarter’ point). It contains the middle 50% of the data and is sometimes used instead of the range when the sample size of the data set is very large (n = 100 or more).

Hence, for quantitative data, the distribution of data needs to be assessed before deciding on the appropriate summary statistics.

The easiest way to assess the distribution of data is to look at a histogram of the values (Figure 2.1).

The data are separated into sections (bars) – in this example the bars correspond to 5 ml categories – and the height of the bars correspond to the number of people in that particular section (i.e. blood loss category). Data are said to be normally distributed if the shape of the histogram is a symmetric upturned U-shape or bell-shape.

This is true for the blood loss data, and hence, blood loss would be said to be normally distributed.

Figure 2.2 shows a histogram of the operating time, and is an example of not normally distributed data.

The histogram shows a very skewed distribution (not a symmetric bell shape). These data are ‘positively skewed’ (the tail of the distribution is towards the right), which is
2.3 Confidence Intervals

Confidence intervals are a common occurrence in medical data where just a few patients have high abnormal values. These values are called ‘outliers’ and would have a large influence on the average (mean) value, which would make it an inappropriate summary statistic. Median values are unaffected by outliers. For ‘negatively skewed’ data, the tail of the distribution is towards the left, and there would be a few small abnormal values (outliers).

There are a number of ways of checking data distributions. Any combination of these four properties of a normal distribution can be used.

- Symmetric histogram
- Mean is approximately the same as the median
- Standard deviation is less than mean
- No outliers

Figure 2.3 shows a flow chart to aid the selection of the most appropriate summary statistics.

2.3 Confidence Intervals

‘The estimated mean change in maximum voiding pressure (MVP) after treatment with a muscle relaxant was 16 cmH\(_2\)O with 95% confidence interval (8 cmH\(_2\)O, 24 cmH\(_2\)O).’

The main purpose of confidence intervals (CIs) is to indicate the precision with which an estimate is calculated from the study sample. It presents a range of values in which the population value (the ‘true’ value) may lie with a reasonable level of confidence. The (im)precision is indicated by the width of the CI; the narrower the
interval is, the better the precision. The width depends on three factors. The width decreases (and precision increases) with a larger sample size, lower variability between subjects, and lower confidence (a 90% CI will be narrower than a 95% CI).

It is important to note that the interpretation of the CI does not directly relate to the actual observations. That is, a 95% CI does not contain 95% of observations. Instead, it relates to the accuracy of the estimated effect size (e.g. the mean difference pre to post for a single group of patients).

CIs can be thought of as bridging the gap between summary statistics and formal significance tests (our next topic).

If the 95% CI in the example is changed to (−4 cmH20, 36 cmH20), then, because it contains zero, it means that a zero-change in MVP is feasible. Hence, the study has not shown good evidence that there is any increase in MVP with muscle relaxant. This reflects the result that would be obtained by a formal significance test. That is, there is no significant change in MVP.

2.4 Significance Tests

When carrying out a clinical study, the aim is to measure the strength of evidence provided by the data for and against a specific proposition.

Suppose we have two types of surgery, X and Y, and wish to find out whether the complication rate after X is lower than after Y.

The results of the study are depicted in Table 2.2:

<table>
<thead>
<tr>
<th>Observed postoperative complication rates</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>After surgery X</td>
<td>5%</td>
</tr>
<tr>
<td>After surgery Y</td>
<td>10%</td>
</tr>
</tbody>
</table>

Do these data show enough evidence that, in general, patients having surgery X have a significant chance of a lower complication rate than those having surgery Y?

To answer this question, we carry out a statistical significance test.

In carrying out such a test, we are looking to see whether the data from the study supports one of two scenarios or hypotheses. One scenario is that the complication rates are the same (the null hypothesis). The other scenario is that the complication rates are different (the alternative hypothesis).

In general terms:
Null hypothesis:
Effects of X and Y are the same
Alternative hypothesis:
Effects of X and Y are different

To find out which scenario is best supported by the data, we calculate a ‘p-value’.

The p-value is a probability. Probabilities correspond to the chance of something (e.g. an event/situation) happening or being true. It takes values between 0 and 1.

A probability of 0 means that there is no chance of the event happening or the situation being true. A probability of 1 means that we are certain that the event does happen or that the situation is true.

In the context of significance tests, the p-value corresponds to the probability of the null scenario/hypothesis being true, given the evidence from the study data. It is derived using a mathematical formula on the study data.

If the p-value is small (by convention ≤ 0.05), then we say that the null scenario (that X and Y have the same effect) is unlikely to be true. Hence, we say the alternative scenario (that X and Y have different effects) is likely to be true. We state, therefore, that the difference between X and Y is ‘statistically significant’.

If the p-value is large (by convention > 0.05), then we say that the null scenario (that X and Y have the same effect) could be true. We state, therefore, that the difference between X and Y is ‘not statistically significant’.

In the example, the p-value for the comparison of complication rates was 0.15.

How should this be interpreted?

It is greater than 0.05, and hence, we conclude that the data have not given us sufficient evidence to determine that there is a difference between X and Y. Thus, patients having surgery X do not have a significant chance of a lower complication rate than those having surgery Y, and we say the difference is not statistically significant.

2.4.1 What Statistical Test Should Be Used?

This depends on the type of data and the specific comparison being made.

Figure 2.4 shows the process for selecting the appropriate test for the comparison of different groups of subjects when the outcome is a quantitative or numerical measure (Example 2.3).

Example 2.3 Peak flow rate is to be compared between two groups of patients with benign hypertrophy, one receiving cimetidine and one receiving vitamin C.

If peak flow rate follows a normal distribution, then an independent t-test should be used. However, if peak flow rate values are skewed, and therefore not normally distributed, then a Mann-Whitney U-test should be used.

Note that the independent t-test is also called the two-sample t-test or the Student’s t-test.

Figure 2.5 shows the process for selecting the appropriate test for the comparison of related groups when the outcome is a quantitative measure (Example 2.4).
Example 2.4  Postvoid residual in a cohort of men with benign prostate hyperplasia is to be compared before and after transurethral resection of the prostate (TURP) surgery.

If postvoid residual follows a normal distribution, then a paired $t$-test should be used. However, if postvoid residual values are skewed, and therefore not normally distributed, then a Wilcoxon signed-rank test should be used.

Related groups of data refer to the situation where the groups (or data sets) have a one-to-one correspondence with each other. This could be where the data sets are repeated measurements on the same cohort of subjects. For example, two related data sets or ‘groups’ could be presurgery MVP and postsurgery MVP on a cohort of 100 men. Each presurgery data value can be one-to-one matched with the postsurgery data value from the same person.

Another example of two related groups or data sets is when subjects in one group are individually one-to-one matched, with respect to specific characteristics such as sex, age, illness severity, geographical location, etc., to the subjects from the other group.

Figure 2.6 shows the process for selecting the appropriate private test for the comparison of groups when the outcome is a qualitative or categorical measure for both independent and related (dependent) groups (Example 2.5).
Example 2.5  Complication rates following surgery are
to be compared between 100 patients with benign pro-
tate hyperplasia undergoing traditional transurethral
resection of the prostate (TURP) and 100 undergoing
laser resection. The rates are 20% in the first group and
25% in the second group.
The occurrence of a complication is a categorical outcome,
and the comparison is between two independent groups of
men. The numbers of men in the two samples is large, and
the number of men having complications is not small. Hence,
the most appropriate test is the Chi-square test.

The main test for the comparison of independent
groups is the Chi-square test. However, if the sizes of the
groups are small (less than 10) or the number having the
outcome is very small (less than 5), then a more appro-
priate test is Fisher’s exact test.

If the outcome has more than two categories, and these
categories are ordered (e.g. mild, moderate, or severe
pain), then a linear trend test is a more powerful way of
comparing the outcome between independent groups.

2.5  Relationships between
Variables

If we have two different quantitative measures from each
individual of a particular subject cohort, then we can
assess whether the measures are associated (Figure 2.7).

The best way of looking at the relationship between
two variables is by a scattergram, which plots the value of
one variable against the value of the other variable.

Figure 2.8 shows a scattergram of prostate-specific
antigen (PSA) compared with prostate total volume val-
ues plotted for a cohort of patients with clinical suspi-
cion of prostate cancer (PCa).

It is clear that there is a positive relationship between
the two measures. High values of prostate total volume
are matched with high values of PSA.

2.5.1  Correlation

A quantitative summary statistic, which describes the
association is a correlation coefficient.

This statistic takes values between −1 and 1. A value close
to zero means that there is little evidence of a relationship. For
normally distributed data, a Pearson correlation, which
assesses the linear relationship between measures, is used. A
Pearson correlation of 1 denotes a perfect positive linear rela-
tionship where all points on the graph lie on a straight line
with positive slope. In a similar way, a Pearson correlation of
−1 denotes a perfect negative linear relationship where all
points on the graph lie on a straight line with negative slope.

For the data in Figure 2.8, the Pearson correlation is
0.74, denoting a moderate positive relationship.

If data are not normally distributed, then a Spearman
correlation, which describes the ‘monotonic’ association
(i.e. whether there is a consistent positive or negative

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Figure 2.7 Flowchart V: the process for selecting the appropriate statistical analysis for assessing the relationship between measures in a
cohort of subjects.
change of one variable with another, but not necessarily a linear relationship), can be used. This correlation again takes values between −1 and 1.

### 2.5.2 Prediction

Correlation coefficients just describe the degree of association between variables. To go one stage further and describe the actual relationship between two variables and be able to predict values of one variable from the other, you need to carry out a regression analysis.

In fitting a linear regression line between the two variables, the equation of the fitted line can be written in terms of the slope of the line and the point at which it crosses the y-axis (the vertical axis), or the intercept.

For the PSA and prostate volume data, the best fitting line has a slope of 0.4 and an intercept of −8.9 (see Figure 2.9).

That is, PSA can be predicted by volume from the equation

\[ PSA = -8.9 + 0.4 \times \text{volume}. \]

### 2.6 Diagnostic Tests

How well do diagnostic tests (where the test results are positive or negative) diagnose whether someone has the disease or not?

For a cohort of subjects who have a gold-standard diagnosis of disease, the results of the diagnostic test can be presented as a two-by-two cross-tabulation (Table 2.3).

Here, for example, the letter ‘a’ denotes the number of subjects who were test positive and had a gold-standard diagnosis of the disease.

The most important measures of diagnostic accuracy are sensitivity and specificity.

**Sensitivity:**
Proportion of true disease positive correctly identified by the test \( = \frac{a}{a + c} \)

**Specificity:**
Proportion of true disease negative correctly identified by the test \( = \frac{d}{b + d} \)

The higher the value the better the diagnostic accuracy. Sensitivity and specificity take values between 0 and 1 but are often expressed as percentages.

Other measures of diagnostic accuracy are positive and negative predictive values. Again, the higher the value the better the accuracy.

**Positive predictive value (PPV)**
Proportion of test positive who are true disease positive (have the disease) \( = \frac{a}{a + b} \)

**Negative predictive value (NPV):**
Proportion of test negative who are true disease negative (do not have the disease) \( = \frac{d}{c + d} \)

If the proportion of subjects with disease in one cohort is different than that in another cohort, then the sensitivity and specificity values should remain the same, but the PPV and NPV will vary.

The accuracy of test is the proportion of subjects correctly classified \( \frac{a + d}{a + b + c + d} \).

### Table 2.3 Diagnostic tests.

<table>
<thead>
<tr>
<th></th>
<th>Disease +ve</th>
<th>Disease –ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>a (true positive)</td>
<td>b (false-positive)</td>
</tr>
<tr>
<td>Test negative</td>
<td>c (false-negative)</td>
<td>d (true negative)</td>
</tr>
</tbody>
</table>
2.7 Study Design

There are two main types of studies, observational and experimental.
Observational studies are those in which there is no intervention; the study subjects are simply 'observed'.
Experimental studies are those in which there is some type of intervention (e.g. drug treatment).

2.7.1 Observational Studies

Cohort studies are those in which a group (or cohort) of subjects are followed up over time, and information is obtained at baseline and at the end of follow-up (Example 2.6).

Example 2.6
Cohort study of relationship between having a brother diagnosed with prostate cancer and self-risk of prostate cancer.

<table>
<thead>
<tr>
<th>Brother diagnosed</th>
<th>Brother not diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>40</td>
</tr>
<tr>
<td>No prostate cancer</td>
<td>226</td>
</tr>
<tr>
<td>Total</td>
<td>266</td>
</tr>
</tbody>
</table>

Risk of prostate cancer: 40/266 = 0.15; 272/7006 = 0.039
Relative risk: 0.15/0.039 = 3.8

The question being asked here is, 'Do risk factors identified at baseline predict future disease?'

Case-control studies compare a group of subjects with a disease (cases) with a group of subjects without the disease (controls; see Example 2.7).

Example 2.7
Case-control study of relationship between smoking and bladder cancer.

<table>
<thead>
<tr>
<th>Smoker</th>
<th>Non-smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>62</td>
</tr>
<tr>
<td>Controls</td>
<td>56</td>
</tr>
</tbody>
</table>

Odds of cancer: 62/56 = 1.11; 238/1492 = 0.16
Odds ratio = 1.11/0.16 = 6.9

The question being asked here is, 'Do risk factors identified via recall or hospital records differ between the two groups?'

Although the design of the studies is different, both studies are addressing the same question:
‘Is there a relationship between a risk factor and the disease?’

For cohort and case-control studies, there are two statistics which assess the link between risk factor and the disease: the relative risk (RR) and the odds ratio (OR).

2.7.2 Experimental Studies

The most common type of experimental study is the randomised controlled trial (RCT).

For the comparison of two treatments (e.g. either a placebo and an active drug, or a new drug and an old drug), a parallel trial is one in which subjects are randomly divided into two groups and each group receives one of two treatments. An alternative design is a crossover study, in which each subject receives each treatment (one after another) in a random order.

Appropriate randomisation techniques include the roll of dice, the toss of a coin, random number tables, and computer-generated random numbers.

The reason for randomising subjects is that it avoids bias and ensures any differences between treatments groups are the result of chance. Further blinding the patient, researcher, or both will further reduce risk of bias in the trial.
2.7.3 Sample Size

How large should a study be?

It is unethical to conduct a trial that is too small to detect a clinically significant difference because of the waste of time and resources. Such a trial is said to be ‘underpowered’.

Similarly, it is unethical to conduct too large a trial because an effective result could have been reached earlier.

Hence, it is important that a sample size calculation (often called a ‘power calculation’) is carried out at the design stage of the trial. This calculation is based on the minimum clinically important difference that it is considered important to detect, the required power of the study (a minimum of 80%), the significance level (usually 5%), and for continuous outcomes, an estimate of the standard deviation. This form of calculation requires advanced statistical calculations and is integral to properly conducted studies.

2.8 Number Needed to Treat

This is a useful way of assessing treatment benefit from experimental trials comparing a treated and a control group with a yes-or-no outcome (e.g. survived or died).

The number needed to treat (NNT) is the number of subjects needed to receive the treatment to see one additional occurrence of the outcome (e.g. one saved life) in the treatment group.

Treatment outcome rate = number of survivors in the treated group divided by the total number of subjects in the treated group.

Control outcome rate = number of survivors in the control group divided by the total number of subjects in the control group.

\[ \text{NNT} = \frac{1}{(\text{Treatment rate} - \text{Control rate})} \]

A low NNT is better because you would need to treat only a few subjects to see a positive result in one patient.

Example 2.8 In a study comparing the effects of cimetidine and vitamin C on peak flow rate for patients with benign hypertrophy, a significant improvement of 5 ml s\(^{-1}\) or more was seen in 40% of patients in the cimetidine group and 20% of patients in the vitamin C group.

The NNT = \(1/\left(0.4 - 0.2\right) = 5\).

2.9 Systematic Reviews and Meta-Analysis

A systematic review is a review of all the literature on a specific topic, which has been systematically identified, appraised, and summarised to give an overall answer. It provides invaluable information for evidence-based decision making.

Meta-analysis is a statistical technique which combines the results of several studies into a single outcome effect measure. This can be a relative measure, such as a RR or OR, or an absolute measure such as a weighted mean difference. The analysis gives more weight to results from larger studies. The results from a meta-analysis are displayed in a forest plot which shows the individual study results as point estimates with their associated CIs (presented as circles and lines, respectively, with the size of the circle related to the size of the study) as well as the combined estimate with its 95% CI (usually denoted as a diamond).

A systematic review and meta-analysis are considered the highest form of evidence. Although RCTs are considered the gold standard for research, meta-analysis of RCTs is the platinum standard (i.e. highest form of evidence).

**References**

Embryology for the Urologist

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2 Department of Urology, University Hospital of Wales, Cardiff, UK
3 University of Glasgow, School of Medicine, Dentistry & Nursing, Glasgow, UK

Abstract

The urogenital tract is largely derived from the mesoderm. Initial kidney structures appear in the fourth week of embryogenesis, but definitive kidney development occurs from the 5th-10th week. The bladder and urethra start to form at the same time as the definitive kidney. Sexual development is indifferent until the sixth week of gestation, with the sex-determining region Y (SRY) gene being the primary driver for male foetal development. This is largely through further action of anti-müllerian hormone (AMH) and testosterone. The mesonephric ducts become the male genital duct system, and the paramesonephric ducts become the female genital duct system. Testicular descent is initially dependent on AMH and insulin-like hormone 3, and later testosterone. Dihydrotestosterone drives male external genital development. The overall sequence of urogenital development is well established and can explain the majority of congenital malformations that may present to the urologist. Additional details will only be of interest to the subspecialist and the researcher.

Keywords anti-müllerian hormone (AMH); development; dihydrotestosterone; embryology; genital tubercle; gonadal ridges; gubernaculum; insulin-like hormone 3; labioscrotal folds; mesonephric duct; mesonephros; metanephros; paramesonephric duct; pronephros; SRY gene; testicular descent; testosterone; trigone; ureteric bud; urethral plate; urogenital sinus;

Key Points

- Three kidney systems: pronephros, mesonephros, and metanephros.
- The ureteric bud arises from the mesonephric duct and forms the entire upper tract drainage system.
- The mesonephric ducts become the male genital duct system.
- The paramesonephric ducts become the female genital duct system.
- The urogenital sinus gives rise to the bladder and the urethra with the exception of the fossa navicularis and male urethral meatus.
- The sex-determining region Y (SRY) gene, anti-müllerian hormone (AMH), insulin-like hormone 3, testosterone, and dihydrotestosterone are essential in the normal development of the male foetus.
- Testicular descent happens in two phases; initially dependent on AMH and insulin-like hormone 3 and then dependent on testosterone.
- Dihydrotestosterone drives male external genital development.
3.1 Historical Consideration

Embryology stems from the Greek words of ‘embry’, meaning the ‘unborn’, and ‘-ology’, which is the subject of study or a branch of knowledge. [1, 2]

The Greeks were the first to describe their thoughts on the origins of man in the womb. More notably, Aristotle postulated that the foetus was formed in the uterus from a coagulum of blood (menstrual blood), and the foetus itself was fully developed in miniaturised form in the sperm. This chain of thought was carried on for centuries through Europe, even as late as the seventeenth century, when Marcello Malphigi (1672) described poultry eggs as containing a miniature chick and extrapolated that humans were fully formed in the sperm.

In 1694, 21 years after the invention of the microscope by Antonie van Leeuwenhoek, did Nicolaas Harsoeker postulate that humans were formed from the joining of the spermatozoon and ovum, further described by Lazzaro Spallanzani in 1775.

Interestingly, a revelation to the Prophet Mohamed (peace be upon him) in the seventh century detailed descriptions for embryological development, including the formation of the embryo from both the male and female ‘drops’ (i.e. sperm and ovum). Multiple Quranic verses were revealed detailing the formation of the embryo to the fully developed foetus. However, it was not until the nineteenth and twentieth centuries when these revelations were confirmed as fact and held as a true representation of embryo-foetal development.

From the experimental works of Karl Ernst von Baer, Charles Darwin, and Ernest Haeckel, to the chemical and mechanical discoveries of embryology by Otto Warburg, paving the way for Ross Harrison, Frank R. Lillie, and Hans Spemann to describe the more detailed mechanisms of embryonic development throughout the early twentieth century. It was late in the twentieth century, with the advent of more sophisticated instruments such as the electron microscope and spectrophotometer, that embryology in its modern form took place. More notably the work of Keith Moore described the embryological and foetal development to the finest detail, giving rise to the established current knowledge of embryology.

3.2 Introduction

A description of each urological organ will be described individually; hence, overlap and repetition will inevitably exist to allow a detailed understanding of the development of each organ. Three basic cell layers comprise the embryonic disc which becomes the embryo: the ectoderm (originates from the amniotic surface), the mesoderm (originates from inpouring cells from the ectoderm), and the endoderm (yolk sac). The majority of the urogenital tract is derived from the mesoderm. Organ development in general occurs between the 3rd and 10th week of gestation (Table 3.1).

3.3 Embryology of the Kidneys and Ureters

The basic unit of the kidney is the renal pyramid, which is arranged like a bunch of flowers in a vase (Figure 3.1). The flowers are the glomeruli; the stalks are the collecting tubules; and the vase is the calix. The design of the normal pyramid is important in preventing reflux of urine up into the renal parenchyma.

There are three paired kidney systems during foetal development (Figure 3.2), with only the third system being of functional importance. First, the pronephros forms and rapidly regresses in the cervical region of the intermediate mesoderm during the fourth week. The pronephros in humans is both rudimentary and segmented.

Later in the fourth week, the unsegmented mesonephros forms from the intermediate mesoderm in the upper thoracic to upper lumbar segments. These appear as a pair of sausage-shaped swellings on the posterior abdominal wall on either side of the mesentery – the genitourinary ridges. A faint groove demarcates each ridge into a medial gonadal and lateral nephrogenic part (Figures 3.3 and 3.4). These swellings lengthen and acquire primitive nephron-like structures, which is a collection of capillaries that form a glomerulus at the medial extremity, and Bowman’s capsule, which forms around
3.3 Embryology of the Kidneys and Ureters

3.3 Embryology of the Kidneys and Ureters

the glomerulus, forming the renal corpuscle. These simple excretory units may function briefly before regressing in the eighth week. The mesonephros functions for a short time during early foetal life by producing urine from the sixth through to the eighth weeks of development.

On the lateral aspect and adjacent to the mesonephros, the mesonephric ducts advance distally to drain into the cloaca (this is the primitive hindgut which goes on to form the bladder and rectum) at the caudal end of the embryo. Whilst the caudal aspects of the tubules are differentiating, the cranial tubules and the glomeruli degenerate, with the majority of the mesonephros absent by the end of the second month of gestation. The mesonephric system disappears completely in the female around the eighth week. In the male, the mesonephric ducts (also known as the wolffian ducts) persist, giving rise to the efferent ductules of the testes, the epididymis, vasa, seminal vesicles, and appendix epididymis.

Table 3.1 Table of developmental timings.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Development starts</th>
<th>Disappears</th>
<th>Comments, ultimate structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pronephros</td>
<td>4th week</td>
<td>4th week</td>
<td>No functional relevance</td>
</tr>
<tr>
<td>Mesonephros</td>
<td>4th week</td>
<td>8th week</td>
<td>No permanent function</td>
</tr>
<tr>
<td>Mesonephric duct (male)</td>
<td>4th week</td>
<td>—</td>
<td>Central zone of the prostate, ejaculatory ducts, vas deferens, seminal vesicles, epididymis, and efferent ductules</td>
</tr>
<tr>
<td>Mesonephric duct (female)</td>
<td>4th week</td>
<td>8th week</td>
<td>Remnants: epoophoron, paroophoron, Gartner cyst</td>
</tr>
<tr>
<td>Metanephros</td>
<td>5th week</td>
<td>—</td>
<td>Permanent kidney including glomeruli, convoluted tubules, loop of Henle. Urine production from 10th week.</td>
</tr>
<tr>
<td>Ureteric bud</td>
<td>5th week</td>
<td>—</td>
<td>Collecting ducts, minor calyces, major calyces, renal pelvis, ureter</td>
</tr>
<tr>
<td>Urogenital sinus</td>
<td>5th week</td>
<td>—</td>
<td>Bladder, posterior urethra (male) or entire urethra (female), anterior urethra (male) up to the edge of the glans penis</td>
</tr>
<tr>
<td>Gonadal ridges</td>
<td>Germ cells migrate in 6th week</td>
<td>—</td>
<td>Testes or ovaries</td>
</tr>
<tr>
<td>Paramesonephric duct (male)</td>
<td>6th week</td>
<td>8th week</td>
<td>Remnants: appendix testes, utricle</td>
</tr>
<tr>
<td>Paramesonephric duct (female)</td>
<td>6th week</td>
<td>—</td>
<td>Fallopian tubes, uterus, and the upper two-thirds of the vagina</td>
</tr>
<tr>
<td>Genital tubercle enlargement (male)</td>
<td>6th week</td>
<td>—</td>
<td>Penis. Urethral plate closes to form tubular urethra 12th week</td>
</tr>
<tr>
<td>Urethral endoderm and surrounding mesoderm (male)</td>
<td>13th week</td>
<td>—</td>
<td>Prostate</td>
</tr>
<tr>
<td>Ingrowth of ectoderm from the tip of the glans penis (male)</td>
<td>15th week</td>
<td>—</td>
<td>Fossa navicularis and urethral meatus</td>
</tr>
<tr>
<td>Testicular descent (abdominal)</td>
<td>8–15th week</td>
<td>—</td>
<td>AMH and insulin-like hormone 3 dependent</td>
</tr>
<tr>
<td>Testicular descent (inguinal)</td>
<td>24–28th week</td>
<td>—</td>
<td>Testosterone dependent</td>
</tr>
<tr>
<td>Testicular descent (scrotal)</td>
<td>28–33rd week</td>
<td>—</td>
<td>Testosterone dependent</td>
</tr>
</tbody>
</table>

AMH, anti-müllerian hormone.

Figure 3.2 Locations of pronephros (fourth week), mesonephros (fourth to eighth weeks), and metanephros (from fifth week) in the embryo.
Third, the metanephros (the permanent kidneys) develops from the fifth week from metanephric mesoderm in the most caudal region of the nephrogenic ridge, the lateral aspect of the genitourinary ridge. As the tail end of the foetus curls up, the hindgut is curled with it and so are the nephrogenic ridges with their wolffian ducts, which twist upwards and inwards. Branches from the most caudal part of the wolffian (mesonephric) ducts enter the metanephros. These branches, or outgrowths, are called the ‘ureteric buds’ (Figure 3.5). In contrast to the first two systems, excretory units only form by a process called ‘reciprocal induction’ between the ureteric bud and metanephric tissue caps.

The collecting ducts develop from the ureteric bud (fifth week, Figure 3.6). The ureteric bud subdivides and induces formation of the glomeruli in the mesenchyme of the metanephros. The branches of the bud then grow peripherally into the cortex, dilating and splitting repeatedly until about 15 generations of ducts have formed (Figure 3.7). The first four or five generations of the dividing ureteric branches become dilated and incorporated in the eventual renal pelvis (Figure 3.8). The next four or five generations form the major calices and collecting tubules (Figure 3.8) [3]. The successive generations elongate and converge on the minor calyx (seventh week), thereby forming the renal pyramid in the flower–vase configuration described previously. Subsequent generations elongate and converge to form renal pyramids, and ultimately, they form around one million collecting ducts per kidney (until the fifth month).
The metanephric tissue caps covering each collecting tubule form renal vesicles which develop into nephrons. Capillaries grow into the opposite end of the nephron giving rise to glomeruli (Figure 3.9). From about the 10th week, urine is produced by the metanephros; however, nephrons continue to form until birth. After birth, no further nephrons will form (approximately 700,000 per kidney), but existing ones will continue to grow. This growth is responsible for the change from lobulated kidneys at birth to kidneys with a smooth outline.

The metanephros ascends during weeks 6–10 as a result of the elongation of the sacral and lumbar regions of the embryo as well as loss of the initial curvature of the embryo. The arterial supply originates from the aorta,
and serial arteries are formed and regress during renal ascent. Some vessels may remain as accessory renal arteries.

During the fourth to sixth weeks of gestation, while the caudal end of the foetus curls up and bends the hindgut into a U configuration, the mesoderm grows down into the gap between the future rectum and bladder, thus forming the urorectal septum (Figure 3.10). This septum separates the cloaca into a primary urogenital sinus (ventrally) and rectum (dorsally). The Wolffian ducts lie in this wedge-shaped septum, and grow down with it. They also become bent into a loop and take the ureteric buds with them (Figure 3.10) [4].

Part of this septum is incorporated into the bladder to form the trigone, and because of the incorporated loop of the Wolffian duct, the ureteric duct comes to open into the bladder cephalad to the duct. In males, the Wolffian duct becomes the vas deferens and seminal vesicles, whilst in the females these ducts regress in the absence of testosterone [4]. At this stage, the tail end of the foetus is roughly 1-cm long and the space between the tail and the umbilical cord is filled by the cloacal membrane. On either side of this membrane are the two small genital tubercles (Figure 3.11). This membrane is formed by tightly packed ectoderm and endoderm cells with no intervening mesoderm. As this

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**Figure 3.7** The ureteric bud splits repeatedly until about 15 generations of ducts have formed. The first generation becomes the renal pelvis, the second the major calyces, the third to fifth minor calyces, and the remainder become renal pyramids and collecting ducts.

**Figure 3.8** As the ureteric bud approaches the metanephros, it branches repeatedly. The branches induce the formation of glomeruli. The first four or five generations of branches become incorporated into the renal pelvis.

**Figure 3.9** The metanephric tissue caps covering each collecting tubule form renal vesicles which develop into nephrons. Capillaries grow into the opposite end of the nephron, giving rise to glomeruli.
Figure 3.10 The urorectal septum grows down between the future bladder and rectum.

Figure 3.11 The cloacal membrane disappears and the phallic tubercles meet in the midline.
membrane dissolves, the two genital tubercles fuse to form the united phallic tubercle (Figure 3.11).

While all this is taking place, the mesonephros is withering away, but as it regresses, the Wolffian duct generates a second duct, parallel and lateral to it, the Müllerian duct (Figure 3.12). As the urogenital ridge twists round, so the Müllerian ducts approach each other, meet in the midline in front of the Wolffian ducts, and burrow down in the urorectal septum (Figure 3.12). The urorectal septum is partially absorbed into the trigone, and the Müllerian ducts open into the urethra medial to, and in front of, the Wolffian ducts.

The subsequent fate of the Wolffian and Müllerian ducts is determined by the X and Y chromosomes. Until the fourth week, the urogenital ridge is neuter. At four weeks it is invaded by gonadal cells, which migrate by amoeboid movements from the yolk sac across the coelom and burrow into the gonadal ridge (Figure 3.13). By the sixth week, it is estimated that there are about 60,000 gonadal cells in each gonadal ridge. The male ones are active at once; the female gonadocytes stay dormant for another two weeks.

### 3.3.1 Relevant Congenital Malformations

Partial or complete ureteric duplication results from early splitting of the ureteric bud. In a complete duplex system, the Weigert-Meyer rule states that the ureter

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**Figure 3.12** (a) A second (Müllerian) duct forms on the lateral side of the mesonephros. (b) The Müllerian duct rolls towards each other, meet in the midline in front of the Wolffian ducts, and burrow down into the urorectal septum to form the uterus and fallopian tubes in the female.
draining the lower moiety tends to reflux as a result of a shorter submucosal tunnel positioned laterally and superior; the upper pole tends to obstruct, be ectopic, or form ureteroceles and is positioned medially and inferiorly (Figure 3.14). An ectopic ureter may drain into the bladder, bladder neck, or prostatic urethra in males, or into the vagina, uterus, or ovary in females (Figure 3.15). The pathophysiology of duplex kidney is explained by the insertion of the ureter into the bladder, whilst the lower pole tends to reflux due to a shorter submucosal tunnel, and the upper pole tends to obstruct, be ectopic, or form ureteroceles.

Failure of renal ascent gives rise to a pelvic kidney (Figure 3.16). Midline fusion of both kidneys during their ascent gives rise to a horseshoe kidney, with further ascent limited by the root of the inferior mesenteric artery. The midpoint joining both kidneys is known as the isthmus (Figure 3.17). Crossed fused renal ectopia results from both kidneys ascending on the same side of the body and fusing in the process (Figure 3.18).

Renal agenesis results from failed reciprocal induction, intrinsic defects within the mesenchyme, or involution of a multicystic dysplastic kidney. Multicystic dysplastic kidney may be the result of faulty ureteric bud development. Renal dysplasia results from defects in reciprocal induction or from obstruction during the foetal period.

### 3.4 Embryology of the Bladder

The foetal hindgut is curled, following the outline of the tail end of the embryo, in the shape of a hook (Figure 3.19). The caudal most part of the hindgut remains in communication with the allantois and will form the bladder. As stated, the urorectal septum descends at four to six weeks to separate the cloaca into the urogenital sinus anteriorly and the anal canal posteriorly. The cloacal membrane dissolves to open both canals (Figures 3.20 and 3.21).

As the allantois shrinks it becomes a solid cord – the urachus – linking the apex of the bladder to the umbilicus. In clinical terms, the urachus becomes the median umbilical ligament upon closing. If it remains patent, the patient will have a congenital umbilical fistula. The urogenital
sinus itself will give rise to the bladder, the posterior urethra (male) or entire urethra (female), and the anterior urethra (male) up to the edge of the glans penis. These are all endodermal (originates from yolk sac) in origin.

The male anterior urethra is not initially tubular, but rather a flattened urethral plate, which is pulled forwards with the growing phallus (Figure 3.22). It then folds in sideways and closes along the midline at around 12 weeks (Figure 3.23 and 3.24). The terminal part of the male
urethra (fossa navicularis and external urethral meatus) is formed by ingrowth of ectoderm (derived from amniotic sac) from the tip of the glans penis (15 weeks).

The lower ends of the mesonephric ducts (due to become the vasa efferentia) and the lower ends of the ureters become incorporated into the posterior wall of the bladder, and thus form the trigone (Figures 3.25 and 3.26). Descent of the testes then causes the vas deferens on either side to swing anteriorly over the ureter (‘water under the bridge’).

### 3.4.1 Relevant Congenital Malformations

Failure of fusion of the urethral folds results in hypospadias. Epispadias results if the genital tubercle (see discussion in this chapter) forms in the urorectal septum with part

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**Figure 3.18** Crossed renal ectopia.

**Figure 3.19** The foetal hindgut bends round and the urogenital septum descends to separate the bladder from the rectum; the patent urachus keeps the future bladder in continuity with the allantois.

**Figure 3.20** The urorectal septum descends at four to six weeks to separate the cloaca into the urogenital sinus anteriorly and the anal canal posteriorly. The cloacal membrane dissolves to open both canals.
of the membrane cranial to the genital tubercle. Exstrophy of the bladder (which always includes epispidias) is caused by failure of the abdominal wall to form.

### 3.5 Embryology of the Indifferent Genital System

The gonads begin their development from the urogenital ridge, located behind the coelom. They divide longitudinally, in the third week, to form the gonadal or genital
ridge on the medial side and the embryonic mesonephros on the lateral side, which later becomes the urinary tract. Paramesonephric ducts (müllerian ducts) develop from these genital ridges.

Between weeks five and six of embryonic development, the germ cells arising from the yolk sac integrate into the gonadal ridge after travelling by amoeboid movement through the umbilical cord and the coelom (Figures 3.27–3.28). Upon the arrival of germ cells, primitive sex cords form in the still indifferent gonad. Failure of gonadal development occurs if the germ cells do not reach the gonadal ridges because they trigger the development of the gonad into ovary or testis [5].

In the human embryo, the gonads remain undifferentiated until about week seven of development. Depending on the XY genetic constitution they then differentiate into the testes or the ovaries [6].

Figure 3.25 The lower ends of the mesonephric ducts (due to become the vasa efferentia) and the lower ends of the ureters become incorporated into the posterior wall of the bladder, and thus form the trigone. Descent of the testes then causes the vas deferens on either side to swing anteriorly over the ureter.

Figure 3.26 The urogenital septum brings down the wolffian ducts, which will become the ureters.

Figure 3.27 Cloacal folds form in the third week and will become genital folds. The genital tubercle forms at the same time. Indifferent labioscrotal folds form lateral to the genital folds.

3.6 Embryology of the Male Genital System

Once in the gonadal ridge, the presence of the sex-determining region Y (SRY) gene located on the short arm of the Y chromosome leads to testicular development and male phenotyping. Downstream from SRY
produces steroidogenesis factor (SF1) and SOX9 that stimulate testicular cellular differentiation. This induces the first step of the organogenesis of the testes, the formation of gonadocytes, and proliferation of Leydig cells and sustentacular cells of Sertoli (Figures 3.29 and 3.30) [7]. This development not only relies on the presence of the SRY gene, but also the lack of the DAX1 gene (which can down regulate the SRY gene action) and WNT4 gene, which is responsible for female gonadal development.

These cells then proliferate with the aid of SRY gene proteins and form the primary sex cords. These further proliferate and extend into the medulla of the gonad to form the testis or medullary cords. Once here, the cords branch with their deep ends anastomosing to form the tubules of the rete testis. The gonadal cords further develop to give rise to the testicular cords which differentiate to become the semiferous tubules. The tubuli recti are formed from the narrowing of the deeper portion of the semiferous tubules, and it converges into the tubuli recti. The tubules’ connections with the germinal epithelium are discontinued with the formation of a dense network of fibrous connective tissue known as the ‘tunica albuginea’ [5].

Male genital development depends on the SRY gene, anti-müllerian hormone (AMH; also called müllerian inhibitory substance [MIS]), insulin-like hormone 3, testosterone, and dihydrotestosterone (DHT).

The gene does two things consecutively:

1) It makes the gonadocytes differentiate into Sertoli cells which secrete another simple polypeptide, the müllerian duct-inhibiting factor. This has a dramatic effect: the entire müllerian duct system disappears within a single day, leaving behind only the tiny vestige of the utriculus masculinis in the verumontanum (Figure 3.31). MIS also inhibits the formation of the uterus and fallopian tubes (the müllerian structures) [7–9].

2) Approximately one week later (approximately week eight), the SRY gene enables the differentiation of the germ cells located between the testicular cords into Leydig cells derived from the mesenchyme of the gonadal ridge. These contain 17-ketosteroid reductase which is involved in the synthesis of testosterone, which is activated by the enzyme 5-alpha reductase to 5-alpha DHT. This active substance reacts with a cytosol receptor in the phallic tubercles and wolffian ducts to secrete growth factor. This results in the two changes necessary to convert the neuter foetus into the male. The cytosol receptor factor is a product of one of the genes in the X chromosome.

In the presence of testis determining factor (SRY protein), medullary cords of the testis, and the rete testis...
Embryology of the Male Genital System

3.6

Formation of the tunica albuginea follows. Sertoli cells (from epithelium) and Leydig cells (from mesenchyme) form dependent on the SRY protein. SRY protein stimulates AMH production by Sertoli cells (seventh week), which in turn causes Leydig cells to produce testosterone and insulin-like hormone 3 (ninth week). The testis cord continues to remain solid until the onset of puberty, when it acquires a lumen to form the
seminiferous tubules, which connects with the rete testis and enters the ductuli efferentes, which are remnants of the mesonephric system. The ductus deferens is formed when rete testis is joined to the wolffian duct with the aid of the ductuli efferentes [5].

AMH causes involution of the paramesonephric ducts. Only small remnants from the paramesonephric ducts persist (i.e. appendix testes, utricle). Testosterone influences development of the mesonephric ducts and male external genitalia. Mesonephric ducts differentiate into the central zone of the prostate, ejaculatory ducts, vas deferens, seminal vesicles, epididymis, and efferent ductules (Figures 3.33 and 3.34).

3.6.1 The Descent of the Testis

Testicular descent happens in two phases, guided by the action on the gubernaculum (Figure 3.35).

1) Passive phase: Dependent on AMH/MIS and insulin-like hormone 3 guiding abdominal descent to the inguinal ring (8–15th week)

2) Active phase: Dependent on testosterone through the inguinal canal (24–28th week), and to the base of the scrotum (28th–33rd week).

During their descent, the testes acquire a layer of peritoneum, which becomes the tunica vaginalis.

During development the testis begins its journey in the lumbar area of the retroperitoneum. It transfers from here to the scrotum near the end of the third month of pregnancy. This is mediated by testosterone and the gubernaculum (Figure 3.36), a lump of jelly, which forms an expanding track, which leads to and inserts into the genital swelling, the future scrotum [10]. Ectopic testes are formed when the gubernaculum leads them in the wrong direction, such as towards the penis or the thigh, and incomplete descent occurs if the gubernaculum fails to form a path to the scrotum (Figure 3.37) [11–13].

(a) (b) (c) (d)

Figure 3.33 (a–d) Testosterone from the Leydig cells cause the phallus to grow and the urethra to roll in from either side.
**Figure 3.34** In males, the Wolffian duct becomes the vas deferens, epididymis, and seminal vesicles.

**Figure 3.35** Testicular descent happens in two phases: (1) dependent on AMH and insulin-like hormone 3 during abdominal descent to the inguinal ring (8–15th week) and (2) dependent on testosterone through the inguinal canal (24–28th week) and to the base of the scrotum (28–33rd week). Both phases are guided by the gubernaculum. During their descent, the testes acquire a layer of peritoneum, which becomes the tunica vaginalis.

**Figure 3.36** Normal migration of the testicle.
3.6.2 Relevant Congenital Malformations

As the testis descends, it is accompanied by the processus vaginalis. The lumen of the processus vaginalis is normally obliterated within a few weeks of birth; however, if it persists, it gives rise to defects such as a congenital hernia, hydrocele, an encysted hydrocele of the cord, or an abdominoscrotal hydrocele (Figures 3.38 and 3.39) [14]. Maldescent of a testis results in an undescended testis. Malposition of the gubernaculum or an abnormally long
gubernaculum result in an ectopic testis. Failure of, incomplete, or inappropriate development of the genital system leads to disorders of sexual differentiation.

In males, the müllerian duct lingers as two tiny vestiges, the utriculus masculinis in the verumontanum and the appendix testis, neighbouring the appendix epididymis which is a vestige of the Wolffian duct (Figures 3.31 and 3.34) [5]. If there is a congenital deficiency of MIS, phenotypical males are born with fallopian tubes and a uterus, usually found by chance at laparoscopic orchidopexy or hernia repair, and occasionally, associated with testicular tumours [7].

3.7 Embryology of the Prostate

As described previously, the male foetus develops in the presence of a Y chromosome, which encodes the SRY protein, thus enabling testicular differentiation and the production of androgens such as testosterone. In addition to the actions of SRY protein and androgens, a third factor is required for male development, AMH, also known as MIS [15]. This causes the müllerian (paramesonephric) duct to degenerate, forming the prostatic utricle (or utriculus masculinis). Blandy originally described this as, ‘a volcanic crater on the summit of the verumontanum’.

Figure 3.39 Various types of hernia and hydrocele. (a) Common hydrocele, (b) encysted hydrocele, (c) ‘double’ hydrocele, (d) hernia and hydrocele, (e) ‘hernia magna’, and (f) abdominoscrotal hydrocele.
The prostate forms in the mesenchyme of the urogenital septum. The cloacal membrane, a thin film which covers the convexity of the hindgut, regresses to leave gaps in front of and behind the urogenital septum, and in so doing, forming the urethra and anus. Running down in this septum are the müllerian and wolffian ducts and the ureteric buds (Figure 3.40).

At approximately week eight, the Leydig cells of the foetal testis secrete testosterone [16, 17], and as a consequence, the human prostate begins its development at about the 10th week of gestation. The initial outgrowths of the epithelial ‘prostatic’ buds from the urethra into the urogenital sinus (UGS) occur in response to the binding of 5α-dihydrotestosterone to androgen receptors localised in the surrounding mesenchymal tissue [18–21]. There are five pairs of buds. The top pairs are derived from mesoderm (i.e. wolffian structures) and form the transitional, periurethral, and central zones of the prostate, whereas, the bottom pairs are derived from endoderm and form the peripheral zone.

These prostatic buds begin as solid cords of epithelial cells that elongate and undergo extensive branching morphogenesis during the latter stages of foetal growth to develop primitive lumens [22]. During weeks 13–15, serum testosterone elevates and remains high until week 25, which in turn induces epithelial differentiation. At this point, the three important epithelial populations, other than the stem cells, are distinct: luminal, basal, and neuroendocrine cells [22]. The stromal component compromises of fibroblasts, smooth muscles, and myofibroblasts. At week 25, the testosterone level diminishes, and the gland remains in a quiescent state until puberty. The central zone is primarily sensitive to testosterone, whereas the peripheral and transitional/periurethral are sensitive to DHT.

Summary: DHT prompts development of the prostate from urethral endoderm and surrounding mesoderm (13–16th weeks), giving rise to the transitional zone and peripheral zone. The central zone is formed from the mesonephric duct.

3.8 Embryology of the Penis and Urethra

Two crucial events occur in the male embryo, between the fifth and seventh week:

- the disappearance of the müllerian ducts
- the transformation of the phallic tubercles

Both events are orchestrated by the two sex chromosomes. On the Y chromosome, the SRY gene controls germ cell differentiation into Sertoli cells (whose müllerian inhibiting factor causes the müllerian ducts to disappear). By the eighth week of gestation, the mesenchymal cells of the genital ridge differentiate into Leydig cells which secrete testosterone, which enters the wolffian ducts and the phallic and genital tubercles. These tissues contain 5-alpha reductase, an enzyme which activates testosterone to a more potent form, DHT. DHT binds to a cytosol receptor protein and sets off the changes in growth, which allow the wolffian ducts to develop into the vasa efferentia, seminal vesicles, and epididymis. The phallic and genital tubercles become the penis, scrotum, and urethra (Figure 3.41). A gene on the X chromosome codes the cytosol receptor...
protein. Each step on this ladder of events is carried out by a certain enzyme coded by a single gene. In the absence of this organised testicular development, the differentiated gonads will develop into ovaries by the 13th and 14th weeks of gestation [23]. Each step may go wrong and result in one of the variations of intersex.

By week seven, the cloacal membrane dissolves, and the primitive bladder opens on the ventral aspect of the genital tubercle (Figure 3.42). This elongates to form the penis under which a groove is folded in on either side to form the urethra (Figure 3.43). Rods of mesenchyme in each fold differentiate into the corpora cavernosa and corpus spongiosum. At the tip of the penis, a groove demarcates the glans through which a solid cord extends and then becomes canalised as, the terminal urethra (Figure 3.44). Skin grows forwards from the coronal sulcus to enclose the glans in the prepuce and then becomes adherent.
The scrotum is formed by the meeting together in the midline of the two genital tubercles over the urethra (Figure 3.45).

All these processes must be complete within a critical window of time. If the genital folds and penis are not completed by the 12th week they never will be. However much androgen is given later on, all it can do is slightly enlarge the penis [24, 25].

Summary: Under the influence of DHT (formed from testosterone by the action of 5-α-reductase), the penis, scrotum, and prostate form. DHT causes elongation of the genital tubercle after six weeks to form the phallus with the urethral plate. The genital and labioscrotal folds on either side move caudally and fuse along the midline, which carries the urethra to the tip of the formed penis and forms the scrotum with the midline scrotal septum. DHT sets off the train of events leading to the growth and fusion of the phallus, in-rolling of the urethral tube, formation of the scrotal sac, and the downward migration of the testes [7, 8].

The wolffian ducts are dependent on testosterone to develop and form the epididymis, vas deferens, and seminal vesicles.

### 3.9 Neuter State

Without a Y chromosome or its SRY genes, the foetus stays neuter. The neuter state seems at first glance to be female: There is no phallus; the müllerian ducts persist; and the wolffian ducts fail to turn into the vas deferens.

### 3.10 Embryology of the Female Genital System

The parmesonephric ducts form the basis of the female genital system. In the absence of the SRY gene, default development is down the female pathway. The mesonephric ducts regress and only leave a few remnants, including Gartner’s cysts, paroophoron, and epoophoron. The parmesonephric ducts develop into fallopian tubes, uterus, and the upper two-thirds of the vagina (Figure 3.46).

With regards to external genitalia, the genital tubercle develops into the clitoris, the urogenital sinus forms the introitus and vestibule of the vagina (distal one-third), the genital folds become the labia minora, and the labioscrotal folds become the labia majora (Figure 3.47).
3.11 Embryology of the Adrenal Gland

There are two distinct components of the adrenal gland: cortex and medulla. The cortex is derived from the mesoderm. At about the fifth to sixth weeks of life, the foetal cortex develops arising from the genitourinary ridge, subsequently surrounded by a second wave of mesothelial cells, which will eventually form the definitive cortex near the developing gonads and kidneys; tiny rests of adrenal cortical tissue are common in the renal cortex, retroperitoneum, and testis as well as the broad ligament near the ovary (Figures 3.48 and 3.49). After birth, the foetal cortex regresses except for its outermost layer, which differentiates into the reticular zone. The adrenal cortex shares many of the enzymes of gonads – notably those for the synthesis of steroids – so that some inborn errors of metabolism affect them both.
In the seventh week of foetal life, neuroblasts from the sympathetic system of the neural crest (ectodermal cells) invade the medial aspect of the developing adrenal cortex to form the medulla. After a week, they differentiate into sympathicoblasts and pheochromocytes containing the intracellular catecholamines, adrenaline, and noradrenaline.

Cells derived from the neural crest migrate on each side of the aorta to form the sympathetic chains. It is from these paraganglia cells that extra-adrenal neuroectodermal tumours (paragangliomas) arise.

In foetal life, the adrenals are larger than the kidneys and are still about one-third of their size at birth.

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4

Principles of Urologic Oncology
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Abstract

Understanding the basic concept of the cell cycle and the theories behind cancer development and its progression is vital for understanding the principle of oncological therapies. Cancer can evade the immune system by various methods, which gives rise to repeated use of therapeutic agents such as chemotherapy and radiotherapy. In this chapter, the principle concepts of cancer growth and treatment are explained.

Keywords carcinogenesis; cancer growth; chemotherapy; radiotherapy

Key Points

- Cancer occurs as a result of a multifactorial process, including genetic mutations, presence of carcinogens, and the actions or inaction of gene regulators.
- Hallmark of cancers are: (i) to sustain proliferative activity, (ii) to evade growth suppressors, (iii) to resist cell death, (iv) to acquire replicative immortality, (v) to induce angiogenesis, and (vi) to activate invasion and metastasis.
- Radiotherapy and chemotherapy are effective in treating many cancers as primary treatment modalities.

4.1 The Scope of Urologic Oncology

In the human body, there are roughly 300 different types of cells and 200 types of human cancers have been recorded. Urological malignancies account for more than 30% of all human organ neoplasias. A large part of urology, therefore, concerns the diagnosis and treatment of cancer. Most of these malignancies are cancers from epithelia of the urinary organs such as renal tumours from the tubular epithelia, urothelial cancer from bladder and upper tract epithelia, and malignancies from the testicles, the prostate, and the penis. Other malignancies such as sarcomas or lymphomas are rare.

The natural history of urological cancers is rather diverse. Testicular carcinoma is rapidly progressive and highly aggressive. In contrast, prostate cancer (PCa), now the most common organ malignancy in men, is often a disease occurring in the elderly with slow progression. Urothelial cancers are a heterogeneous group characterised by more molecular subtypes than is apparent histologically. They arise as a result of exposure to carcinogens excreted in the urine. Because the carcinogenic exposure will continue after treatment, urothelial carcinomas have a high recurrence rate.

Renal cell carcinoma is often detected incidentally on routine imaging and as the incidence increases with age, concepts of active surveillance for small renal tumours in elderly patients have been proposed. Organ-preserving tumour surgery with preservation of renal function has become the standard for small renal tumours. Penile cancer is mostly an aggressive squamous cell carcinoma with the majority related to human papilloma viruses.

4.2 Carcinogenesis

There are many influences that can cause DNA damage and start a carcinogenic development. Mutagenic influences can be chemicals, ionising and ultraviolet (UV) radiation, viruses, or chronic inflammation.
Mutagenic chemicals which cause many human cancers are either direct- or indirect-acting carcinogens. Direct-acting carcinogens are electrophiles that react with oxygen and nitrogen atoms in the DNA structure, altering nucleotides and disturbing normal base pairing. Indirect-acting carcinogens are unreactive and water-insoluble but become activated by the introduction of electrophilic compounds, often through the action of liver enzyme systems (e.g. cytochrome p450), which normally detoxifies noxious chemicals by making them water-soluble and thus can be excreted.

Some RNA viruses have amino acid sequences which are almost but not exactly the same as those of a natural human gene. If such a virus also possesses the enzyme reverse transcriptase, it can create a copy of itself in DNA, which will be taken up into the DNA of the human cell, like a kind of genetic cuckoo, and may have oncogenic effects [1, 2].

Human papilloma virus (HPV) is a DNA virus that causes genital warts. It produces two tumorigenic proteins (E5, E7), which stimulate proliferation by binding to growth receptors (E5) and by inhibiting a protein involved in cell cycle control (E7 and the Rb tumour suppressor protein). HPV virus types 16 and 18 induce squamous cell cancers of the genitals in both genders (i.e. penis, vulva, cervix, and anus) [3]. HPV DNA has also been found in the genome of some types of bladder cancer.

### 4.2.1 Genetics of Cancer

Cancer is essentially a genetic disease characterised by genome instability. There may be inherited somatic mutations with resulting genetic defects which predispose to tumour development at a relatively early age (e.g. renal cancer in von Hippel-Lindau syndrome). These account for roughly 10% of cases. However, the majority of cancers are sporadic and develop through a series of multiple-chance mutations triggered by mutagenic influences.

For a cancer to develop, several or many mutations in genes that normally control cell proliferation need to accumulate. This may take years, and therefore, sporadic cancers are a disease mainly of the elderly.

### 4.2.2 Mitotic Cycle

Mitosis is the basis of cell replication in normal and cancer tissues. There are four phases of the mitotic cycle (Figure 4.1). First, there is a relatively long gap phase (G1) after the previous cell division when the newly divided cell seems to be resting. Mitosis takes about one hour and cells may live for hours or years, the difference depends on the duration of this first gap (G1). The next phase is that of protein synthesis (S), and DNA is now rapidly synthesised, doubling the original quantity. There follows a second relatively short gap phase (G2) between the completion of DNA synthesis and the beginning of mitosis (cell division), the final phase.

![Figure 4.1 Mitotic cycle.](image-url)
During mitosis, the genome is most vulnerable to mutations. Genes are helices of DNA strung together in the chromosomes which coil and uncoil in different phases of mitosis. In prophase, they are coiled in tight lengths which are apt to break and stick to each other, so that there may be crossing over during mitosis (Figure 4.2). Whole chromosomes are entirely duplicated, while small lengths, even single genes, can also become inserted into an adjoining chromosome. Normal human cells contain 23 pairs of chromosomes. Cancer cells, in contrast, usually have an abnormal number of chromosomes (aneuploidy) and often contain fused elements from different chromosomes (translocations) resulting from disordered mitosis (Figure 4.2).

It is in the brittle stage of prophase between G1 and S that the chromosomes are vulnerable to outside influences. Ionising radiation may cause short chains of genetic material to fall out of the DNA strand. Missing nucleotides are rapidly cemented back into position by the polynucleotide ligase enzyme, but not always in the correct order, and a wrong sequence may act either as a faulty gene or cause malfunction of genes. Such bogus genes may function normally, however, they may fail to respond to a switch-off signal [4]. An alkylating agent can insert a single pair of bases into a chromosome during the S phase, and this trivial alteration can lead to a mutation [5].

The acquisition of the multiple developmental steps in tumorigenesis depend on a succession of alterations in the cellular genome. Mutations occur frequently in dividing cells (e.g. epithelia). Some mutations confer selection advantages to subclones of cells. Several additive mutations enable these subclones to outgrow others and eventually become dominant in a local tissue environment. Multistep tumour progression is the succession of clonal expansions by the chance development of a mutant genotype [6].

### 4.2.3 Genetic Instability of Cancer

Normally, the stability of the genome is maintained by systems which detect and repair DNA defects, keeping the rate of spontaneous mutations very low. If there is too much DNA damage for repair, these cells are induced to die by programmed cell death (apoptosis). Thus, damage is repaired or severely damaged cells are eliminated, maintaining genomic stability.

Cells with mutations on their way to tumorigenesis often avoid and disable the normal control mechanisms [7]. They also often increase their rate of acquiring further mutations by increased sensitivity to mutagenic agents. Progressive tumour development is characterised by increasing genomic instability with gains and losses of gene copy numbers across the cell genome. Several distinctive patterns of DNA mutations in many tumour types have been described [8].

Each cancer is a clone that essentially develops from a single cell. Multiple mutations are required for a cancer clone to develop (‘multiple hit theory’). This theory is supported by the epidemiological fact that the occurrence of most types of cancer increases dramatically with age. With normal cell cycle control mechanisms, the chance development of multiple mutations takes many years, even decades to occur.

In precancerous lesions, a series of mutations, which often occur in a well-defined order, have been identified. Such early somatic mutations occur in genes that are central to genomic control. Examples are the APC gene leading to the inappropriate expression of Myc, a transcription factor that induces expression of many genes which are needed for the transit from the G1 to the S phase of the cell cycle. Other mutations commonly occurring early in carcinogenesis are those of the K-ras gene and the DCC gene [2]. The latter leads to inactivation of the p53 gene, which controls apoptosis in cells with damaged DNA (Figure 4.3).

Inherited mutations – mutations in a germ line – will render an individual to have a mutated version of a gene in one allele. The other allele will have a normal gene and usually this will be adequate to prevent cancer formation. However, a chance mutation in the same gene in the normal allele can occur, and this chance is higher if only
one normal gene is present. Therefore, these individuals will be at a higher risk of cancer development than individuals with two normal alleles (hereditary predisposition). This applies to about 10% of human cancers and usually occurs earlier in life.

### 4.2.4 Oncogenes and Tumour Suppressor Genes

Oncogenes are genes which stimulate excessive proliferation when mutations occur (e.g. myc, ras, Bcl-2). The normal gene without mutations is a proto-oncogene. For a proto-oncogene to develop into an oncogene, a gain-of-function mutation is required by point mutation, localised reduplication (gene amplification), or chromosomal translocation. Any of these can result in overexpression of the gene product. Gain-of-function mutations that convert a proto-oncogene into an oncogene act dominantly because only one allele needs to be affected for an abnormally high expression of the gene product to be expressed. Often, several oncogenes are found in a cancer, and they can enhance each other’s effects (‘cooperativity’).

Tumour suppressor genes encode proteins that control normal cell growth and proliferation, and if they acquire mutations, cell cycle control is disturbed. Five classes of proteins are encoded by tumour suppressor genes: intracellular proteins which inhibit cell cycle progression (e.g. p16 cyclin-kinase inhibitor), membrane receptors for growth inhibitor signals (e.g. tumour-derived growth factor β), checkpoint control proteins (e.g. p53), apoptosis promotors, and proteins (enzymes) involved in DNA repair [9]. Many cancers have inactivating mutations of tumour suppressor genes (e.g. of APC, p53, RB, p16) (Figure 4.4). These are loss-of-function mutations leading to an underexpression of the gene product. Because both alleles of the cell have to be affected for the gene product to be abnormally low or non-functional, mutations in tumour suppressor genes act recessively.

In a somatic cell which contains a mutant tumour suppressor gene, the normal allele will usually maintain normal and functional expression of the encoded regulatory protein. This cell is heterozygous for the tumour suppressor gene. For the mutation to become effective, this heterozygosity has to be lost (loss of heterozygosity [LOH]). This can occur through errors during mitosis involving the chromosomes (non-disjunction, mitotic recombination).

There are many known effectors regulating cell cycle control which can become oncogenes or defective...
tumour suppressor genes and control complex intracellular pathways (e.g. cyclins, cyclin-dependent kinases [Cdks], Rb) [10]. Cyclins are mitogenic activators stimulating cyclin-dependent kinases. The p16 protein (a tumour suppressor) inhibits cyclin-D-dependent kinase. The Rb protein binds a transcription factor complex (E2F), which when unbound activates DNA synthesis [11]. Mutations of p16 or Rb are often found in cancers (Figure 4.4). An essential checkpoint is the p53 gene (‘the caretaker of the genome’), and mutations of this gene are found in more than 50% of human cancers [12]. Uncontrolled proliferation of cell clones with mutations can be compared to a car going at high speed, whereby oncogenes are a defect accelerator (which cannot be released) and defective tumour suppressor genes are a nonfunctioning brake. Thus, if both defects occur simultaneously, uncontrolled driving at high speed (proliferation) will occur.

4.3 Molecular Biology of Cancer Growth

Cancer cells are characterised by continuous and unrestricted proliferation, leading to unrestricted growth. There are several biological capabilities which need to be acquired during multistep carcinogenesis. These are the ability (i) to sustain proliferative activity, (ii) to evade growth suppressors, (iii) to resist cell death, (iv) to acquire replicative immortality, (v) to induce angiogenesis, and (vi) to activate invasion and metastasis (‘hallmarks of cancer’) [13]. In addition, cancers have to resist elimination by the immune system and have an altered energy metabolism.

4.3.1 Sustaining Proliferation

Normal tissues control the production and release of growth-promoting signals that initiate entry into the mitotic cycle, maintaining homeostasis and normal tissue architecture. Cancer cells deregulate these control mechanisms. The promoting signals are usually growth factors that bind to cell-surface receptors coupled to intracellular tyrosine-kinase domains. These respond by sending signals through intracellular signalling pathways that regulate the cell cycle. Some of this growth-inducing signalling is affected by releasing growth factors into the intercellular space and is transferred from cells to their neighbours (paracrine stimulation).

Cancer cells acquire the ability to sustain proliferative signalling. This may be by the production of growth factors by the cancer cells themselves (autocrine stimulation), by inducing cells of the tumour stroma to produce growth factors or by becoming hyper-responsive to normal levels’ growth factors [10]. Some cancer cells may become independent of growth factor stimulation altogether. In some cancer types, somatic mutations lead to the continuous activation of intracellular signalling pathways downstream from the activation of cell membrane receptors (e.g. B-Raf/MAP-kinase pathway, PI3-kinase). Another mechanism can be defects in feedback mechanisms which normally negatively regulate proliferation (e.g. Ras-oncoprotein, PTEN phosphatase, mTOR pathway).

Paradoxically, excessive growth signalling (e.g. produced by oncoproteins such as ras, myc, and raf) may lead to opposite responses in some cancer cells (i.e. the induction of a dormant state [senescence] or cell death [apoptosis]) [14].

4.3.2 Evading Growth Suppressors

In normal cells, potent pathways negatively regulate cell proliferation, and some of these depend on intact tumour suppressor genes (e.g. Rb, p53), which are often inactivated in cancer cells. The gene products (RB, TP53) are central control nodes of two complementary regulatory cellular circuits that control whether cells go into proliferation or into senescence or apoptosis. RB transduces mainly growth-inhibitory signals that originate largely outside of the cell. TP53 receives input from stress and abnormality sensors within the cell. If there is excessive genomic damage or disturbed metabolism, TP53 can arrest further cell-cycle progression until things have normalised or it can trigger apoptosis (Figure 4.3).

Cancer cells also need to evade ‘contact inhibition’. Some known effectors of normal contact inhibition are
proteins such as the Merlin protein (product of the NF2 gene), which acts on cell-surface adhesion molecules (e.g. E-cadherin), and the LKB1 protein, which may be deregulated or deficient in cancer cells (Figure 4.3).

### 4.3.3 Resisting Cell Death

There are different forms of cell death: apoptosis, autophagy, necrosis, and a dormant state (senescence). The 'programmed' cell death (apoptosis) is triggered by intracellular mechanisms in response to various physiologic stresses. Apoptosis can be initiated by both intracellular and extracellular mechanisms, the intrinsic and the extrinsic system (working via the Fas-receptor). This leads to activation of proteases (caspase 8 and 9) inducing proteolysis and disassembly of the cell [4]. The 'apoptotic trigger' is controlled by the balance of pro- and anti-apoptotic effectors. Inhibitors of apoptosis are members the Bcl-2 family, pro-apoptotic signalling proteins are, for example, Bak and Bax, which are released from mitochondria and cytochrome C, which activates intracellular caspasases.

A critical intracellular ‘damage sensor’ is the TP53 protein which activates apoptosis when there is too much DNA damage. Many cancers evade cellular apoptosis by inactivation of the function of TP53. Other tumour cells can increase the expression of anti-apoptotic regulators (e.g. Bcl-2), can downregulate pro-apoptotic factors (Bax, PUMA), or can increase ‘survival signals’ (e.g. insulin-like growth factors 1/2).

‘Autophagy’ is another physiologic response to cellular stress. It occurs most notably in the case of nutrient deficiency and triggers the breakdown of intracellular organelles (ribosomes, mitochondria). The catabolites are reused for energy metabolism, and this allows survival of the cell in stressful environments. Autophagy is also regulated by a system of promoting and counteracting effector mechanisms. The pathways involve the PI3-kinase, AKT, and mTOR kinases which block both apoptosis and autophagy. They can be downregulated in cancer cells. Paradoxically, autophagy allows survival of cancer cells in stressful situations such as chemotherapy and radiotherapy. Thus, this survival response may enable the persistence and eventual regrowth of surviving cancer cells.

Necrosis leads to bursting of cells, which is in contrast to apoptosis where they shrink and are consumed by their neighbours. Bursting necrotic cells expulse their contents into the environment, and in contrast to apoptosis and autophagy, release proinflammatory signals. These signals recruit inflammatory cells and can be actively tumour-promoting by inducing angiogenesis, proliferation, and invasiveness.

Senescence is the induction of a quiescent state in which cell proliferation is stopped, but the cell does not die. This state may also be induced in response to stress-ful changes in the microenvironment. Senescent cells can remain dormant for a long time but may be reactivated and turn on proliferation again later.

### 4.3.4 Enabling Replicative Immortality

Normal cells are only able to pass through a limited number of cycles of cell division. After repetitive cell cycles, either senescence is induced, or cells undergo apoptosis. Very few cells of a cancer cell population attain immortality with an unlimited number of cell cycles. A crucial factor for achieving immortality seems to be the expression of the enzyme telomerase.

Telomeres are the ends of chromosomes and consist of arrays of a very short DNA sequence (TTAGGG). As DNA polymerases are unable to replicate the very ends of a double-stranded DNA molecule, a reverse transcriptase (telomerase) – if expressed – adds repetitive TTAGGG sequences to the ends of the chromosomes. Most normal human cells do not have a telomerase, and thus, the continual loss of TTAGGG repeats from the chromosomal ends (telomeres) with each cell cycle limiting the number of further possible cell divisions. The progressive loss of telomeres is thought to be a mechanism of human ageing. Cancer cells that express telomerase can attain cellular immortality [15].

### 4.3.5 Inducing Angiogenesis

Cells need nutrients and oxygen as well as the evacuation of metabolic waste products and CO₂. A cancer can grow to roughly 10⁶ cells without its own blood supply. For further growth, the tumour has to develop new vasculature (Figure 4.5). The basal lamina of existing capillaries has to be destroyed, endothelial cells have to migrate to form new tubes (vasculogenesis), and new vessels have to sprout (angiogenesis). In cancer, this is stimulated by growth factors such as basic fibroblast growth factor (bFGF), transforming growth factor-α (TGFα), and vascular endothelial growth factor (VEGF).

Temporary angiogenesis is a part of wound healing. In cancer, an ‘angiogenic switch’ has to be activated early on. Again, this angiogenic signal is controlled by a system of counteracting effectors, by promoters of angiogenesis (e.g. VEGF-A), fibroblast growth factor (FGF) and by antagonists such as angiogenin, endostatin, thrombospondin-1 (TSP-1), and direct antagonists of the VEGF receptor. VEGF signalling occurs through three receptor tyrosine-kinases (VEGFR 1–3) as a complex cascade. VEGF gene expression can be upregulated by hypoxia as well as by oncogene signalling. VEGF ligands can also be released in the extracellular space by matrix-degrading proteases (e.g. MMP-9).

The essentially irregular signalling which stimulates tumour angiogenesis characteristically results in neovascularization with disordered capillary sprouting, convoluted
4.5 Reprogramming Energy Metabolism

Otto Warburg first observed that cancer cell metabolism is different from that of normal cells [16]. Under aerobic conditions, normal cells process glucose in the cytosol to pyruvate via glycolysis and in the mitochondria to CO₂. Under anaerobic conditions, glycolysis prevails, and little pyruvate is transferred to the oxygen-consuming mitochondria. Cancer cells limit their metabolism largely to glycolysis even under aerobic conditions (i.e. aerobic glycolysis). This seems paradoxical because the efficiency of regulating the EMT, which often is most prominent in the tumour periphery (invasion front). Cancer cells that migrate are characterised by a loss of cell-to-cell adhesion molecules (e.g. E-cadherin). In contrast, embryonic promoters of migration are often upregulated (e.g. N-cadherin).

Less is known about colonisation. Cancer cells need to adapt to foreign tissue microenvironments to grow into nodules. Colonisation is not identical with vascular transit because circulating tumour cells can be detected in many patients without metastases. Also, micrometastases often never progress to macroscopic nodules. Some primary tumours release suppressor factors that render micrometastases dormant as shown by the sometimes explosive metastatic growth soon after surgical resection of the primary tumour. Dormant micrometastases may also be kept inactive by a lack of nutrients or by an inability to locally activate angiogenesis. Certain tissue micro-environments may be hostile to colonisation, whereas others can be inducive.

Metastatic colonies may proceed to disperse further to new sites in the body as well as back to the primary tumour (‘reseeding’). The phenotypes and gene expression programmes of the population of cancer cells within primary tumours may be significantly modified by this reverse migration.

4.4 Tumour-Promoting Inflammation

Virtually every cancer contains immune cells, but this varies considerably. Originally this was thought to reflect an attempt by the immune system to fight malignancy. However, it is now understood that the tumour-associated inflammatory response largely has the paradoxical effect of enhancing progression. Inflammation contributes to the tumorigenic capabilities by supplying growth, survival and proangiogenic factors, as well as, extracellular matrix modifying enzymes to the microenvironment.
ATP production by glycolysis is much lower (about 18-fold) compared to oxidative phosphorylation [17]. Cancer cells achieve this by upregulating glucose-transporters (e.g. GLUT1), thereby increasing glucose transport to the cytoplasm. This is a feature that positron emission tomography (PET) scan imaging with radiolabelled glucose analogues (18F-fluorodeoxyglucose [FDG]) utilises to visualise malignant lesions.

This metabolic switch characteristic of cancer is associated with activated oncogenes (e.g. RAS, Myc), down-regulated suppressors (e.g. p53), and often increased levels of hypoxia-inducible factors (HIF-1α, -2α) which upregulate glycolysis and induce angiogenesis. This preference for low oxygen metabolism allows growth under unfavourable hypoxic conditions.

4.6 Evading Immune Destruction

Patients who are immunocompromised have an increased incidence of cancers; however, most of these are induced by viruses. Although the theory that the immune system monitors and destroys small malignancies has been challenged, there are anti-tumoral immune responses in some cancers. However, some highly immunogenic cancer cells develop the ability to evade immune destruction by disabling components of the immune system that have been activated to eliminate them. Cancer cells may paralyse infiltrating cytotoxic lymphocytes (CTLs) and natural killer (NK) cells by secreting tumour growth factor (TGF-β) or by recruiting inflammatory cells which are immunosuppressive (e.g. regulatory T-cells).

4.7 The Tumour Microenvironment

Solid cancers are highly complex tissues where neoplastic cells constitute only one compartment (the parenchyma). In addition, there is a lot of stroma consisting of vasculature as well as inflammatory and other cells. The population of cancer cells within a tumour is highly heterogeneous, sometimes but not always reflected in histological diversity with regions marked by different degrees of differentiation, proliferation, vascularity, inflammation, and invasiveness.

An important subclass of cancer cells in a tumour are cancer stem cells (CSCs). Only these seem to have the ability to seed new tumours [18]. The number of CSCs in a tumour is highly variable. As CSCs can regrow after toxic treatment, they are thought to be the source of recurrence because they are more resistant to toxic treatments. CSCs often share transcriptional profiles with some normal tissue stem cell populations.

4.8 The Rate of Cancer Growth

The rate of tumour growth depends on its rate of proliferation. As tumours become larger, the rate of proliferation often slows down (i.e. the Gompertzian effect) (Figure 4.6). Tumour doubling time (DT) depends on the difference between the rates of proliferation and cell death. In small tumours, the DT is fairly constant. After 20 DTs there will be 10^6 cells (1 mg), after another 10 DTs the resulting 10^9 cells will weigh about 1 g (Figure 4.7). After another 10 DTs, the tumour will now have 10^12 cells and weigh about 1 kg [19]. Such a large tumour by then will have outgrown its blood supply and will have slowed its rate of further growth considerably. If tumour growth is more rapid than its own blood supply can support, often internal necrosis occurs (as in large renal cancers). Tumour DT varies greatly in different cancers. In terms of DT, the tiny tumour which seems ‘early’ to the surgeon has already been present for two-thirds of its possible natural life.

4.9 Principles of Treatment

4.9.1 Diagnosing and Treating Solid Tumours

Cancers are diagnosed either on the basis of symptoms, incidentally by imaging done for unrelated reasons, or detected during a check-up for an asymptomatic patient. Obtaining a biopsy from a lesion before surgical excision is not necessarily needed. PCa requires histological
verification before treatment. Bladder cancer is resected transurethrally, so biopsy and treatment are one step. Renal cancer is characterised reliably by imaging, and percutaneous biopsy is rarely required. Testicular cancer should not be biopsied at all because breaching the anatomic scrotal barriers can induce metastatic spread. The superficially accessible penile cancer should be biopsied before treatment.

Tumour markers are proteins that can be measured in serum and can be useful for the diagnosis and for monitoring treatment response. In urology, this applies to prostate and testicular cancer. The availability of prostate-specific antigen (PSA) testing has increased the ability to detect early PCa. Its unrestrained use has led to the increased detection of low-risk cancers and to controversial discussions about overdiagnosis and overtreatment. Testicular cancers often produce α-fetoprotein or human chorionic gonadotropin (β-HCG), which are foetal proteins which are not produced by healthy adults. These markers are especially useful for monitoring chemotherapy response. Also in testicular cancer, serum lactate dehydrogenase (LDH) is a marker of disease burden in metastatic stages.

4.9.2 Estimating Prognosis by Staging, Risk Stratification, and Nomograms

Treatment of cancer requires adequate grading and staging. The histological diagnosis should provide an assessment of tumour differentiation and the degree of aggressiveness (WHO tumour grading). Staging implies imaging by computed tomography (CT) or magnetic resonance imaging (MRI) to assess tumour extent, involvement of regional lymph nodes, and metastases.

For some cancers, grading and staging allows a prognostic risk classification. Stratifying tumours into low-, intermediate-, and high-risk groups has been shown to be useful for treatment decisions in prostate and non-muscle-invasive bladder cancer. A similar classification, including tumour markers, is used for testicular cancer.

For some cancers, validated nomograms have been devised, based on data of several thousand patients, for the estimation of the likelihood of metastases and progression (e.g. Partin tables in PCa, European Organisation for Research and Treatment of Cancer [EORTC] tables in non-muscle-invasive bladder cancer).

4.9.3 When to Treat and When Not to Treat

When and how to treat a neoplasm is sometimes a difficult decision. Tumour stage and extent of disease burden will indicate whether cure is possible, unlikely, or clearly impossible and whether systemic treatment will be needed additionally or on its own.

Curative treatment aims at complete removal or destruction of the malignancy with a chance of long-term survival. In localised disease, treatment with curative intent is the treatment of choice for most patients. If the patient is very old or unfit because of chronic diseases (comorbidity) and the tumour is unlikely to lead to symptoms, treatment may not be indicated or it may be deferred. This applies to localised PCa in patients with a life expectancy of less than 10 years, and it can apply to patients with small renal tumours.

Palliative treatment does not aim for cure but for reducing symptoms (e.g. pain), alleviating functional problems (e.g. renal hydronephrosis), or delaying progression and prolonging life (e.g. by palliative chemotherapy). Quality of life (QoL) should always be considered. Palliative treatment is often multimodal, combining surgery, radio- and chemotherapy with pain management and supportive treatment. The objectives which can be achieved should be discussed with the patient.
4.9.4 Active Surveillance and Watchful Waiting

The term ‘active surveillance’ is usually applied to PCa. It implies that after histological diagnosis, treatment is deferred or not done at all because the tumour seems unlikely to progress, and curative treatment is offered if signs of progression develop. Therefore, regular examinations and bloods tests are required. In contrast, ‘watchful waiting’ implies that no treatment is undertaken at all until the patient becomes symptomatic. This is an option in patients who are very elderly and have comorbidities. Sometimes these terms are also used for the observation of small renal tumours in elderly patients by regular imaging to see whether these lesions are growing and do require treatment after all.

4.10 Oncologic Surgery

4.10.1 Surgery of the Primary Tumour

Complete surgical removal of a solid organ malignancy remains the most reliable curative treatment option. The chance is highest if the cancer is confined to an organ. Involvement of regional lymph nodes reduces the chances of recurrence, even with regional lymphadenectomy. With systemic metastatic disease, surgery alone, however, cannot be curative.

Radical surgery of a carcinoma usually implies complete organ removal. Organ sparing by excision of only the cancer is a concept which has only been established for renal and penile cancers. Partial cystectomy for muscle-invasive bladder cancer is not a reliably curative option and organ sparing in testicular cancer in patients with only one testicle is still an experimental approach.

4.10.2 General Principles in Tumour Surgery

There are several basic principles of tumour surgery. First, exposure needs to be adequate to gain safe access to the tumour vessels. Whenever possible, the main supplying vessels should be secured and ligated before handling the tumour itself. Second, the tumour must be handled as little as possible (i.e. not touched) to avoid haematogenous dissemination of tumour cells. Also, the tumour should not be injured and never be incised to avoid spillage of tumour cells (e.g. intraperitoneally). Mobilisation of a tumour or tumour-bearing organ should include surrounding connective tissue as far as possible to achieve adequate and negative surgical margins. This can be difficult, and in some procedures, such as radical prostatectomy, anatomically limiting. Positive surgical margins (i.e. microscopically incomplete tumour resection) decreases the chance of long-term survival considerably. The width of a negative margin can be very narrow for some cancers as in partial nephrectomy or in penile cancer.

4.10.3 Regional Lymphadenectomy

The first metastatic spread from cancer occurs to the regional lymph nodes. The removal of the regional lymph nodes, even if they are macroscopically normal, with the surgery of the primary tumour is therefore considered a standard for most organ malignancies. An exception is renal cancer where regional lymphadenectomy of normal nodes does not improve survival.

4.10.4 Surgery for Metastatic Disease

Surgery for singular or limited metastatic disease may be indicated in some slowly proliferating cancers. For renal cancer, where metastatic disease may appear many years after primary treatment, surgery for limited metastatic disease, especially pulmonary metastases, prolongs survival. In testicular cancer, postchemotherapy surgery for hepatic metastases can be indicated together with retroperitoneal lymph node dissection.

4.10.5 Radiotherapy

It is the use of ionising radiation for the treatment of malignancy with curative intent or as part of palliation for symptom relief. In a linear accelerator machine, electrons (from an electrical source) are accelerated with microwaves to high energies and are abruptly stopped when they collide with a tungsten metal filament. The energy released from the collision produce X-rays, which are focused into a beam and used on a target organ. γ-rays are produced by the nuclear decay of radioactive elements, the excess energy emitted from an unstable nucleus as it decays into a stable form. Both x-rays and γ-rays are electromagnetic radiation.

As the radiation hits the target organ, it causes direct and indirect damage. Direct ionisation of the atoms causes damage which leads to chemical bond breakage and biological cascades that lead to the death of the targeted cell area. Indirect damage is caused when the radiation interacts with atoms and molecules within the cells to produced free radicals. These are highly reactive molecules that can cause damage to the cells and organs. An example of this interaction is when the radiation hits the water in the cells. This leads to ionising the water molecule to form: H₂O + H₂O⁺ (ion radical) + e⁻ (free radical). The H₂O⁺ then reacts with other water molecules to form hydroxyl radicals (OH⁻): H₂O + H₂O – H₂O⁺ + OH⁻.

OH radicals cause two-thirds of the damage to the cells and tissue. While free radicals become more reactive by oxygen, the damage to the DNA of cells becomes permanent.
The effect of radiation on normal and malignant tissue is understood through the principle concepts of: repair, redistribution, reoxygenation, and repopulation.

- Repair: Once the damage is done to the DNA, the cell either undergoes immediate apoptosis or cell death (lethal damage) or repair (sublethal damage). Fractionation of radiation allows effective cancer killing without exceeding the tolerance of the healthy normal tissue to repair itself.

- Redistribution: DNA damage that is not initially lethal to the cell can still cause cell death during subsequent cellular division. As cancer cells divide faster than normal cells, the interval between fractionation is critical to allow adequate killing of cancer cells, while repairing of healthy cells. Cells in the S phase of the cell replication cycle are most resistant to radiotherapy, whereas those in the M phase are the most sensitive. Cells in the S phase survive the radiotherapy treatment and with time will progress to the G2 and M phases (after four to six hours), whereby they are replicating and replacing the dead cells.

- Reoxygenation: Tumour cells close to blood vessels are well oxygenated, whereas those in the centre are farther and less oxygenated (i.e. hypoxic). After radiotherapy, well-oxygenated cells die, whereas the remaining cells are more hypoxic and tend to survive longer as more resistant to the free radical damage. Oxygen diffuses into these areas to reoxygenate the cells, making them more sensitive to the next radiation exposure and the cycle continues.

- Repopulation: During fractionated radiotherapy, tumour cells continue to divide to repopulate the tumour bulk. However, as tumour cells divide faster, there is more DNA damage to these repopulated cells and will lead to subsequent death, whereas normal cells will repopulated healthily.

Over the last few decades, there have been many improvements in radiotherapy. Advances in radiation planning and delivery have increased its efficacy while reducing toxicity [20]. Modern CT-based radiotherapy planning relies on improved conformity of treatment portals and use of multiple treatment angles (Figure 4.8). Toxicity can be better predicted and reduced through volumetric calculation of normal tissue doses [21].

Intensity-modulated radiation therapy (IMRT) has developed tumour- and organ-motion tracking techniques as well as innovations in target positioning. Image-guided radiation therapy (IGRT) uses imaging carried out at each treatment session to allow millimetric adjustments in patient positioning. Techniques limiting respiratory organ motion – which applies even to the prostate – such as respiratory gating, adjustment of field sizes, and tumour tracking are increasingly being used. Precise target definition allows better normal tissue sparing and facilitates the safe delivery of higher doses and fractions (i.e. dose escalation), increasing the likelihood of cure. Adaptive radiation therapy (ART) uses a feedback process for dynamic treatment planning with each fraction.

Radiotherapy can be given as percutaneous external beam radiotherapy (EBRT) or as an internal application of radioactive material which is inserted into the tumour or an organ (brachytherapy). The ability of radiation to penetrate tissues is related to radiation energy: the greater the energy the deeper the penetration. Radiation dose is measured in terms of the energy absorbed during the interaction of radiation with tissue (1 Gy = 100 rad). There are differences in the effect of radiation from different energy sources. With conventional X-rays, most of the absorption is at the surface of the skin; for gamma rays, the maximum absorption is about 5 mm below the surface. With linear accelerator megavoltage, the maximum absorption is about 20 mm below the skin surface (Figure 4.9). In bone, lower energy radiation produces a higher absorbed dose.

The results of percutaneous radiotherapy can be improved by additionally using radiosensitising chemotherapy (i.e. radiochemotherapy). The one definitive exception to radiotherapy in urological oncology is renal cancer, which is completely resistant to radiotherapy and chemotherapy. Radiotherapy has indications for the treatment of metastatic lesions, especially in the skeletal system, if metastatic bone lesions are painful or show signs of instability and are likely to lead to pathological fractures.

Radiotherapy needs time for its effect on malignant cells. The most vulnerable stage of proliferating cancer cells to radiation is the M phase with rapid DNA synthesis, which is a tiny window in time during the mitotic
cycle. Radiotherapy fractioning ensures that repetitive exposure destroys as many cancer cells as possible, allows normal tissue to recover, and reduce toxic side effects. Small volume irradiation is tolerated more than large. Radio-resistance is related to the survival of CSCs as the source of continuous cancer evolution and plasticity. These can be considered a ‘moving target’ that can be hard to eradicate by radiotherapy [22].

The early morbidity after radiotherapy is the result of three processes: (i) acute inflammation (e.g. radiation cystitis), (ii) the death of stem cells, and (iii) the vascular response [21]. The early changes are most marked in the skin and the bowel where cell turnover is most rapid, but because enough stem cells remain, these epithelia usually recover. Late morbidity results from the aftermath of the inflammatory process, which includes fibrosis and changes within small blood vessels, which lead to ischaemia and sometimes necrosis (e.g. distal ureteral stenosis after radiotherapy for cervical cancer). Infertility can occur with doses as low as 3 to 6 Gy. A concern in long-term survivors of radiotherapy is the potential of inducing second malignancies, the incidence rate for this risk is about 1% per year [23].

4.10.5.1 Radiosensitivity of the Urogenital Tract

The normal kidney is rather radio-sensitive. A dose of more than 2000 rad within five weeks will give rise to acute nephritis after several months, often leading to hypertension. Protection of the kidney is therefore vital.

In the bladder, the sequelae of radiation vary and are largely unpredictable. An early ‘cute radiation cystitis’ may occur and can be made worse by infection [24]. Chronic radiation cystitis may occur after 6–24 months with sometimes severe symptoms and haematuria. Treatment is symptom based. Symptoms may subside, but often slowly get worse. In severe forms, it may be complicated by ischaemic necrosis with fistulae formation.

4.10.6 Chemotherapy

Chemotherapy is treatment with drugs that interfere with cell replication (Table 4.1). Cancers with a fast proliferation rate are most sensitive to chemotherapy (e.g. testicular cancer).

Chemotherapy can be truly life-saving as in testicular cancer with long-term cure rates of 98–99% [25]. In other urological cancers, its role is adjunctive to surgery, where it may improve outcomes, or palliative as in metastatic urothelial and PCa.

As cancer cells proliferate and divide more quickly than replicating normal tissues, chemotherapy affects cancer growth most. However, proliferating normal tissues (i.e. bone marrow, epithelium, and hair follicles) are also affected, resulting in loss of hair, mucosal erosions of the gastrointestinal tract, haematological toxicity with the reduction of all cellular blood elements, and loss of spermatogenesis. These toxic side effects are temporary and dose dependent. Lasting toxicity can also occur with some drugs (e.g. renal damage with cisplatin, peripheral neuropathy with vinblastine). Because of the effect on bone marrow, immunity against infection is also
depressed. Severe leucopenia can result in life-threatening septicaemia. Patients with leucopenia and fever require isolation, prophylactic antibiotics, and bone marrow stimulation by growth factors (e.g. filgrastim).

Though single-drug chemotherapy can be effective (e.g. docetaxel for castration-resistant PCa), the effects are higher if several drugs with different mechanisms are combined (polychemotherapy) (Table 4.2). Chemotherapy needs to be given repeatedly to achieve a lasting effect. It is therefore given in treatment cycles or courses of usually 21 days, whereby treatment is given during the first few days and about two weeks are allowed for recovery. As part of a multimodal treatment, chemotherapy may be used before (i.e. neoadjuvant) or after (i.e. adjuvant) the primary treatment (surgery or radiotherapy) (e.g. chemotherapy before radical treatment of muscle-invasive bladder cancer).

The efficacy of chemotherapy in terms of response and survival is related to the sensitivity of the tumour but also to the patient's general condition in terms of comorbidity and total tumour burden. The general condition can be assessed by the performance status (e.g. the Karnofsky score; Table 4.3) [26].

The effect of chemotherapy is assessed by the measurable response of lesions on imaging, usually CT scanning. A measurable shrinkage or disappearance of lesions is called a response, and a complete response is the disappearance of all measurable lesions for more

<table>
<thead>
<tr>
<th>Table 4.1 Cycle action of common chemotherapeutics.</th>
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<tr>
<td>Cellular cycle phase specific</td>
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<tr>
<td>● S-phase</td>
</tr>
<tr>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Thiouracil/Fluorouracil</td>
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<tr>
<td>Methotrexate</td>
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<td>Mercaptopurine</td>
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<tr>
<td>● M-phase</td>
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<tr>
<td>Vincristine/vinblastine</td>
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<tr>
<td>Docetaxel/paclitaxel</td>
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<tr>
<td>Cellular cycle nonspecific</td>
</tr>
<tr>
<td>● Alkylating agents</td>
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<tr>
<td>Mitomycin C</td>
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<tr>
<td>Cisplatin</td>
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<td>Carboplatin</td>
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<td>Cyclophosphamide</td>
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<td>● Topoisomerase II</td>
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<td>Doxorubicin</td>
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<td>Etoposide</td>
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<td>Cellular cycle independent</td>
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<td>Bleomycin</td>
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<th>Table 4.2 Mechanisms of action of commonly used chemotherapy drugs.</th>
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<tr>
<td>Antimetabolites (purine antagonists, pyrimidine antagonists, ribonucleotide reductase inhibitors)</td>
</tr>
<tr>
<td>6-mercaptopurine, methotrexate, 5-fluorouracil, methotrexate hydroxyl urea</td>
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<tr>
<td>Antagonists of DNA polymerase</td>
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<tr>
<td>Cytarabine n-loss derivatives, nitrosoureas, platinum derivatives</td>
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<td>Mitomycin C mitoxantrone</td>
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<td>Antagonists of topoisomerase</td>
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<tr>
<td>Etoposide, anthracyclines mitoxantrone irinotecan</td>
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<tr>
<td>Protein degradation inhibitors of mitosis</td>
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<td>Asparaginase vinca alkaloids taxanes</td>
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<th>Table 4.3 Karnofsky performance scale.</th>
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<tr>
<td>Normal: no complaints; no evidence of disease</td>
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<tr>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
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<tr>
<td>Normal activity with effort: some signs or symptoms of disease</td>
</tr>
<tr>
<td>Cares for self: unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>Able to care for most self needs: requires occasional assistance</td>
</tr>
<tr>
<td>Requires occasional considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>Disabled: requires special care and assistance</td>
</tr>
<tr>
<td>Severely disabled: hospitalisation is indicated although death not imminent</td>
</tr>
<tr>
<td>Very sick: hospitalisation necessary; active supportive treatment is necessary</td>
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<tr>
<td>Dead</td>
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than four weeks. Partial response (PR) is defined as a shrinkage of more than 50% for more than four weeks; if there is neither progression nor measurable shrinkage, this is called stable disease (SD). In the worst case, there is progression under chemotherapy (i.e. progressive disease [PD]). In the latter case, a change in the chemotherapy regimen is needed, whereas PR and CR indicate successful treatment. However, with PR and even with CR, the duration of these responses are decisive. Often, an SD response has to be considered a success because of a lack of more effective alternatives.

Unique to urology is the intracavitary application of chemotherapy into the bladder, which is used in non-muscle-invasive bladder cancer as an adjunct to transurethral resection (e.g. mitomycin C).

4.10.7 Targeted Drugs

Advances in the understanding of the molecular biology of cancer have led to the development of drugs which affect specific intracellular pathways or effectors. Inhibitors of the tyrosine-kinase mechanism (e.g. sunitinib and sorafenib) or the mTOR-pathway (e.g. everolimus) are used in metastatic renal cancer to inhibit angiogenesis and slow down progression. In PCa, drugs targeting the androgen-receptor (e.g. abiraterone and enzalutamide) can prolong survival in castration-resistant disease.

4.10.8 Immunotherapy

Immunotherapy is used on bladder, prostate, and renal cell cancers. The intravesical treatment with attenuated mycobacteria (BCG) is used as an adjuvant for high-risk non-muscle-invasive bladder cancer and as the primary treatment for carcinoma in situ. In metastatic renal cancer, systemic immunotherapy with interferon and interleukin (often combined with fluorouracil) used to be the only systemic treatment before the introduction of targeted drugs with responses limited almost exclusively to pulmonary metastases. Recent advances have been made with the advent of drugs acting on programmed death ligand receptors which decrease the ability of a neoplasm to evade immune activity. These drugs, e.g. nivolumab, can prolong survival considerably in metastatic renal and urothelial carcinoma.

4.10.9 Radionuclide Treatment

The intravenous injection of radionuclides can be used to treat bone metastases. In PCa, some radionuclides (e.g. strontium\(^{89}\)) have an effect on bone pain but considerable bone marrow toxicity. Alpharadin (radium\(^{223}\)) is a more targeted radionuclear treatment for metastatic bone lesions of PCa without bone marrow toxicity. Prostate-specific membrane antigen (PSMA)–ligated radionuclides also act on soft tissue metastases in PCa.

4.10.10 Multimodal Treatment

The combination of several treatment modalities should theoretically improve treatment outcomes. Locally advanced cancers, positive surgical margins, and the presence of regional lymph node metastasis often require multimodal treatment, combining surgery with chemotherapy or radiotherapy. Surgery and chemotherapy is often combined (e.g. in bladder cancer), but there are no established combinations of surgery and radiotherapy in uro-oncology. For PCa, radiotherapy is often combined with hormone ablation.

4.10.11 Interdisciplinary Care and Centralization

Multidisciplinary care of cancer patients by a team of surgeons, radiotherapists, medical oncologists, pathologists and psychologists as well as other specialists has become a standard in many countries. This is time-consuming but is generally expected to improve patient care. Ideally, all members of an interdisciplinary care team should be specialised in uro-oncology.

Centralization of care of patients with certain cancer entities to high-volume centres has been instituted in some countries (e.g. Great Britain, Sweden) and it is believed that this will improve outcomes. Better outcomes for surgery have been shown to depend on surgical volume for some procedures (e.g. radical cystectomy). Centralization also seems of importance for rare cancers (e.g. penile cancer).

**Expert Opinion**

Cancer development, growth, and metastasis is a highly complex process, but much of our clinical knowledge is still empirical. The increasing understanding of the molecular biology of cancer does bring new therapeutic options and also increases our understanding of why many therapies still fail. Cure is still the only reliably possible in the early stages of cancer, and it becomes increasingly evident that multimodal treatment is required for many cancers. Hopefully, the rapid progress in research will improve our therapeutic abilities decisively in the future.
References


Part II
Kidney and Ureter Anatomy

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Abstract

The kidneys are retroperitoneal organs encased by layers of fascia and fat and are responsible for excreting the end products of the metabolism and excess water to maintain the body’s electrolyte and fluid balance. With slight variation in size and location on either side of the 12th dorsal vertebra, they receive arterial supply directly from the aorta and drain directly into the vena cava. Converging to the renal sinus, the basic functional structure of the kidneys are the renal pyramids, projecting into minor calyces as papillae. The minor calyces unite to form the three or more major calyces which drain into the infundibula. From the upper, middle, and lower poles, together forming the renal pelvis, the urine is pushed downwards in a funnel-shape pelviureteric junction that continues in the ureter. The ureter is a muscular tube that actively propulses the excreted by-product, the urine, with a peristaltic movement and receives its blood supply from most major arteries in its course, which anastomose longitudinally. The ureter ends by burrowing into the bladder in an oblique manner, giving rise to a functional valve that prevents reflux.

Keywords: kidney; renal pelvis; ureter; glomeruli; nephron; pyramids; calyx; renal artery; renal

Key Points

- The kidney develops from the metanephros, the mesonephros becomes the gonad, and the pronephros disappears.
- Retroperitoneal organs are closely related to vital organs such as the aorta, vena cava, the liver, duodenum, stomach, spleen, pancreas, and colon.
- Each kidney has an artery and vein; however, variations with multiplicity and location exist, and polar vessels are uncommon.
- The vasculature of the kidneys is segmented, allowing for partial resection of renal tissue without compromising the blood supply of the remnant kidney.
- Papillae drain the kidney into minor calyces, which group to form major calyces, together forming the renal pelvis.
- The ureter is a muscular tube that has a pacemaker-triggered peristaltic movement, conveying the urine bolus to the bladder.
- The ureter has two critical locations: the pelviureteric junction and the vesicoureteral junction.
- The ureter has a rich blood supply, anastomosing into longitudinal arteries along its length, allowing segmental resections without compromising blood supply.
5.1 Comparative Anatomy

The main function of the simplest renal system, such as the excretory vacuole of the amoeba, is to regulate osmolarity. The basic unit of the mammalian kidney is the renal pyramid. It is arranged like a bunch of flowers in a vase. The flowers are the glomeruli, the stalks are the collecting tubules, and the vase is the calix (Figure 5.1).

In the adult human, the pyramids are compressed so that the external surface is smooth, but the original lobulation can be seen in the foetal kidney where it resembles a bunch of grapes and is similar to aquatic mammals such as porpoises, whales, and otters [1]. Some mammals like rabbits have only one large calyx, whereas others like pigs and man have about a dozen calices. In man, the design of the pyramid is important in preventing reflux of urine up into the renal parenchyma.

Figure 5.1 Anterior relations the kidneys (a) on the left the duodenum and colon, (b) on the right, (c) liver.
5.1 Comparative Anatomy

5.1.1 Topographical Anatomy

The kidneys lie protected from injury by the spine, ribs, and a thick packing of fat. Each kidney is about 11 cm in length, 6 cm wide, and 3 cm thick. A rough way to determine the vertical length of a kidney is to multiple the height of a vertebral body by 2.5. The left kidney is usually longer than the right kidney. The right kidney also tends to sit lower down than the left because of the liver. The average weight of a kidney is 150 g in a male and 135 g in a female. Superiorly, they are level with the upper border of 12th dorsal, and inferiorly, of the 3rd lumbar vertebra. The mid pole of the right kidney is level with the 12th rib and that of the left kidney is level with the 11th and 12th ribs.

5.1.2 Anatomical Relations

- Superiorly: the respective suprarenal glands on either side.
- Medially: the great vessels are on the right the inferior vena cava and on the left the aorta.
- Anteriorly: on the right, the liver, hepatic flexure of the colon, and second and third part of the duodenum (anterioriomedially, because this part lies retroperitoneally, it can be mistaken for a dilated pelvis); on the left, the stomach, spleen, jejunum, and splenic flexure of the colon, and the pancreas (anterioriomedially). Each kidney is overlain by bowel: on each side a part of the duodenum, as well as colon, and must be reflected when approaching the kidney anteriorly (Figure 5.1). This relationship with the retroperitoneal duodenum is important because sometimes it can be mistaken for a dilated renal pelvis.
- Posteriorly: each kidney is related to the subcostal and ilio-hypogastric and ilio-inguinal nerves, quadratus lumborum, and psoas muscle (Figure 5.2), lateral to which is the entire thickness of the abdominal wall made up of the transversal, internal, and external oblique muscles. Posterior to the 12th rib lies the broad sweep of latissimus dorsi and the trivial slips of serratus posterior inferior. The diaphragm separates the kidneys from the thoracic cavity and its pleura, by descending and forming the costo-diaphragmatic recess.
- Arterial: The renal arteries are given off at the level of L1 and L2. The left renal artery has a relatively short course straight to the left kidney, but the right renal artery has a longer course because it has to travel posterior to the inferior vena cava. There may be more than one renal artery; the most common renovascular anomaly.
- Venous: The drainage of the right kidney is via the very short right renal vein, straight into the inferior vena cava. On the left hand side, there is a marked difference. The left renal vein collects venous blood from the left suprarenal gland and the left gonad, as well as from the left kidney. The right suprarenal gland gonad drains via the right suprarenal vein and right gonadal vein, respectively, into the inferior vena cava.

Figure 5.2 Posterior relations of the kidneys.
5.2 Renal Fasciae

Originally, the kidney is enveloped in a loose packing of fat (Zuckerkandl fascia) (Figure 5.3), contained within a thin, firm fascia (Gerota fascia). The Gerota fascia is a multilaminated structure that is fused posteromedially with the muscular fasciae of psoas major and quadratus lumborum [2]. This fascia then extends anterolaterally as a bilaminated sheet and then divides into the anterior lamina, which passes anteriorly to the kidney to form the anterior perirenal fascia and the thicker posterior lamina. This posterior lamina continues as the lateral conal fascia, blending ultimately with the parietal peritoneum [2].

Gerota fascia is the most important layer surgically. This is a layer of connective tissue encapsulating the kidneys and the suprarenal glands. Anteriorly, the fascia passes anterior to the kidney, its vessels, the abdominal aorta, and inferior vena cava and fuses with the anterior layer of the other kidney. Posteriorly, it fuses with the psoas major and the sides of the vertebral bodies. Superiorly, the anterior and posterior segments fuse to envelope the suprarenal gland and make attachments with the diaphragmatic fascia. Inferiorly, the anterior and posterior segments do not fuse, but go on separately to fuse with the connective tissue of the iliac fossa and the iliac fascia, respectively.

5.3 Macroscopic Appearances

The cross-section of the kidney shows two distinct zones, the cortex and medulla. The cortex contains the glomeruli. The medulla is divided into an inner and outer zone according to the presence of the long or short loops of Henle (Figure 5.4). Between each pyramid is a portion of cortex, the column of Bertin (Figure 5.4).

5.4 Arterial Supply

The paired renal arteries leave the aorta just 3–4 cm below the origin of the superior mesenteric artery. The right renal artery is longer and mostly located higher than the left, as it passes posterior to the inferior vena cava, right renal vein. The left renal artery passes behind the left renal vein, pancreatic body, and definitely lower than the splenic vein. Classically each kidney is supplied by a single renal artery. However, anatomic variations are common, where two or three renal arteries can supply the kidney with frequencies of multiple arteries ranging between 9 and 76% [3].

Figure 5.4 Diagrammatic section through the kidney.

Figure 5.3 The fasciae surrounding the kidney. Note that Gerota fascia is tough enough to tamponade haemorrhage from the ruptured kidney. Ao, aorta; IVC, inferior vena cava.
The arterial supply to the kidney was first mapped out by F. T. Graves in 1954 using injection-corrosion casts of the renal vessels [4]. He found that there were five main renal segments arranged like fingers of a hand and each of these had its own artery (Figure 5.5). The segments are divided into the apical, upper, middle, lower, and posterior segments. This knowledge makes it easier to interpret angiograms, but it must be understood that variations are common; one or more of the segmental or polar arteries may spring independently from the aorta. Where the kidneys are not in their anatomical position (i.e. pelvic kidney), the segmental arteries may arise from any nearby vessels (e.g. aorta, lumbar, common, or internal iliac arteries). In addition, polar arteries occur frequently, and these need to be remembered during a nephrectomy.
Each segmental artery supplies a discrete segment of the kidney; therefore, an occlusion of a branch can potentially lead to complete infarction of a complete segment of parenchyma. However, vascularity from neighbouring segments often occurs. These segments do not correspond to the pattern of the calices and pyramids, as in the bronchopulmonary segments, which makes it more difficult to plan a partial nephrectomy. However, it does make it possible to carry out any operation on the kidney in a virtually bloodless field once the main segmental renal artery is occluded, with the only slight blood loss from the venous system.

Each segmental artery divides into branches that run toward the cortex where they give off arcuate arteries, from which every glomerulus receives its afferent arteriole (Figure 5.6). The efferent arterioles from the glomerulus run among the proximal and distal tubules. The efferent arteries from the innermost row of glomeruli (juxtaglomerular) send long straight branches down into the papilla, among the collecting tubules and long loops of Henle. On entering the medulla, these afferent arterioles divide into 12–25 descending vasa recta and supply the aforementioned structures. An important feature of the vasa recta is that both the ascending and descending vessels are grouped into vascular bundles, where they are intimately apposed, locating them close to the limbs of the loops of Henle and the collecting ducts. The proximity of the descending and ascending vessels with one another and adjacent ducts provides the structural basis for the countercurrent mechanism that concentrates the urine.

The vasa recta open into wide, thin walled capillaries in the tip of the renal papilla, which ramify between the ascending loops of Henle and collecting tubules.

5.5 Renal Veins

The renal veins, unlike the arteries, communicate freely with each other (Figure 5.7). Tributaries from each renal pyramid drain into larger veins around the pyramid that end in the main renal vein. Interlobular veins drain the superficial part of the cortex, and these pass to the corticomedullary junction and receive some ascending vasa recta. These then end in arcuate veins and anastomose with other neighbouring veins to form the renal vein. The extensive communication between the various veins means that obstruction of one or more of the tributaries has little effect on overall drainage.
Usually there is one large renal vein draining each kidney. The renal vein is located anterior to the renal artery, although as is the case with much of the human anatomy, the position can vary up to 1–2 cm cranially of caudally relative to the renal artery. On the left side, the renal vein receives the suprarenal and gonadal veins joining the inferior vena cava laterally. In comparison to the right renal vein, the left enters the inferior vena cava slightly more cranially and anterolaterally than the right. On the right side, the renal vein is much shorter draining directly into the lateral to posterolateral aspect of inferior vena cava without receiving any tributaries, while the right gonadal and adrenal veins end in the inferior vena cava directly.

5.6 Common Vascular and Anatomic Variations

The vascular anatomy can vary in up to 50% of kidneys (9). The most common variation is multiple renal arteries (10) and is more common on the left side. These additional arteries may enter through the hilum or as a branch of the main artery or into the parenchyma directly as a separate branch from the aorta. The presence of these polar arteries can make dissection and mobilisation of the kidney a real struggle because these arteries are often shorter than their normal counterparts. As well as making mobilisation of the kidney a challenge, these arteries, especially the lower pole arteries, can lead to extrinsic compression on the ureter at the ureteropelvic junction, leading to ureteropelvic junction obstruction. When the kidney is ectopic, the presence of multiple renal arteries is more common, and the origin of these multiple renal arteries is varied. Furthermore, polar arteries, which tend to be short and difficult to dissect, can greatly hinder the mobilisation of the kidney, in view of a partial nephrectomy, whereas lower pole polar arteries can give rise to a pelviureteric junction obstruction.

Multiple renal veins are not as common as renal arteries, but they still exist (9). The most common variation is that of duplicate renal veins draining the right kidney via the right renal hilum. The other major variant is that involving the left renal vein. This may cross posterior to the aorta or may even divide and sandwich the aorta on its course to the inferior vena cava. The final surgically important variant is the lumbar veins; these may enter the renal vein on either side from a posterior position and may cause significant haemorrhage if not properly recognised and torn during surgery.

5.7 Lymphatics

The kidneys have a profuse lymphatic system that largely follow the vasculature through the columns of Bertin and then form multiple large trunks within the renal sinus. On reaching the hilum, branches from the renal capsule, perinephric tissues, renal pelvis, and upper ureter join the parenchymal branches to form three to four main trunks that run medially into the cisterna chyli. When the ureter is obstructed, these lymphatics act as an efficient safety-valve

Upon leaving the hilum, there is a slight symmetry in the drainage of the left and right side. On the left side, the main drainage is into the left lateral para-aortic nodes, and there will occasionally be additional drainage into the retrocrural nodes, or there may be direct drainage into the thoracic duct above the diaphragm. On the right side, drainage is into the right interaortocaval and right paracaval nodes, as well as the nodes sandwiching the aorta anteroposteriorly.

5.8 Innervation of the Kidney

The kidney has the second richest innervated organ per unit of tissue mass second only to the adrenal gland [5]. Sympathetic preganglionic nerves originate from the eighth thoracic to first lumbar spinal segments. These fibres then travel to the coeliac and then the aorticorenal ganglia. The postganglionic fibres then reach the kidney via the autonomic plexus along the renal artery.

The function of the autonomic innervation is the control of vasmotor activity of the kidney. The sympathetic innervation causes vasoconstriction, and the parasympathetic innervation causes vasodilatation. An important point to make is that even without this autonomic control, the kidney can function perfectly well, as demonstrated in a transplanted kidney.

5.8.1 The Nephron

The nephron is the basic functional unit of the kidney, consisting of two parts: (i) the glomerulus, where the water and solutes are filtered from the blood and (ii) the tubules where the filtrate is processed.

5.8.2 The Glomerulus

The glomerulus consists of a convoluted arteriole, which is invaginated into Bowman capsule on a stalk, the mesangium (Figure 5.8) [6]. At the base of the stalk, the afferent arteriole is surrounded by the macula densa. These are endothelial cells containing granules that are the precursor of renin. The juxtaglomerular body, which contain beta-adrenergic receptors, is a pressure-sensing mechanism that responds to changes in blood pressure in the afferent arteriole (Figure 5.9).

The endothelium of the arteriole of the glomerulus and the epithelium lining Bowman capsule are separated by a basement membrane that serves as a filter to retain
cells and proteins in the blood (Figure 5.10) [6]. This basement membrane rests on specialised epithelial cells that have interlocking foot-processes (podocytes) (Figure 5.11) [6]. These, along with the capillary epithelium, form a selective barrier across which urinary filtrate pass. The filtrate drains into Bowman capsule and then moves to the proximal convoluted tubule. This is a thick-walled, metabolically active structure whose brush border increases the surface area offered to the glomerular filtrate. The proximal tubule is composed of a thick cuboidal epithelium covered by dense microvilli, the brush border. The microvilli do most of the metabolic work involved in the reabsorption of salt and water. They are also the cells that give rise to renal cell carcinomas.

From the proximal tubule, the glomerular filtrate passes to the loop of Henle. Some of these loops are
5.8 Innervation of the Kidney

Bowman capsule
Afferent arteriole
‘Juxtaglomerular’ cells – mesangial pericytes of afferent arteriole (renin precursor granules) → renin with haemorrhage, upright posture, hypoglycaemia heat stress etc.

Straight connecting tubule
Efferent arteriole
Adrenergic vasoconstriction

Figure 5.9 The juxtaglomerular body.

Figure 5.10 The basement membrane lies between the endothelium of the glomerular arteriole and the epithelium of Bowman capsule.
short, whereas others, especially those from the innermost row of nephrons next to the medulla, are long and reach to the tip of the papilla. As the loops ascend out of the medulla, the loop thickens to become the distal convoluted tubule. These tubules also have metabolically active cells, but unlike the proximal tubules, do not have a brush border. The distal tubules return to a position adjacent to the originating glomerulus and proximal tubules. Another turn and the distal tubules become the collecting tubules. The collecting tubules receive filtrates from 10 to 15 nephrons, becoming the collecting duct and descend through the medulla to open at the tip of the papilla. The collecting tubule is thin walled and its cells are metabolically inert.

### 5.8.3 Renal Papillae, Calyces, and Pelvis

Each renal papilla is made up of collecting tubules, loops of Henle, the vasa recta, and veins. Typically, there are 7–9 papillae in each kidney, but can vary between 4 and 18. The papilla protrudes into the calyx and the collecting ducts open through a series of oblique slits along the sides of the papilla. The configuration is such that when the pressure is increased inside the papilla, the collecting ducts are occluded; thereby urine is not forced up into the parenchyma of the kidney (Figure 5.12). The papillae are organised in two longitudinal rows, orientated at roughly 90° to each other. Each of the papillae are cupped by a minor calyx.

Not all papillae are perfectly formed, especially those in the upper and lower poles, where compound papillae are a common congenital anomaly. In such anomalies, there is no valve mechanism to prevent the reflux of urine (Figure 5.13). This malformation becomes important in reflux nephropathy, where the parenchyma...
becomes much scarred because of the reflux. These compound calyces are the result of renal pyramid fusion.

The blood supply to the papillae is twofold: (i) via the vasa recta, which loop down from the efferent arterioles of the glomeruli and (ii) via the smaller arteries entering at the base of each papilla from the rim of the calyx (Figure 5.6).

After the cupping of a papilla, each minor calyx narrows into an infundibulum, and these combine to form two or three major calyceal branches. These calyces are commonly termed the upper, middle, and lower pole calyces. The calyces are lined by the same pattern of smooth muscle and transitional epithelium as along the whole length of the ureter. For the smooth muscle to work efficiently as a pump, it must be free to contract, expand, and move up and down (Figure 5.14).

These calyces combine to form the renal pelvis. The renal pelvis can be a relatively small intrarenal pelvis, but it can also be a large extrarenal pelvis, commonly mistaken as a dilated system. The pelvis is enveloped by a slippery layer of fascia that is easily stripped off when operating on a hydronephrotic kidney. Outside this layer, there is a thick packing of sinus fat. The slippery layer of fascia continues down the ureter, and this allows it to writhe behind the peritoneum with each wave of peristalsis and to move freely up and down with respiration. The pelvis then narrows to form the ureteropelvic junction, marking the start of the ureter.

5.8.4 The Ureters

The ureters are tubular structures responsible for the transportation of urine from the kidneys to the bladder. The length ranges from 22 to 30 cm, and they have a wall made up of multiple layers. The innermost layer is made up of transitional epithelium, surrounded by the lamina propria, which is a connective tissue layer. These two layers make up the mucosal lining. The next layer is made of smooth muscle that, as mentioned previously, is continuous with that of the calyces and the renal pelvis. However, one slight difference is that within the ureter, the smooth muscle layer is divided into an inner longitudinal and an outer circular layer. These muscular layers allow peristalsis of urine. The outermost layer is the adventitia, which is a thin layer enveloping the ureter, its blood vessels, and lymphatics.

The ureter is often divided into three segments: the upper (proximal), middle, and lower (distal) segments. The upper segment starts from the renal pelvis to the upper border of the sacrum. The middle segment is the part between the upper border and lower border of the sacrum. The lower segment is from the lower border of the sacrum to the bladder.

5.8.4.1 The Anatomic Relations of the Ureter

Each ureter lies posterior to the renal artery and vein at the ureteropelvic junction. They then descend anterior to the psoas major muscle and the ilioinguinal nerves, just anterior to the tips of the lumbar transverse vertebral processes. Approximately a third of the way down, the ureters are crossed by the gonadal vessels. They then cross the bifurcated common iliac arteries and run along the anterior border of the internal iliac artery toward the bladder, which it pierces in an oblique manner (Figure 5.15). It is this oblique entry of the ureter into the bladder, the intramural segment of the ureter that acts as a nonreturn valve preventing vesicoureteric reflux [7]. This valve can be congenitally defective such as that seen in those with short intramural segments, or rendered ineffective as a result of injury, such as surgery or disease, all of which leads to reflux. Many congenital abnormalities of this oblique tunnel are seen in association with a duplex kidney and ureterocele. In its lower third, the ureters pass posterior to the superior vesical branch of the internal iliac artery also called ‘umbilical artery’. On the right side, the ureter is related anteriorly to the second part of the duodenum, caecum, appendix, ascending colon, and colonic mesentery. The left ureter is closely related to the duodenojejunal flexure of Treitz, descending and sigmoid colon, and their mesenteries.

To find the ureter during an operation, the surgeon’s most useful landmark is the bifurcation of the common iliac artery. When operating on the lower third of the ureter, it is helpful to first ligate and divide the superior vesical artery.

In males, the ureter passes under the vas deferens just as it approaches the bladder. In females, the ureter runs through the cardinal ligament (the ligament of Mackenrodt) (Figure 5.16). They are also crossed...
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Figure 5.15 Main ureteral relations.

Figure 5.16 (a) Ureters running through the cardinal ligament. (b) Uterine prolapsed causing compression on ureters.
anteriorly by the uterine arteries within the pelvis. It is at this point that the ureter can be easily damaged during operations on the uterus.

Because of the close proximity of the ureters to several bowel segments, they can be involved in inflammatory and malignant processes that affect the terminal ileum, appendix, right or left colon, and sigmoid colon.

### 5.8.4.2 The Calibre of the Ureters

The normal ureter does not have a uniform calibre throughout its course. There are two areas of distinct narrowing: the ureteropelvic and the ureterovesical junctions. At the ureteropelvic junction, the renal pelvis tapers into the proximal ureter. At the ureterovesical junction, there is a true physical narrowing as the ureter burrows through the bladder wall to enter at it at the ureteric orifice, the intramural ureteric segment. As mentioned, this acts as a valve preventing vesicoureteric reflux [7].

A third point where there is possible hindering of passage of the urine bolus or a stone is where the ureter crosses the iliac vessels. This area of hindrance is caused by two factors: the extrinsic compression from the iliac vessels and the necessary angulation of the ureter to enter the pelvis.

It is at these three points where urinary calculi are often lodged, causing ureteric colic. As well as narrowing, the knowledge of the angulations of the ureter is vital during ureteroscopy.

### 5.8.5 Renal Pelvis and Ureteral Blood Supply

The blood supply to the renal pelvis is profuse and comes from branches of all the main segmental arteries, and these communicate freely within the pelvis. The abundant blood supply allows the construction of long flaps of renal pelvis to repair hydronephrosis without the fear of necrosis [8].

The ureter receives its blood supply from multiple arteries along its course. The upper ureter is supplied by the inferior segmental branch of the renal artery and is reinforced by the gonadal artery, abdominal aorta, and the common iliac artery. On entering the pelvis, smaller branches come off the internal iliac artery or its branches; the vesical and uterine arteries to supply the ureter.

Important to the surgeon is the knowledge that the abdominal ureter receives its blood supply medially and the pelvic ureter receives its blood supply laterally.

Upon reaching the ureter, the arteries run longitudinally within the adventitia of the ureter to form an extensive plexus (Figure 5.17). It is this longitudinal supply that allows the mobilisation of the ureter from the surrounding retroperitoneal tissues without compromising its blood supply, as long as there is no damage to the adventitia. If the longitudinal artery of the ureter is pulled on, it becomes even narrower; hence, in any operation on the ureter, it is essential to avoid tension.

The venous and lymphatic drainage of the ureter runs with the arterial supply; therefore, there is segmental variation in its drainage. Within the pelvis, ureteral lymphatics drain to the internal, external, and common iliac nodes, whereas in the abdomen, the left para-aortic nodes drain the left ureter and the right ureter drains into the paracaval and interaortocaval lymph nodes. The lymphatic drainage of the upper ureter and renal pelvis joins that of the corresponding kidney.

#### 5.8.5.1 Ureteral Innervation

Preganglionic sympathetic fibres from the 10th thoracic to 2nd lumbar spinal segments supply the ureter. The postganglionic fibres arise from several ganglia found in the aorticorenal, superior, and inferior hypogastric (pelvic) autonomic plexuses. The parasympathetic input to the upper ureter is through vagal fibres via the coeliac plexus and fibres to the lower ureter are from second to fourth sacral segments.

Fine microscopic analysis of the ureter shows a network of fine plexuses in the muscular wall of the ureter [4]. However, these do not propagate ureteral peristalsis, as this continues perfectly and is seen in a completely denervated transplanted kidney. The wave of peristalsis originates and is propagated from the intrinsic smooth muscle pacemaker sites located within the minor calyces and the excitation of the propagation is carried from one cell to the next through close junctions.

The entry of the ureter into the bladder is along an oblique tunnel, which provides a nonreturn valve preventing vesicoureteric reflux. This valve can be congenitally defective or put out of use by injury or disease.
Many congenital deformities of this oblique tunnel are seen in association with duplex kidney and ureterocele (Figure 5.18).

5.8.5.2 Renal and Ureteric Pain

The renal pain fibres are stimulated by distension within the renal capsule, collecting system, or ureter. As well as distension, direct irritation to any of them can stimulate nociceptors. These pain signals travel with the sympathetic fibres, and the pain is felt in the segmental distribution of the kidney or ureter (T8 to L2). The pain is felt over the distributions of the subcostal, iliohypogastric, ilioinguinal, or genitofemoral nerve fibres. This can result in pain in the flank, groin, or scrotum or labia.

Expert Opinion

1) The kidney and ureters are easy surgical organs, meaning that they can stand a lot of injury. Segmental resections of the ureter and partial nephrectomy of the kidneys can be safely done without vascularity problems. Renal function mostly recovers even after a severe acute tubular necrosis. The vascularity of the distal ureters is different, and it is better not to do segmental resections but rather a reimplantation. Incisions of the ureters should be transversal (as much as possible) so as not to cause strictures.

2) A couple of anatomic peculiarities:
- Aberrant vessels: polar arteries
- Different anatomy of the adrenals left and right
- Recognize the different anatomy of the adrenal and gonadal veins and pay attention to the dangerous lumbar veins.

References

Kidney and Ureter Physiology

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Abstract

The kidneys play an important role in regulating the internal environment of the human body. They eliminate waste products, maintain fluid and electrolyte balance, and have a hormonal function. Kidneys ensure that the internal environment is maintained for normal function of the body. They also secrete various substances that regulate bone metabolism, vascular tone, and haemopoiesis. Understanding renal physiology is essential to understanding disease process and providing clinical care to patients.

Keywords  glomerular filtration rate; acid–base balance; acidosis; renal tubule; erythropoietin; vitamin D

Key Points

- Kidneys play a vital role in maintaining homeostasis by adjusting the water and salt excretion to maintain a constant extracellular fluid volume and osmolality, which is called 'osmoregulation'.
- Kidneys maintain the acid–base balance by excretion of hydrogen ions, reabsorption of filtered bicarbonate, and nonionic transport of NH4+ (ammonium ions) in the form of NH3 (ammonia).
- Kidneys maintain vascular tone through the renin-angiotensin system. If the mean renal blood pressure drops below 90 mm Hg, renal baroreceptors will trigger the release of renin, which will catalyse the cleavage of angiotensin I from angiotensinogen. Angiotensin-converting enzyme (ACE) produced in the lung will cleave angiotensinogen I to produce angiotensin II, which has a potent vasoconstrictive action. This process occurs in about 30–60 minutes.
- The endocrine function of the kidney is vital and includes the production of renin, erythropoietin production in response to hypoxia, which is thought to be produced in the glomerular mesangial cells, and renal tubular cells. The kidney is also responsible for activating vitamin D3.
- Glomerular filtration rate (GFR) is the rate of filtered fluid through the kidneys per unit time.
- Renal tubules have two main functions: secretion and reabsorption, both which help to regulate fluid and acid–base balance.
- Obstructive uropathy is the most common correctable cause of renal failure caused by impaired flow of urine.
- The ureter is not merely a conduit; it plays an active role in the propagation of urine from the kidney to the bladder and is responsive to the physiological and pathological changes that take place in the urinary tract (e.g. diuresis, obstruction, or infection).

6.1 Glomerular Filtration Rate

Kidneys are supplied by renal arteries that branches directly from the abdominal aorta. Renal arteries divide progressively, leading to a glomerular capillary plexus. The glomerulus is the functional unit of the kidney. In a normal physiological condition, 20% of the cardiac output (625 ml min⁻¹ per kidney) flows through the 2.5–3 million glomerular capillary plexus, losing about 170 l of plasma water per day, completely recycling
it every 30 minutes and the whole body water four times a day [1].

The fenestrations of the capillary gives the plasma direct access to the basement membrane whose effective mesh has been measured with molecules of known molecular weight, (40,000 mol wt), that is, the glomerular filtrate is plasma minus its proteins [1].

Filtration depends not only on the size of the molecule but also on its electrical charge. The proteins of the glomerular basement membrane carry a negative charge which repels negatively charged protein molecules (e.g. albumen). The blood pressure within the glomerular arteriole is about 60 mm Hg. The plasma oncotic pressure is about 25 mm Hg, so that there is a filtration pressure of about 35 mm Hg (Figure 6.1).

Glomerular filtration rate (GFR) is the rate of filtered fluid through the kidneys per unit time. It is controlled by three factors: (i) the difference in hydrostatic pressure and oncotic pressure between the capillary membrane and Bowman capsule, (ii) the renal plasma flow, and (iii) the glomerular permeability, which is the least important factor [2].

Vascular tone of the afferent arterioles changes in response to the change in the mean arterial pressure, a mechanism called 'autoregulation'. Therefore, GFR is maintained at a constant level despite the variation in the systemic blood pressure. Autoregulation becomes less effective in controlling GFR when the mean arterial pressure drop below 70 mm Hg. A feedback mechanism from the macula densa in response to the sodium and chloride excretion has also been suggested [3].

GFR can be measured by various methods [4]. The gold standard is inulin clearance. Inulin is a fructose polysaccharide that is filtered by the glomerulus but is neither absorbed nor secreted in the renal tubule, which are the key points to adequately measuring the GFR. Inulin is infused intravenously until a steady state is reached. Its concentration is measured in blood and urine collected over a timed period.

\[
\text{GFR} = \frac{U \times V}{P}
\]

where \( U \) is the urine concentration of inulin, \( V \) is the volume of urine per minute, and \( P \) is the plasma concentration of inulin.

Inulin is difficult to administer and difficult to measure; therefore, it is not routinely used in clinical practice. The most widely used method to estimate GFR is creatinine clearance. Creatinine clearance rate is the volume of blood plasma that is cleared of creatinine per unit time. It is easy to perform, relatively cheap, and readily available. The endogenous creatinine is produced at a constant rate with limited daily variation. This method assumes that creatinine is neither excreted nor reabsorbed in the renal tubule. Nevertheless, some of the creatinine is excreted in the proximal tubule, which overestimates the true GFR [5]. When GFR is very low, measured creatinine clearance can exceed true inulin clearance by 50–100% [6].

In the clinical practice, there is a major practical drawback to the measurement of creatinine clearance in that it demands an exact timed collection period. Usually, the patient passes urine before going to sleep and notes the time. In the morning the bladder is emptied and the time is noted again; the overnight urine specimen plus a blood sample taken early in the morning is sent to the laboratory [7, 8]. This system only works when the patient is reasonably well and cooperative, which is not always the case.

Isotope compounds can also be used to measure GFR such as \(^{51}\text{Cr-ethylene-diaminetetra-acetic acid (EDTA)},\)

![Figure 6.1 Filtration in the glomerular arteriole.](image-url)
diethylenetriaminepentaacetic acid (DTPA) labelled with $^{140}\text{La}$ or $^{99}\text{technetium}$. These substances are much more efficient and accurate, although more expensive [9].

Measuring plasma level of urea and creatinine is the most widely used method to estimate GFR. Creatinine levels vary between individuals and an estimated GFR (eGFR) can be calculated based on patient age, sex, and body mass using the following more common formulas [2].

1) Crockcroft-Gault formula:
\[
\text{eGFR} = \left(140 - \text{Age}\right) \times \frac{\text{Mass (Kg)}}{1.04 \text{ if female and 1.23 if male}} \times \frac{\text{Serum Creatinine (μmol l}^{-1})}{72}
\]

2) Modification of diet in renal disease (MDRD) formula:
\[
\text{eGFR} = 32788 \times \frac{\text{Serum Creatinine}^{-1.154}}{\text{Age}^{-0.203}} \times \begin{cases} 1.21 & \text{if Black} \\ 0.742 & \text{if female} \end{cases}
\]

(Creatinine levels in μmol l$^{-1}$ can be converted to mg dl$^{-1}$ by dividing them by 88.4).

6.1.1 Disorders of Glomerular Filtration

Glomerular filtration may be impaired in underperfusion from dehydration, low blood pressure, sepsis, cardiac failure, hepatorenal failure syndrome, and nephrotoxic drugs.

6.2 Renal Tubules

Renal tubules have two main functions: secretion, which is the removal of substances from the blood into the lumen, and reabsorption, which removes substances from the lumen to the blood. Renal tubules extend from the renal cortex to the inner medulla, and it is subdivided into different sections each has specialised function.

6.2.1 Proximal Convoluted Tubules

Proximal convoluted tubules (PCTs) extend from the Bowman capsule to the loop of Henle. PCT is responsible for reabsorption of 60% of the glomerular filtrate including 80% of water. Sodium, potassium, calcium, and bicarbonate ions are mainly reabsorbed in the PCT. All of the filtered amino acid and glucose are also recovered in here. PCT is responsible for the secretion of drugs and toxins that are too large to be filtered in the glomerulus. Most common diuretics act on the proximal tubule to reduce sodium and water reabsorption.

Sodium reabsorption occurs by means of passive and active process. Passive reabsorption accounts for 15% of the total sodium reabsorption and is driven by the electrochemical gradient created by chloride anion [10]. The active mechanism of sodium reabsorption is driven by a sodium/potassium ATPase pump. It is an energy-dependent mechanism which moves three sodium ion into the peritubular capillaries and two potassium ion in the opposite direction. Water will passively follow sodium ions. Glucose and amino acid will be cotransported with sodium ion.

The majority of filtered bicarbonate is reabsorbed in the PCT. Bicarbonate is coupled with the hydrogen ion to form water and carbon dioxide. Both will then diffuse passively and combine inside the cell to form a hydrogen and bicarbonate in a reaction facilitated by carbonic anhydrase enzyme. Most of phosphate and calcium ions are reabsorbed in the PCT.

6.2.2 Loop of Henle

The main function of loop of Henle is creating hyperosmolar medullary interstitium to facilitate urine concentration process in the collecting ducts. The loops of Henle can be subdivided into three parts: thin descending limb, thin ascending limb, and thick ascending limb (Figure 6.2). Each segment has a specified physiological
function, and a specialised peritubular capillary plexus called ‘vasa recta’ surround the loops. The thin descending limb is highly permeable to water and relatively impermeable to salt. The thin ascending limb has no active transport of salt, and it is impermeable to water. The thick ascending limb is entirely impermeable to water. The reabsorption of solute in this segment occurs though an active process. [11].

6.2.2.1 The Countercurrent Theory
Filtrate in the loop of Henle and blood flow in the peritubular capillaries are running in the opposite direction creating a countercurrent. In the thick ascending segments, sodium is removed from the filtrate into the cell through Na/K/2Cl transporter that is located in the apical membrane of the columnar epithelial cell. Sodium is then removed from the cell in exchange for potassium through an active process involving the Na/K ATPase pump, reducing the sodium concentration and osmolality of the filtrate and increasing them in the interstitial fluid (Figure 5.2) [12]. The filtrate, which flows down the descending limb, starts off being isosmotic with systemic plasma and glomerular filtrate. As it descends through the hyperosmotic zone, water diffuses out and the filtrate becomes more concentrated. As it rises up through the thick limb of the loop of Henle, it brings a high concentration of sodium chloride to the active sodium/potassium exchange pump, and sodium is pumped out into the interstitial tissue, raising its osmolality still further. The ability of the sodium pump in the thick segment of the ascending limb of the loop of Henle to establish a modest concentration difference across the wall of the ascending limb is augmented by countercurrent flow to achieve a large difference in osmolality [13, 14].

Several control mechanisms are involved in this process of water conservation: the pituitary antidiuretic hormones, arginine vasopressin being the most important of these. Receptors for arginine vasopressin are found along the entire length of the renal tubule [13].

The atrial natriuretic peptide is a polypeptide secreted by the human atrium, which causes diuresis and loss of sodium. It is of interest to urologists because it is secreted whenever obstruction of urine is relieved. It may play a part in the diuresis which occurs when the bladder is catheterized for chronic retention. Both proximal and distal tubules take part in this postobstructive diuresis [15].

Diuretics, which prevent reabsorption of sodium in the proximal tubule, mean that more sodium reaches the distal tubule to be exchanged for potassium; hence, hypokalaemia can be seen after prolonged administration of diuretics.

6.2.3 Distal Convoluted Tubule
The distal convoluted tubule (DCT) extends from the loop of Henle to the collecting duct. It is essential for the reabsorption of sodium and calcium ions. It also form the macula densa, part of the juxtaglomerular apparatus that senses the change in sodium ion concentration. Ten percent of the filtered sodium is reabsorbed in the DCT via an active basolateral sodium potassium ATPase pump. Thiazide diuretics work on this part to inhibit sodium and chloride absorption and cause diuresis.

Unlike the other parts of renal tubules, calcium reabsorption occurs through calcium channels in the apical membrane and not through the paracellular route. Calcium ion reabsorption in this part is controlled by parathyroid hormone [16].

6.2.4 Collecting Ducts
Collecting ducts (CDs) are the final part of renal tubule and are divided into cortical and medullary ducts. CDs are lined by two types of cells. Principal cells reabsorb sodium and secrete potassium into the lumen. Intercalated cells are responsible for hydrogen and bicarbonate secretion and play a role in acid–base balance. Antidiuretic hormone is secreted from the hypothalamus to the posterior pituitary gland. It is released in response to increase in plasma osmolarity. It increases the permeability of the medullary part of the CD to water and increases urine concentration.

6.3 Hormonal Function of the Kidney

6.3.1 Renin
Renin is secreted by the juxtaglomerular cells in the zona glomerulosa, situated on the afferent arteriole of the glomerulus, in response to a fall in blood pressure [17]. Renin is an enzyme which splits angiotensinogen (a globulin) into angiotensin I (decapeptide) which in turn is converted to angiotensin II (a potent vasoconstrictor). Angiotensin II causes an increased cardiac output and constriction of the peripheral arterioles. Angiotensin II is important for maintaining GFR when the renal blood flow decreases. It also stimulates the secretion of aldosterone to conserve sodium and increase the total extracellular fluid volume.

6.3.2 Erythropoietin
Erythropoietin, a potent haematopoietic growth factor, is produced primarily by the kidneys. It stimulates division of erythroid colony forming units in the bone marrow to form red blood cells [18]. In renal failure, lack of erythropoietin results in anaemia, but
6.5 Acid–Base Metabolism

Fortunately, synthetic erythropoietin, made by recombinant DNA technology, is available for patients on dialysis [19].

6.3.3 Vitamin D

The kidneys play a vital role in vitamin D metabolism. Vitamin D is synthesised in the dermis from cholecalciferol (vitamin D₃). Vitamin D₃ is inactive and requires two hydroxylation to become active. The first hydroxyl group is added in the liver to form 25-hydroxycholecalciferol (calcidiol). The second hydroxyl group is added in the renal tubular cells to form 1,25 dihydroxycholecalciferol (calcitriol), the active form of vitamin D. The kidneys also control bone mineralisation through the reabsorption of calcium ion. Parathyroid hormone significantly increases calcium reabsorption in the distal tubule. It also reduces phosphate reabsorption in the PCT [2].

6.4 Special Disorders of Renal Tubules

Cystinuria is an autosomal recessive disorder. Mutation affects SLC3A1 and SLC7A9 genes on chromosome 2, leading to deficiency in transporter protein of four amino acids arginine, ornithine, lysine, and cystine [20]. The first three are highly soluble, whereas failure of cystine reabsorption in the proximal tubule results in recurrent stone formation.

6.4.1 Hartnup Disease

Hartnup disease is an autosomal recessive disorder in which the deficiency involves the transport of tryptophan across the renal tubule and bowel wall. The loss of tryptophan in the urine is not important, but reduced uptake from the bowel results in deficiency of nicotinamide, resulting in cerebellar ataxia and pellagra [21].

6.4.2 Fanconi Syndrome

In Fanconi syndrome, the proximal tubule is converted into a short, thin functionless tube. As a result, there is failure of reabsorption of glucose, several amino acids, and phosphate. There is usually proteinuria and acidosis [21].

6.4.3 Renal Glycosuria

In renal glycosuria, there may be incomplete reabsorption of glucose from the filtrate, resulting. Renal glycosuria is harmless, but it must be distinguished from diabetes [21].

6.4.4 Renal Tubular Acidosis

Renal tubular acidosis (RTA) is a disease that occurs when the kidney fails to secrete hydrogen ions, resulting in acidic blood and alkaline urine. There are four types of renal tubular acidosis. Type 1 (distal RTA) is characterised by the inability to secrete hydrogen ions, leading to an alkaline urine which predisposes to calcium phosphate stone formation, metabolic acidosis, hypocitraturia, and hypokalaemia. Type 2 (proximal RTA) is characterised by failure of bicarbonate reabsorption; however, it is also associated with increased urinary citrate excretion but does not form stones. Type 3 (variant RTA) is a combine proximal and distal types. Type 4 (hyperkalaemic RTA) is seen in patients with hypoaldosteronism or pseudohypoaldosteronism (i.e. failure of kidney to respond to aldosterone) [22].

6.4.5 Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus results from the failure of the kidney to respond to antidiuretic hormone. It could be hereditary or acquired. The hereditary form is an x-linked recessive disorder that affects males. The condition is characterised by excessive diuresis and subsequent dehydration [23].

6.5 Acid–Base Metabolism

The kidneys play an important role in acid–base metabolism (Figure 6.3). The majority of acid production in the body comes from carbohydrate, fat, and protein metabolism. Metabolic by-product carbon dioxide is converted to hydrogen ion and bicarbonate. The majority of acid production is eliminated by the lung. However, fixed acid which cannot be eliminated by the lungs has to be secreted by the kidneys [2]. In the renal tubule, bicarbonate is formed from carbon dioxide and water in a reaction catalysed by carbonic anhydrase [24]. The majority of bicarbonate is reabsorbed in the PCT and the remainder is reabsorbed in the DCT. A hydrogen ion is secreted in the renal tubule in exchange with a sodium ion through Na⁺-H⁺ pumps. It is also secreted through H⁺-ATPases proton pump [2].

In the distal tubule, glutaminase forms ammonia from glutamine, which combines with H⁺ to form ammonium.

The buffering systems are as follows:
- Bicarbonate: $H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$
- Phosphate buffer: $H^+ + PO_4^{3-} \leftrightarrow H^+ + HPO_4^{2-} \leftrightarrow H^+ + H_3PO_4$
- Ammonia buffer: $NH_3 + H_2O \leftrightarrow NH_4^+ + OH^-$
Obstructive uropathy is the most common correctable cause of renal failure caused by impaired flow of urine [25]. Characterised by three phases. In phase 1 (within 1.5 hours of unilateral post-obstruction), the pressure rises inside the renal pelvis until the filtration pressure is exceeded and filtration ceases. The rise in pressure results in stretch of the tubular cells, which trigger a transient release of prostacyclin, prostaglandin E, and nitrous oxide. The net effect is a transient increase in the renal blood flow to maintain GFR by dilating afferent arterioles. In phase 2 (1.5–5 hours), efferent arteriole vasoconstriction mediated by angiotensin II and thromboxane A2 drops the renal blood flow, while the pressure continues to rise. In phase 3 (after 5 hours), angiotensin II and thromboxane A2 cause the afferent arterioles to vasoconstrict, which further reduces the renal arterial blood flow and also the pressure reduces. In bilateral obstruction, the third phase does not exist, which leads to continual increase in intrarenal pressure.

Within 24 hours, renal blood flow falls to only 40% of the preobstruction level [26, 27]. Hypoxia of the renal tissue promotes the synthesis and release of inflammatory mediators, which recruit macrophages and promote interstitial fibrosis and scarring.

Splitting of the renal tissue can occur because of increasing pressure, mainly at the edges of the calyces, which allows urine to enter the renal lymphatics and veins. This is demonstrated as stranding on radiological images.

There are two practical implications of this phenomenon. First, microorganisms in the upper tract can gain immediate access to the bloodstream (i.e. obstruction complicated by infection is easily followed by sepsis). The second is that when urine finds its way into the lymphatics or veins of the kidney, the pressure inside the lumen of the renal pelvis will fall, and filtration will start again. Thanks to this safety-valve mechanism, acute obstruction in the human kidney does not mean that the kidney ceases to function. An apparently nonfunctioning kidney may recover completely after the obstruction has been relieved.

Following the relief of obstruction, renal blood flow increases to 60% of the normal. GFR remains at 50% of its normal levels. Postobstructive diuresis is more common following bilateral renal obstruction. Postobstruction diuresis can occur, loosely defined as >200 ml of urine an hour. This is mainly a physiological process (90% of cases) because of the disruption of the medullary osmotic gradient, enhanced medullary blood flow, fluid overload, and diuretic effect of excess urea, which is adaptive and aimed at clearing out the
accumulated fluids and metabolic wastes. Although 10% can be pathological as a result of secretion and accumulation of arterial natriuretic peptides (due to over stretching of the atria) in unilateral obstruction, excess ANP is excreted by the other kidney; furthermore, loss of antidiuretic hormone sensitive of the collecting ducts can also lead to large fluid losses. The diuresis can be clinically driven by administrating unnecessary large volumes of intravenous fluids during the recovery phase [15].

6.7 Ureteric Physiology

The ureter is not merely a conduit for urine but rather an organ that represents a high degree of integration with the kidney and the bladder by being responsive to both physiological and pathological changes [28]. The propagation of urine starts from the kidney with the pelvicalyceal system and the renal pelvis having greater frequency of contractions to push the urine into the upper ureter [29]. As the urine moves into the upper ureter to be propelled further, the contractile activity at the pelviureteric junction (PUJ) protects the kidney from reflux of urine from the upper ureter [29]. As urine flow increases, the block at the PUJ loses this effect, and a rhythmic contraction pattern takes place between the pacemaker activity in the upper parts of the ureter and the rest of ureter, hence producing an equal and continuous wave of ureteric contractions [30, 31]. The peristaltic wave originates in the most proximal portion of the ureter, and urine is propelled distally forming a bolus. For the bolus of urine to be propelled efficiently, the peristaltic wave must completely coapt the ureteral walls. The resting ureteral pressure is approximately 0–5 cm H2O and ureteral contractions that occur in response to urine flow, which is about two to six times per minute, induces further increase in pressure that can go up to 20–80 cm H2O [32].

The vesicoureteric junction (VUJ) allows the urine to enter the bladder as a one-way transport of urine. The peristaltic wave forces the urine through the VUJ, and the energy of the contractile wave dissipates. In normal flow conditions, the ureter can transport a specific amount of urine per unit time. As the rate of flow increases, the ureter does not form a bolus and coapt but rather forms a continuous column of fluid, and the ureter serves as a simple pipe for transport (Figure 6.4).

Different conditions can affect the adequacy of urine transport. Inadequate transport can result from increased or reduced amount of fluid entering the ureter per unit time. If the rate of flow is quite high, a normal nonobstructed ureter may dilate and impede adequate urine transport. Also a minor degree of obstruction to outflow may not cause significant dilatation at low flow rates.

Figure 6.4 In diuresis, the ureter dilates (a), the peristaltic contractions become less occlusive (b) until eventually the ureter acts as an open pipe (c).
Urine transport across the VUJ is dependent on the relationship between the ureteral intraluminal pressure and intravesical pressure. During normal flow rates, the ureteral contractile pressure exceeds the intravesical pressure with the urine passing into the bladder. In a case when the ureter is dilated and inadequately contracting or at very high flow rates, the ureter does not coapt to form a bolus and the pressure in the column of urine within the ureter must become higher than the intravesical pressure for urine to pass into the bladder. The normal bladder maintains a relatively low intravesical pressure during the filling phase that facilitates the transport of urine across the VUJ [33]. The abnormal bladder with increased intravesical pressure can impair ureteral emptying. Therefore, the initial ureteric response is by increasing its peristaltic frequency [34]. After a certain point, the ureter starts to dilate and urinary stasis occurs. The intravesical pressure at which the ureter may start to decompensate is about 40 cm H₂O.

The VUJ does not relax to allow the passage of urine [35]. It rather maintains an antireflux mechanism and facilitates the passage of the urine bolus by the sliding action of the distal ureter within its sheath as the bolus of urine is ejected into the bladder [36]. This mechanism of telescoping of the ureter within its sheaths decreases the VUJ resistance to flow and facilitates urine passage into the bladder. Various factors may affect the transfer of urine across the VUJ, which can be obstruction at the UVJ, raised intravesical pressure, or during very high flow rates that may exceed the transport capacity of the normal UVJ.

6.8 Whitaker Test

The Whitaker test is urodynamic study in which a contrast media is directly injected into the renal pelvis to delineate the anatomy while simultaneously monitoring renal pelvic and bladder pressures. It is used to differentiate a real obstruction form a permanent change in musculature of the upper urinary tract. The test can be also applied in postoperative patients to confirm the improvement in flow aided with an excretory urogram before urinary diversion is removed [37].

The classic technique is carried out by running water or saline into the ureter at a rate calculated to be greater than the maximum urine flow in diuresis, while at the same time the pressure is measured in the system (Figure 6.5). This suffers from the disadvantage that it is necessary to pass a fine needle and cannula into the dilated renal pelvis.

Pressure difference between the renal pelvis and bladder are measured as follows:
- >22 mm H₂O: Obstructed
- 18–22 mm H₂O: Equivocal
- <18 mm H₂O: Non-obstructed

![Figure 6.5 Whitaker test. Saline or water is infused into the renal pelvis through a percutaneous cannula while the pressure is monitored.](image)

**Expert Opinion**

Understanding the role of the kidney and ureters in maintaining homeostasis is vital as both structures work in interesting harmony. Various urological conditions affect the functional dynamics of the kidney and ureter. Medical or surgical management of these conditions adds to the number of variables that needs to be considered when offering a certain treatment modality. As with any treatment of the underlying condition, which can be an obstructing stone, prostate cancer, or a kidney tumour, there is always a concern in maintaining renal function. This notion acts as a start and end points in the process of decision making in clinical practice.
References


7

Renal Failure

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Abstract

This chapter gives an introduction to the aetiology, assessment, and treatment of acute kidney injury, chronic kidney disease, and end-stage renal disease. Acute kidney injury (AKI) is common in patients who are hospitalised and is associated with significant morbidity and mortality. Early recognition is crucial to improving outcomes. Pre-emptive renal transplantation is the treatment of choice for end-stage renal disease in patients who meet requirements.

Keywords  acute kidney injury (AKI); acute tubular necrosis; chronic kidney disease; dialysis; end-stage renal disease

Key Points

- Acute kidney injury (AKI) can have prerenal, parenchymal, or postrenal causes.
- Acute tubular necrosis is the most common cause of AKI, and management is mainly supportive.
- Early nephrological consultation is recommended in patients with AKI.
- Pre-emptive renal transplantation should be the aim in all patients with progressive chronic kidney disease, who meet requirements.
- Home-based dialysis therapies offer a greater degree of patient autonomy.
- Patients with severe frailty and multiple morbidities may not be suitable for renal replacement therapy.

7.1 Acute Kidney Injury

7.1.1 Definition

Acute kidney injury (AKI, previously known as ‘acute renal failure’) is a condition in which a person has a rapid decline in kidney function over hours to days, leading to an accumulation of by-products of metabolism and disturbances in fluid, acid–base balance, and electrolyte balance. It is defined as any one of the following: Increase in serum creatinine (SCr) by $>0.3 \text{ mg} \text{ dl}^{-1}$ $(>26.5 \text{ μmol} \text{ l}^{-1})$ within 48 hours, increase in SCr to $>1.5$ times baseline, which is known or presumed to have occurred within the last 7 days, or urine volume $<0.5 \text{ ml} \text{ kg}^{-1} \text{ h}^{-1}$ for 6 hours [1, 2]. The AKI Network (AKIN) group and Kidney Disease: Improving Global Outcomes (KDIGO) developed the definition so that it redefines the entire spectrum of acute renal dysfunction to capture all patients with rises in SCr that are of clinical significance but may not result in complete failure of kidney function [1, 2].

7.1.2 Stages of AKI

AKI is classified as mild, moderate, or severe according to the degree of rise of serum creatinine and the urine output, as shown in Table 7.1. This method of grading AKI has been validated clinically by studies showing an increased risk of mortality with increasing severity of AKI (correcting for comorbidity) [3, 4].
7.1.3 Classification of AKI

AKI is classified based on aetiology into pre-renal, renal (intrinsic), and post-renal.

7.1.3.1 Prerenal AKI

This is usually as a result of a decrease in effective intrarenal vascular volume due to haemorrhage or fluid losses. Renal arterial obstruction and intrarenal ischaemia as a result of various causes can also lead to prerenal AKI (Table 7.2). The hallmark of prerenal AKI is the reversibility of renal dysfunction without any structural damage to renal parenchyma, following treatment of the underlying pre-renal cause.

7.1.3.2 Intrinsic AKI

Renal parenchyma can be damaged by tubulointerstitial diseases, glomerular diseases, or vasculitis. Prerenal causes, if untreated or severe, can lead to acute tubular necrosis (ATN) which by far is the most common cause of AKI amongst patients in hospitals. A variety of small vessel inflammatory diseases can affect the kidney leading to AKI. Some of these aetiologies are shown in Table 7.3.

7.1.3.3 Postrenal or Obstructive AKI

The obstruction to urine flow can occur anywhere in the urinary tract, from the tubules, as a result of crystal nephropathy, down to the prostate. Common causes of obstructive AKI are shown in Table 7.4.

7.1.4 Clinical Assessment

A thorough clinical assessment is essential to differentiate AKI from chronic kidney disease and to identify the aetiology and mechanism of AKI. This includes the
clinical history that can point towards prerenal AKI in the presence of gastrointestinal fluid losses, systemic sepsis, and so on. Medication history is important because a variety of drugs can cause prerenal AKI and allergic interstitial nephritis. Many causes of intrinsic AKI (e.g. vasculitis, sarcoidosis, and systemic lupus erythematosus) may be associated with systemic symptoms such as fever, arthralgia, and fatigue. Lower urinary tract symptoms or a history of pelvic malignancy may suggest an obstructive cause.

Physical examination should focus on assessing volume status (i.e. heart rate, blood pressure, jugular venous pressure, skin turgor, presence of oedema, or lung crackles) and identifying sepsis early. Rash, arthritis, or red eyes may suggest vasculitis. Pelvic examination to look for enlarged bladder, prostatic enlargement, and gynaecological malignancy is essential in the presence of relevant symptoms.

Bedside urine dipstick examination is mandatory. Haematuria and proteinuria are present in glomerulonephritis. Leucocytes and nitrites suggest infection. Eosinophiluria may be present in allergic interstitial nephritis.

### Investigations

It is essential that the diagnosis of AKI and its possible cause be identified as a matter of urgency to prevent irreversible damage or to limit damage. In addition to elevated serum urea and creatinine, there may be metabolic acidosis and hyperkalaemia. Hypercalcaemia and hyperuricaemia must be ruled out as possible causes of AKI. Full blood count, C-reactive protein (CRP), and blood cultures are essential to identify sepsis.

Further investigations are directed towards answering two important questions: Is urinary obstruction a possibility and is intrinsic AKI or systemic disease a possibility? Therefore, all patients with suspected or confirmed AKI must have a renal tract ultrasound as soon as possible. If intrinsic AKI is considered, then the following tests must be done: antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-GBM antibodies, myeloma screen, and complement C3 and C4 levels. Blood film examination, serum lactate dehydrogenase (LDH), and haptoglobin levels are useful if haemolytic uraemic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) are suspected.

Indications for performing a renal biopsy for AKI include: (i) unclear cause for AKI, (ii) delayed recovery from presumed ATN, (iii) suspected systemic disease with renal involvement, and (iv) suspected glomerulonephritis.

Several novel biomarkers for AKI have been identified in recent years, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), interleukin-18 (IL-18), and cystatin C. However, these tests are not yet widely used in clinical practice, and they remain the focus of ongoing studies to determine their appropriate role in guiding management of patients at risk for AKI.

### Management

#### 7.1.5.1 Early Nephrology Consultation

Early nephrology referral is recommended because a delay in referral has been associated with increased morbidity and mortality, dialysis dependence, and prolonged hospital stay in patients who are critically ill with AKI [5, 6]. Referral is especially recommended in a timely manner in the following situations:

- Dialysis indications exist
- Unexplained cause and deteriorating AKI
- Possible glomerulonephritis
- Possible autoimmune disease
- Possible pulmonary-renal syndrome
- Possible HUS or TTP

#### 7.1.5.2 Correction of Prerenal States and Maintenance of Haemodynamic Stability

In the absence of haemorrhagic shock, KDIGO guidelines suggest using isotonic crystalloids (physiological saline) rather than colloids (albumin or starches) as initial management for expanding the intravascular volume in patients at risk for AKI or with AKI. Patients with vasomotor shock will need to be cared for in a high-dependency setting with the use of vasopressors. Accurate and regular fluid balance monitoring is crucial to avoid volume overload and pulmonary oedema, especially in patients with oliguria. In established ATN, the focus of management should be towards preventing complications of AKI and maintaining a physiological environment that aids recovery of renal function. Sepsis should be identified and treated early.

#### 7.1.5.3 Treatment of Complications

Hyperkalaemia is a common and dangerous complication in patients with AKI. If serum potassium level is >6 mmol/L, then an electrocardiogram (ECG) must be
undertaken to check for features of hyperkalaemia, and if present, then calcium gluconate is given to stabilise the cardiac cell membrane and prevent arrhythmias. Serum potassium level can be decreased by giving glucose and insulin intravenously (IV) or salbutamol nebulisers. Correction of acidosis with sodium bicarbonate given IV or orally also helps in correcting hyperkalaemia. Hypocalcaemia and hyponatraemia are also common problems in patients with AKI that will need correcting. AKI can also lead to a bleeding tendency because of platelet dysfunction and the presence of sepsis; dialysis may be required to improve this.

### 7.1.5.4 Medication Management

Nephrotoxic agents such as aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme-inhibitor (ACE-I), and angiotensin receptor blockers (ARBs) must be avoided or stopped. Doses of certain medications may need adjusting in the presence of AKI to avoid the risk of accumulation and toxicity.

### 7.1.5.5 Other Supportive Care

Good nutritional support is crucial during recovery from AKI. KDIGO guidelines suggest achieving a total energy intake of 20–30 kcal kg\(^{-1}\) day\(^{-1}\) in patients with any stage of AKI and protein intake of 0.8–1.0 g kg\(^{-1}\) day\(^{-1}\) in non-catabolic patients with AKI not requiring dialysis. A higher protein intake of 1.0–1.5 g kg\(^{-1}\) day\(^{-1}\) is recommended in patients with AKI on dialysis. Nutrition is given preferentially via the enteral route.

Diuretics are not recommended for the prevention or treatment of AKI, except in the management of volume overload. Diuretics are helpful in managing cardiac failure and cirrhosis in patients with AKI when used in conjunction with other measures to improve the underlying haemodynamics.

### 7.1.5.6 Renal Replacement Therapy

In some patients, the AKI is severe enough to require renal replacement therapy (RRT). Usual indications for initiating dialysis in AKI are as follows

- Resistant hyperkalaemia
- Resistant acidosis (e.g. pH < 7.2)
- Pulmonary oedema unresponsive to diuretics
- Uraemic encephalopathy
- Uraemic pericarditis

In patients with haemodynamic instability, continuous renal replacement therapy (CRRT; e.g. continuous venovenous haemofiltration [CVVHF]) is preferred. In most cases, however, intermittent haemodialysis (HD) is given. Because HD is likely to be temporary, this is undertaken using a double-lumen catheter inserted into the jugular or femoral veins. Anticoagulation in the form of heparin is usually necessary to prevent clotting of blood within the dialysis circuit. This significantly adds to the bleeding risk in patients with AKI and must be taken into consideration when surgical, radiological, or vascular interventions are also needed.

Recovery from ATN may take up to 6 weeks but sometimes as long as 12 weeks. Dialysis dependence for longer than 12 weeks would be classified as end-stage renal disease (ESRD).

### 7.2 Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than three months with adverse implications for health [7]. The abnormalities may be structural (detected by imaging), histological (biopsy findings), or electrolyte disturbances. KDIGO has classified CKD based on the glomerular filtration rate (GFR) and the amount of albuminuria. This categorisation also defines the risk of progression of CKD towards ESRD needing RRT (Figure 7.1). CKD and its complications significantly increase the risk of cardiovascular disease.

Although Scr level is used routinely as a marker of renal function, Scr is affected by a number of other factors such as age, gender, race, nutritional state, and diet. Therefore, various equations have been developed to estimate the GFR. Two widely used equations are the Modification of Diet in Renal Disease (MDRD) formula [8] and the Chronic Kidney Disease Epidemiology (CKD-Epi) formula [9]. The CKD-Epi formula is more accurate than the MDRD, especially in subjects with preserved GFR levels.

Common causes of CKD and ESRD include diabetes mellitus, hypertension, glomerulonephritis, cystic renal diseases, and pyelonephritis. The prevalence of CKD stages three to five increases with age. One population-based study in the UK estimated the prevalence in adults ages 45–54 as approximately 3.5% and in adults ages 75–84 as approximately 35% [10].

### 7.2.1 Clinical Assessment

Initial clinical assessment for CKD includes a search for the possible cause to offer specific treatment (e.g. immunosuppression therapy for some types of glomerulonephritis and relieving urinary obstruction). When no specific treatment exists, then the main aim of managing CKD would be to reduce the risk of CKD progression and managing associated complications such as cardiovascular disease, anaemia, metabolic acidosis, mineral bone disorders, and the risk of AKI. Patients with stage 5 CKD and those needing RRT are said have ESRD.
7.2.2 Complications and Their Management

7.2.2.1 Volume Overload
Extracellular volume expansion and total-body volume overload results from failure of sodium and free-water excretion. This generally becomes clinically manifested when the GFR falls to less than 20 ml min^{-1}, although this may occur with higher GFR in patients with diabetes. Loop diuretics are generally necessary to manage fluid volume expansion and blood pressure control in CKD. Reducing salt and fluid consumption in the diet is also essential.

7.2.2.2 Electrolyte and Acid–Base Imbalances
Hyperkalaemia usually does not develop until the GFR falls to less than 20 ml min^{-1}. This especially occurs in patients who ingest a potassium-rich diet, diabetics and those on ACE-i, NSAIDs, or beta-blockers. Treatment is with a low-potassium diet, diuretics, potassium-binding resins, and reducing or stopping ACE-i and ARBs in the short term. Metabolic acidosis often is a mixture of normal anion gap and increased anion gap. Treatment of acidosis with sodium bicarbonate is necessary to manage hyperkalaemia effectively.

7.2.2.3 Skin Manifestations
Itching can be a distressing feature of renal failure. The pathophysiology is still unclear. Anaemia, iron deficiency, hyperphosphataemia, and hyperparathyroidism may all contribute to itching. If treating these conditions does not help with the symptoms, then antihistamines or gabapentin could be tried [11].

7.2.2.4 Anaemia
Anaemia is common in patients with CKD, especially after the GFR falls to <30ml min^{-1}. Once other causes of anaemia have been ruled out (e.g. bone marrow and gastrointestinal disease), then the treatment focuses on correction of iron, vitamin B_{12} and folic acid deficiency and erythropoiesis-stimulating agents (ESAs) [12]. Intravenous iron is frequently required. ESAs are given as subcutaneous injection on a weekly to monthly basis and in patients on HD, it is usually given IV. The aim is to maintain a haemoglobin level between 10 and 12 g l^{-1}.

7.2.2.5 Neurologic Manifestations
Peripheral neuropathy can occur in ESRD resulting in paraesthesiae, weakness and loss of sensation, most marked in the feet. This is mostly irreversible in severe
cases but adequate dialysis treatment and renal transplantation usually helps. Tricyclic antidepressants and gabapentin are used for neuropathic pain with variable effect. Quinine sulphate and clonazepam can be used for restless legs.

Mental changes such as decreased memory and concentration, slow and slurred speech, myotonic jerks, seizures, altered smell and taste, and sleep disturbances are manifestations of advanced uraemia which indicates the necessity of dialysis.

7.2.2.6 Hypertension
Hypertension (HTN) is a common complication of renal impairment from any cause. Also, HTN is a major risk factor for progressive CKD. Therefore, controlling HTN is major goal in patients with kidney disease. The target blood pressure depends on whether or not proteinuria is present, which is also a risk factor for progressive CKD. In ESRD, HTN is usually driven by fluid volume overload, and therefore controlling fluid volume by dietary means and dialysis is crucial.

7.2.2.7 Mineral Bone Disease
Reduction of renal cell mass leads to progressive phosphate retention and failure of renal bioactivation of vitamin D by 1-alpha hydroxylase, with consequent hyperphosphataemia and relative hypocalcaemia. This stimulates an increased production of parathormone, leading to secondary hyperparathyroidism. Ultimately, tertiary hyperparathyroidism can develop where there is failure of the negative feedback mechanism. Adverse consequences of mineral bone disease include vascular calcification, calciphylaxis, resistant pruritus, and anaemia. Correction of these abnormalities require adequate dialysis, gut phosphate binders, and activated vitamin D. Tertiary hyperparathyroidism may need cinacalcet (a calcimimetic agent acting on the parathyroid gland) or parathyroidectomy.

7.2.2.8 Amyloidosis
Beta 2-microglobulin amyloidosis is a disabling condition that affects patients undergoing long-term HD or peritoneal dialysis (PD). It is mainly prevalent in patients who have been on dialysis for a long time (5–10 years). It manifests as pain due to carpal tunnel syndrome, joint capsulitis, arthritis, and bone cysts. More effective dialysis therapies and renal transplantation in recent years is expected to reduce the prevalence of this condition by better clearing beta 2-microglobulin from the blood.

7.2.2.9 Other Uraemic Features
Constitutional: fatigue, generalised weakness, muscle cramps, restless legs
Gastrointestinal: anorexia, nausea and vomiting, gastritis

Pericarditis: potentially lethal complication of uraemia, which if present is an indication for urgent dialysis
Haematologic: platelet dysfunction and bleeding
Sexual: amenorrhea, infertility, impotence

7.2.3 Renal Replacement Therapy
Kidney transplantation is the treatment of choice for ESRD in suitable patients because it improves both the survival and the quality of life (QoL) compared to dialysis. Transplantation before the initiation of dialysis (pre-emptive transplantation) should be the aim as it offers the best outcomes in terms of survival and QoL. Unfortunately, owing to comorbidities, only around 30% of patients who develop ESRD are fit enough to be listed for transplantation. Renal transplantation is covered in greater detail in a separate chapter.

Residual renal function is important in patients starting dialysis. This is especially so for patients because small solute removal is not very good with PD, and maintaining fluid balance will be challenging when the daily urine output is less than 0.5 l. Therefore, nephron-sparing surgery is crucial in the right context. In patients on HD, because residual renal function usually declines significantly within a few months after starting dialysis, salt and fluid restriction in the diet are extremely important in managing fluid balance and blood pressure.

Patients with ESRD have a poorer QoL than the general population [13] but there is no evidence that dialysis or transplantation improves QoL significantly. However, patients who have undergone transplants have been shown to have a better QoL than those on either HD or PD [14]. It is still not clear if there is difference between HD and PD in terms of QoL improvement [14, 15], and therefore, treatment choices have to be individualised after appropriate education of patients with ESRD.

Patients with ESRD, even those who are on RRT, have a higher mortality compared to age-matched general population. There are wide global variations in survival rates of dialysis patients, which is thought to reflect variations in life expectancies and dialysis practices [16]. Survival is also influenced significantly by age. For example, in the UK, the median survival time of incident haemodialysis patients is approximately 10 years for adults ages 45–54 compared to 3.5 years for adults ages 65–74 [17]. The main causes of death are cardiovascular, infection, and withdrawal from dialysis. There are conflicting reports from mainly observational and retrospective studies indicating the lack of a long-term survival advantage of PD over HD.

Dialysate fluid buffers.
7.3 Dialysis

7.3.1 Peritoneal Dialysis

PD is a home-based mode of RRT, which gives a degree of flexibility and control to patients with ESRD in terms of lifestyle. A PD catheter made of silicone or polyurethane placed in the abdominal cavity is an essential requirement for undertaking PD. The PD catheter is inserted into the abdomen under local or general anaesthetic. Medical percutaneous approach, open surgical approach, and laparoscopic method are all used for this purpose depending on local expertise and practice. The tip of the catheter should lie in the pelvic cavity (Figure 7.2). Dacron cuffs on the catheter elicit a fibrous reaction which anchor the catheter to the abdominal wall and help to prevent infection. The catheter is tunneled subcutaneously to exit the skin at an appropriate site. There has been no demonstrable differences in outcomes between insertion techniques or different types of modern PD catheters [18]. Although PD can be started immediately after insertion of the catheter, it is usually started after a period of two to four weeks to allow wound healing and to reduce the risk of leak of dialysate from around the catheter [19, 20].

Absolute contraindications to PD include diaphragmatic defects, peritoneal adhesions, surgically uncorrectable abdominal hernias, and acute ischaemic or infectious bowel disease. Relative contraindications include severe obesity, lack of manual dexterity, abdominal stomas, dementia, and poor personal hygiene.

In PD, the peritoneal membrane acts as a semi-permeable membrane across which solute and water move between the vascular compartment and the peritoneal cavity. PD fluid contains sodium, chloride, calcium, magnesium, water, and a variable concentration of glucose. Bicarbonate or lactate act as buffers. Clearance of uraemic toxins occurs by way of diffusion down a concentration gradient and by convection. The high glucose content in the dialysate exerts an osmotic gradient which helps in moving water from the vascular compartment into the peritoneal cavity and ultimately out of the patient.

In its simplest form, PD is a manual procedure where the patient is taught to perform dialysis exchanges three to four times a day using a sterile technique (continuous ambulatory PD [CAPD]). Here, 2 l of the dialysate is inserted into the abdominal cavity using the PD catheter, allowed to dwell for four to six hours and then drained out, with a fresh volume of dialysate inserted again. Automated PD (APD) or continuous cycling PD (CCPD) is an alternative to CAPD where several exchanges are performed overnight using a machine while the patient sleeps. This is a lifestyle choice for certain patients. However, APD offers other possible advantages such as increasing the dialysis dose and improving water removal. Modern APD machines are relatively small, portable, and easy to use.

7.3.1.1 Complications Associated with PD

1) Drainage problems can occur due to migration of the catheter, so that the tip no longer lies in the pelvis (usually due to constipation). The catheter tip could also get blocked with fibrin, clot, or omentum. Management is by relieving constipation and using urokinase or heparin in the catheter. Repositioning or replacement of the catheter may be required.

2) Leak of fluid from the peritoneal space may occur into various locations (e.g. anterior abdominal wall, inguinal hernia, or pleural space). Leaks are managed by withholding PD and repair of any hernias. Pleural leaks may need cessation of PD and switching to HD.

3) Pain on inflow of fluid may mean that the catheter is not correctly placed in the peritoneal cavity or that the acidity of the fluid is high. It is usually transient. In persistent cases, using less acidic dialysate, incomplete drainage of fluid, slowing the rate of infusion, and catheter replacement are tried.

4) Perforation of the bowel is rare and is most commonly associated with insertion, although slow perforation can also occur as a result of bowel wall erosion. Operative treatment is usually required.

5) Infections associated with PD cause significant morbidity and mortality [21]. Exit site and tunnel infections are caused mainly by *Staphylococcus aureus* and *Pseudomonas* species. These have to be treated aggressively because they could lead to peritonitis. PD-related peritonitis is a serious complication which can become life-threatening, but could also lead to membrane failure. It presents with a cloudy effluent,
fever, abdominal pain, or diarrhoea. Empirical treatment should cover both gram-positive and -negative organisms. Severe and recurrent peritonitis or those caused by fungi require removal of the PD catheter.

6) Encapsulating peritoneal sclerosis (EPS) is a rare but serious complication of PD whose risk increases with time spent on PD. Clinical manifestations include symptoms associated with bowel obstruction, hemo-peritoneum, abdominal mass, and malnutrition. It occurs because of fibrosis of the peritoneum leading to ‘cocooning’ of small bowel. Treatment focuses on maintaining nutrition which may need to be parenteral. Surgical treatment may involve bowel resection and peritoneectomy which are associated with a substantial mortality risk [22].

7.3.2 Haemodialysis

7.3.2.1 Principles
Blood from the patient flows through an extracorporeal circulation over a thin semi-permeable membrane separating it from the dialysate fluid (Figure 7.3). The membrane is usually made of a synthetic material such as polysulfone. A modern dialyser unit (‘the artificial kidney’) is designed in the form of numerous tiny hollow tubes made using the membrane. Blood flows through these tubes with the dialysate fluid flowing in the opposite direction around the tubes (countercurrent flow). During this process, there is diffusion of solutes from the blood into the dialysate and vice versa, depending on concentration gradients Water removal occurs because of a pressure gradient applied across the membrane (ultrafiltration). Along with the water, convection of solutes, including small- to medium-sized proteins, also occurs. The spent dialysate is discarded and blood is returned back to the patient.

Outpatient HD for ESRD is typically provided intermittently three times a week with a minimum of four hours each session. Daily HD can also be undertaken by patients in their own homes and for longer periods (six hours) including the night (nocturnal HD). Although longer and more frequent dialysis improves certain surrogate markers such as blood pressure and hyperphosphataemia, there is no strong evidence of improved mortality; in fact, there is some evidence of increased infectious and access complications associated with frequent HD [23–25].

Relative contraindications to HD include haemodynamic instability, severe heart failure, and inability to cooperate with the procedure.

7.3.2.2 Vascular Access
The chief problem in HD is a well-functioning vascular access. Blood flow rates of 200–500 ml min$^{-1}$ is required in the extracorporeal circulation. To achieve this, the best method is to create a peripheral arteriovenous fistula (AVF; e.g. radiocephalic or brachiocephalic). If this is not possible because of the size of the vessels, then an arteriovenous graft (AVG) is implanted. Four to six weeks are required for the draining vein of an AVF to arterialise and be suitable for needling. An AVG can be used much sooner after its creation. Two needles are inserted into an AVF or AVG to obtain blood and return purified blood. The least preferred option for access would be a tunnelled central venous catheter because it is associated with a high risk of infection, thrombosis and central venous stenosis.

7.3.2.3 Complications of HD
1) Haemorrhage can occur through incorrect management of needles at the time of dialysis.
2) Intradialytic hypotension manifests as dizziness, nausea, cramps, headache, and fainting. Slowing down the rate of fluid removal and intravenous fluid infusion may be required.
3) Dialysis disequilibrium syndrome (DDS) is a rare complication, which occurs in patients with severe uraemia who have been subjected to aggressive dialysis initiation. Rapid reductions in serum osmolality and paradoxical cerebrospinal fluid acidosis results in cerebral oedema. Symptoms include restlessness, headache, tremors and occasionally fits, and coma occurring during or after dialysis. Short initial treatment using dialysers of small surface area and low blood pump settings prevent this problem.
4) Complications of AVF or AVG include aneurysm formation, stenosis, infection, haematomas, and steal syndrome.
5) Complications of central venous catheters include bacteraemia, thrombosis, venous stenosis, and malfunction necessitating replacements.
6) High output cardiac failure is a rare complication. Like the arterial steal, it can usually be corrected by reversing the fistula.

Practice notes with patients on HD:

- Blood electrolyte levels take one to two hours to stabilise after a dialysis session, and therefore, caution is necessary whilst interpreting them.
- Some medications are removed by dialysis, and therefore, should be given at the end of a dialysis session. Always consult a renal pharmacist.
- If major surgery is planned, it will be beneficial to dialyse the day before to optimise fluid and electrolyte status and transfuse blood products if necessary.
- There is an increased risk of renal cancer in patients with ESRD on HD.
- There is an increased risk of bleeding in patients on HD due to the use of anticoagulation of the dialysis circuit. This should be taken into account while planning invasive procedures.

### 7.3.3 Continuous Renal Replacement Therapies (CRRT)

CRRT is used in intensive care units (ICUs) in patients who are critically ill with AKI, especially in those with haemodynamic instability in whom it is preferred over intermittent HD. It is intended to be used continuously over a 24-hour period using double-lumen venous dialysis catheter. Solute removal during CRRT is achieved by convection (haemofiltration), diffusion (HD), or a combination of both the methods (haemodiafiltration). Middle and larger molecular-weight substances are more efficiently removed using haemofiltration as compared to HD. During haemofiltration, negative pressure applied across a semi-permeable membrane causes fluid movement away from blood. Solutes are dragged across the membrane with the fluid resulting in convective transport of solutes away from the blood. This process requires the use of a replacement fluid to replace fluid and electrolytes back into the patient to prevent excessive fluid removal and electrolyte imbalance. Haemodiafiltration combines diffusive and convective methods to improve clearance of both small and large molecular-weight substances. Similar to HD, anticoagulation is needed to prevent clotting of the extracorporeal circuit. This is achieved by either heparin or increasingly using regional citrate infusion.

### 7.3.4 Conservative Management

Maximal conservative management (MCM) is the support of patients with ESRD without resorting to RRT in the form of dialysis or transplantation [26]. This support addresses the patient's physical, emotional, and spiritual needs until the end of life. Nondialytic therapy includes the treatment of renal anaemia with erythropoietin, optimization of fluid balance with diuretics, and symptomatic treatment of uraemic symptoms such as nausea, itching, and pain. There are some data to suggest that selected elderly patients with high extrarenal comorbidity live just as long with MCM as with dialysis [27]. The collective decision to pursue nondialytic therapy is reached after discussion amongst the patient, their families, and the healthcare team. Palliative care teams need to be closely involved in this approach, especially in planning end-of-life care.

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**References**

intensive care units: a Veterans Administration study.  


Renal transplantation and chronic dialysis are the two treatment options for chronic renal failure (end-stage renal disease [ESRD]). ESRD is defined as the need for chronic dialysis, which is the filtration of water and metabolic waste products. Other renal functions (i.e. regulation of blood pressure, of Ca$^{2+}$/phosphate homeostasis and bone metabolism, and of red blood cell production), which maintain physiological homeostasis, cannot be corrected by dialysis. Over the years, patients on dialysis develop secondary hypertension, peripheral vascular disease, hyperparathyroidism, anaemia, infertility, and erectile dysfunction and have a much reduced life-expectancy.

Renal transplantation can restore all the deficient functions of a normal kidney and is a significantly better treatment modality for ESRD than chronic dialysis. The life expectancy of transplant recipients is much higher than that of patients on dialysis and approaches that of healthy individuals, depending on the number of years spent on dialysis treatment. Conditions following from ESRD will be cured or improved (e.g. hypertension). Existing pathology such as atherosclerotic disease cannot be reverted; however, further progression can be halted or slowed down. In children, normal growth is restored. Today, average five-year graft survival after renal transplantation is about 70% and average patient five-year survival is higher than 80%. The results and outcomes of renal transplantation differ amongst countries [1].

Most patients who undergo renal transplantation have ESRD as a result of chronic interstitial nephritis, diabetes, nephrotic syndromes, hypertension, and polycystic disease. In many cases, the exact cause is renal failure unknown. Theoretically, most patients with ESRD are suitable for renal transplantation. In practice, this is not the case. Patients with long-standing ESRD and complicating factors such as obesity, hypertension, peripheral vascular disease or cardiac dysfunction, and advanced age are often poor candidates for transplantation.
although none of these conditions on its own is a contraindication. Only few causes of ESRD are absolute contraindications because these have a high chance of recurrence and will destroy the graft (Table 8.1).

Table 8.1 Approximate risk of recurrence of renal disease in the transplanted kidney.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Approximate Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal glomerulosclerosis</td>
<td>30–50%</td>
</tr>
<tr>
<td>Membrano-proliferative glomerulonephritis</td>
<td>30–50%</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>40–60%</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome (HUS)</td>
<td>50–75%</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>80–100%</td>
</tr>
<tr>
<td>Oxalosis (primary hyperoxaluria)</td>
<td>80–100%</td>
</tr>
</tbody>
</table>

8.1 The Patients and the Kidneys

8.1.1 Organs for Transplantation

Organs from brain-dead donors are the main source for renal transplantation. Although it would be desirable to have all patients with ESRD undergo transplantation, this is not possible because of the shortage of donor organs.

There are a number of ethical and regulatory guidelines and legislations surrounding organ donations. These are highly dependent on cultural and historical attitudes of each country. These vary from organ retrieval from patients who are brain dead without explicit consent to the need for formal written declaration of either the deceased or the next of kin. The number of organ donations varies amongst different countries depending on attitudes and legislation [2] (Table 8.2).

As the need for donor kidneys is much greater than actual donations, measures aimed at increasing the organ pool have been implemented, such as less stringent criteria regarding donor age and comorbidities. This has led to the use of kidneys from much older donors and of so-called ‘marginal organs’. Experience has shown that reasonable results can still be obtained.

An alternative to the use of cadaver donor organs is life donation. Again, legislation differs amongst countries. Some allow it for unrelated and even unconnected persons (e.g. the US and the UK), whereas others restrict it to relatives and closely connected persons. Commercial life donation is illegal in European countries but allowed in some other countries (e.g. Iran). Some Asian countries have programs of using organs from donors who undergo the death penalty (e.g. Singapore and China). ‘Cross-over’ live donor transplantation between couples with an incompatible ABO constellation is legal in only some countries (i.e. Netherlands, UK, US). The US and the UK also allow for so-called ‘altruistic kidney donation’, which is a completely unrelated and anonymous live kidney donations [3].

8.1.2 Organ Allocation

The procurement, allocation, and transplantation of human organs is regulated by law and special authorities oversee this process. In the UK, this is the Human Tissue Authority (HTA). Organ allocation can be on a purely national basis (e.g. UK, Norway, Switzerland, and France), whereas other European countries (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Netherlands, and Slovenia) have formed a multinational institution, Eurotransplant, to increase the donor pool and improve matching.

Allocation is based on age, waiting time, blood group, human leucocyte antigen (HLA) matching, and in some countries (e.g. the UK), on body size of donor and recipient. Children are given priority. The waiting time varies between different programs. In the UK, on average it is three years and in Germany five. Patients with rare blood groups and rare HLA-constellations have a longer wait time.

8.1.3 Waiting Lists and Preparation of the Recipient

Putting a patient on a waiting list for kidney transplantation requires the diagnosis of ESRD. The day on which chronic dialysis begins is counted as the beginning of the wait time. ‘Preemptive renal transplantation’ before a patient has actually become dependent on dialysis is only possible with a live donation.

Contraindications against renal transplantation are conditions which endanger the success of the surgical procedure, risk severe complications of immunosuppression, or

Table 8.2 Organ donation rates in different countries (per million inhabitants/per year in 2012 [2]).

<table>
<thead>
<tr>
<th>Country</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croatia</td>
<td>36.5</td>
</tr>
<tr>
<td>Spain</td>
<td>35.1</td>
</tr>
<tr>
<td>Belgium</td>
<td>32.9</td>
</tr>
<tr>
<td>US</td>
<td>25.6</td>
</tr>
<tr>
<td>France</td>
<td>24.9</td>
</tr>
<tr>
<td>Portugal</td>
<td>24.2</td>
</tr>
<tr>
<td>Slovenia</td>
<td>23.0</td>
</tr>
<tr>
<td>Austria</td>
<td>22.5</td>
</tr>
<tr>
<td>Italy</td>
<td>22.4</td>
</tr>
<tr>
<td>Finland</td>
<td>19.9</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>19.8</td>
</tr>
<tr>
<td>UK</td>
<td>18.3</td>
</tr>
<tr>
<td>Ireland</td>
<td>17.0</td>
</tr>
<tr>
<td>Poland</td>
<td>16.1</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>15.8</td>
</tr>
<tr>
<td>Sweden</td>
<td>15.6</td>
</tr>
<tr>
<td>Canada</td>
<td>14.7</td>
</tr>
<tr>
<td>Hungary</td>
<td>14.3</td>
</tr>
<tr>
<td>Denmark</td>
<td>13.4</td>
</tr>
<tr>
<td>Germany</td>
<td>12.8</td>
</tr>
<tr>
<td>Switzerland</td>
<td>12.0</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>7.9</td>
</tr>
<tr>
<td>Greece</td>
<td>7.0</td>
</tr>
</tbody>
</table>
The Patients and the Kidneys

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Put doubt on the necessary compliance required for successful immunosuppressive treatment [3, 4]. A history of malignancy requires several years of recurrence-free survival before immunosuppression can be considered safe (Table 8.3).

Investigations need to assess cardiovascular fitness for anaesthesia and surgery, to exclude common malignancies, to examine the state of the large pelvic vessels and the degree of renal anaemia, hypertension, and secondary hyperparathyroidism. Chronic or latent infections of the urinary tract should be treated. Bladder capacity and residual diuresis have to be assessed. In severe bladder disorders, preparations for urinary diversion with renal transplantation must be considered.

Pretransplant nephrectomy is indicated for nonfunctioning kidneys that are a source of repeated infections, bleeding, or the cause of medically refractory hypertension. In patients with polycystic kidneys, it is usually not necessary to remove a kidney to make room for a transplant. It is better to leave both native kidneys unless they cause problems because the residual water diuresis increases the quality of life (QoL) under dialysis considerably.

All potential recipients require blood group and HLA typing as well as the assessment of the presence of preformed antibodies. For a successful transplantation, the risk of rejection needs to be minimised. ABO blood group compatibility and as much HLA compatibility as possible is aimed for. Preformed antibodies may exist as a result of previous exposure to HLA-antigens by blood transfusion, pregnancies, or may be have been induced by autoimmune diseases. A high level of preformed antibodies does not preclude successful transplantation, but immunosuppression needs to be more intensive.

8.1.4 Selecting Donors

Potential donors who are brain dead have to be screened for infections and cancer, so that these are not transmitted to the immunocompromised transplant recipient. Contraindications for organ donation in general are listed in Table 8.4.

Brain death implies that there is irreversible loss of brain stem function, and this is based on neurological examination, electroencephalogram (EEG), or cerebral angiography. Usually, these investigations have to be repeated to document irreversibility. Diagnostic criteria for brain death is strict and should be made by physicians not involved with organ procurement and transplantation (Table 8.5). It is the duty of the explanting surgeon to make sure that the appropriate criteria for the diagnosis of brain death have been used.

Concern for the feelings of bereaved relatives as well as the need to release scarce intensive care resources require that surgery for organ retrieval should be

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Cancer-free years required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 5 cm</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>5</td>
</tr>
<tr>
<td>Wilms tumour</td>
<td>2</td>
</tr>
<tr>
<td>Prostate</td>
<td>2</td>
</tr>
<tr>
<td>Bladder</td>
<td>2</td>
</tr>
<tr>
<td>Non-muscle</td>
<td>2</td>
</tr>
<tr>
<td>Muscle-invasive</td>
<td>5</td>
</tr>
<tr>
<td>Colorectal</td>
<td>2–5</td>
</tr>
<tr>
<td>Uterus</td>
<td>2–5</td>
</tr>
<tr>
<td>Cervical</td>
<td>2</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2</td>
</tr>
<tr>
<td>Breast</td>
<td>2–5</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2–5</td>
</tr>
<tr>
<td>Skin</td>
<td>None</td>
</tr>
<tr>
<td>Basal cell</td>
<td>None</td>
</tr>
<tr>
<td>Squamous</td>
<td>None</td>
</tr>
<tr>
<td>Melanoma</td>
<td>5</td>
</tr>
</tbody>
</table>

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<table>
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<tr>
<th>Table 8.3</th>
<th>Recommended minimum recurrence-free survival (years) after curative treatment for cancer before renal transplantation should be considered.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>Cancer-free years required</td>
</tr>
<tr>
<td>Renal</td>
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<td>Prostate</td>
<td>2</td>
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<tr>
<td>Bladder</td>
<td>2</td>
</tr>
<tr>
<td>Non-muscle invasive</td>
<td>2</td>
</tr>
<tr>
<td>Muscle-invasive</td>
<td>5</td>
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<td>2–5</td>
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</tr>
<tr>
<td>Cervical</td>
<td>2</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2</td>
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<td>Breast</td>
<td>2–5</td>
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<tr>
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<table>
<thead>
<tr>
<th>Table 8.4</th>
<th>Contraindications for organ donation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated bacterial sepsis</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B and C positive</td>
<td></td>
</tr>
<tr>
<td>HIV, CMV, EBV, syphilis positive, TB</td>
<td></td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td></td>
</tr>
<tr>
<td>Active systemic renal disease (e.g. systemic lupus erythematosus)</td>
<td></td>
</tr>
<tr>
<td>Potentially metastasizing malignancy</td>
<td></td>
</tr>
<tr>
<td>Severe hypertension</td>
<td></td>
</tr>
<tr>
<td>Severe diabetes</td>
<td></td>
</tr>
<tr>
<td>Significant cardiopulmonary or vascular disease</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure with oliguria</td>
<td></td>
</tr>
<tr>
<td>Intravenous drug users or alcohol abuse</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8.5</th>
<th>Diagnostic criteria for brain death.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of cerebral function</td>
<td></td>
</tr>
<tr>
<td>Absent brainstem function</td>
<td></td>
</tr>
<tr>
<td>No pupillary or corneal reflex</td>
<td></td>
</tr>
<tr>
<td>No tracheobronchial reflex</td>
<td></td>
</tr>
<tr>
<td>No oculocephalic reflex</td>
<td></td>
</tr>
<tr>
<td>No pain response in cranial nerve segments</td>
<td></td>
</tr>
<tr>
<td>No seizures or posturing</td>
<td></td>
</tr>
<tr>
<td>Apnoea in response to acidosis</td>
<td></td>
</tr>
<tr>
<td>Irreversible comatose state</td>
<td></td>
</tr>
<tr>
<td>No sedating, paralysing or toxic drugs</td>
<td></td>
</tr>
<tr>
<td>No profound hypothermia</td>
<td></td>
</tr>
<tr>
<td>No gross electrolyte or endocrine disturbance</td>
<td></td>
</tr>
</tbody>
</table>
performed soon [5]. If consent from the next of kin is required, a trained transplant coordinator is likely to have the necessary skills to present organ donation as an opportunity for good amidst tragedy.

8.1.5 Kidneys from Living Donors

Organs from living donors could potentially make up for the shortage of cadaveric kidneys. There are several advantages of live‐donor renal transplantations: the donor and recipient operations can be planned and performed almost simultaneously so that ischaemia time is minimised. Secondly, persons selected for live kidney donation are healthy, and therefore, live donor kidneys are perfect kidneys in contrast to cadaver kidneys, which are often of comparatively poor quality.

In addition to the contraindications that apply to all donor kidneys (Table 8.4), the potential life donor must not be under emotional, social, or even financial pressures for the donation. The surgery for kidney retrieval has some morbidity, and a small but undeniable risk of mortality. There can be untoward psychological sequelae regardless of whether or not the transplantation is successful. Overall life expectancy is not impaired after kidney donation, but there seems to be a slightly increased risk of developing ESRD. Potential donors, therefore, have to be adequately counselled and need to understand all aspects of the sacrifice they are making.

The donor's medical work‐up has to include split renal function studies, an intravenous urogram or computed tomography (CT), and renal arteriograms as well as investigations aimed at identifying contraindications.

8.2 Technique of Removal of Donor Kidneys

8.2.1 Cadaver Donor

The donor who is brain dead needs to be conditioned for safe procurement of organs in good condition. Blood volume has to be increased by intravenous fluids and diuresis and cardiovascular stability need to be maintained (e.g. mannitol, diuretics).

Anaesthesia is not required for organ removal in donors who are brain dead. However, occasionally there are spinal reflex movements which can be disturbing to the staff and are not helpful for promoting organ donation. It is better to avoid this altogether by relaxation.

Donor kidneys need to be removed with long renal vessels, intact hilar fat, and the fine vessels that supply the ureter. In a heart‐beating donor, there is usually no need for haste, unless there is circulatory instability.

A long midline incision is made from the xiphoid process to the symphysis, for multiorgan removal, the thoracic cavity needs to be opened as well. All organs should be inspected for malignancy or infection. The ascending colon and small bowel are mobilised by incising their peritoneal reflections and placed on the chest (Figure 8.1). The superior mesenteric and coeliac arteries are divided for access to the aorta well above the renal vessels (Figure 8.2). Aorta and vena cava are taped just above the bifurcations, the aorta is clamped at the level of the coeliac artery, and a tube is inserted (Figure 8.3). Cooled preservation solution (4°C) is run in, usually 4L, until the effluent from the vena cava is quite clear. The perfusion cools the organs and reduces their metabolism as well as oxygen demand. Secondly, the organs need to be flushed free of all blood which would otherwise clot in all small vessels.

The aorta and vena cava can be removed en bloc with the kidneys, or they can be split open in the midline and divided posteriorly before removal (Figure 8.4). The latter approach allows for close inspection of additional renal vessels because it is of utmost importance to secure all renal arteries and veins if there are several. The upper two-thirds of the ureters are dissected, preserving their blood supply (Figure 8.5). The kidneys with their patch of aorta and vena cava are then removed and placed in a bowl of cooled perfusion fluid. A slice of splenic tissue is removed for tissue typing. The kidneys are then placed in sterile bags with perfusion fluid and packed into an ice‐cooled container for transportation.

As the feelings of relatives who may wish to see the deceased donor later need to be respected, wound closure should be diligent, including wound dressing, and furthermore, the body should be clean at the end of surgery.
Figure 8.2 (a and b) The superior mesenteric and (c) coeliac arteries are divided between ligatures.

Figure 8.3 Perfusion of the kidneys through a Foley catheter in the aorta.
8.2.2 Living Donor

Every living donor undergoes extensive and careful investigations to make sure that the remaining kidney is perfect, and that there is no unsuspected serious disorder that would put the donor at risk. There are few procedures as stressful for a surgeon as removing a good kidney from a healthy donor and transplanting it to another individual. The expectations of all involved that nothing whatsoever can go wrong are extremely high. It should be explained to the donor that the operation is safe and that there is a normal life expectancy with only one kidney. Mortality as a result of live kidney donation is low (about 0.05%, most of them from pulmonary}

Figure 8.4 The aorta and vena cava are removed en bloc with the kidneys and upper two-thirds of the ureters.

Figure 8.5 (a and b) The aorta and vena cava are slit open in the midline, carefully noting if more than one renal artery is present on either side.
8.2 Technique of Removal of Donor Kidneys

Embolism) [6]. However, there are data suggesting that live donors have a slightly increased risk of later developing ESRD themselves [7].

The choice of which kidney to use from a living donor depends on split renal function and angiography. If one kidney is better than the other, the better kidney should be left to the donor. If there are multiple vessels on one side, it is preferable to use the kidney with single vessels because this makes the transplant surgery easier and safer. If there are no differences between the left and the right side, it is preferable to take the left kidney because of its longer renal vein.

There are different ways of performing live donor nephrectomy: open, laparoscopic, or hand-assisted laparoscopic [8]. Whichever method is used, the main features are that dissection is meticulous, and the kidney removed with long vessel stumps and without any injuries. With open surgery, the incision should be as short as possible. Adequate exposure can be provided by a 12th rib bed approach but also by a subcostal incision, which tends to cause less postoperative pain. The renal vessels are dissected and taped (Figure 8.6). On the left side, care should be taken for the adrenal vein and a large lumbar vein usually entering the left renal vein posteriorly. The hilar fat should be left intact, and injury of the small ureteral vessel must be avoided. Then, the ureter is dissected distally and cut. Finally, first the renal artery is clamped, then the renal vein, and then both are cut. The kidney is placed in cooled preservation solution and organ perfusion is started (Figure 8.7).

It is advisable to have a scrubbed assistant ready to commence organ perfusion immediately because the warm ischemia time is crucial. Only then are the stumps of the renal vessels ligated. Great care must be taken for vascular control as donor complications must be avoided. The scar should be cosmetically acceptable. Perioperative antibiotics for the donor are advisable.

Warm ischemia time consists of the time between clamping of the renal vessels and starting cold organ perfusion plus the time later needed for suturing the vascular anastomoses when the organ is already in the recipient’s body. Total warm ischemia time should be as short as possible. Whether both donor and recipient are operated on at the same time in two theatres or one after the other is not of importance.

8.2.2.1 Preservation of the Kidney

For graft survival, organ conservation by perfusion and storage in a cooled solution is vital. The composition of the perfusate is aimed at reducing cellular oedema and potassium loss and minimising cellular oxygen demand and metabolic activity. There are three different commonly used solutions (Euro-Collins, University of Wisconsin, and histidine-tryptophan-ketoglutarate [HTK]). These solutions differ in composition (Table 8.6) [9, 10]. The HTK solution is widely used in Europe, and the Wisconsin University solution includes a synthetic colloid (hydroxyethyl starch) introduced for livers and is not widely used for kidneys. Using these fluids and keeping the kidney in a sterile ice-cold container can preserve them for many hours.

The success of kidney transplantation is highly dependent on ischemic time. Although kidneys can be transplanted more than 24 hours after removal from the donor, positive results decrease with every hour.

8.2.2.2 Inserting the Kidney

The surgical technique of renal transplantation is the same for kidneys from a cadaver or a living donor. The kidney is usually transplanted extraperitoneally into the contralateral iliac fossa. An oblique groin incision or a pararectal incision can be used. The inferior epigastric vessels can be preserved. The peritoneum is reflected medially, and the common iliac vessels and the bladder are exposed (Figure 8.8).

![Figure 8.6 Living donor nephrectomy. On the left side beware of a circumaortic renal vein, or a large lumbar vein entering the renal vein at this point.](image-url)
Usually, an end-to-side anastomosis of the renal vessels to the external iliac vein and artery is performed (Figure 8.9). In case of recipient atherosclerosis, a patch with as little atheroma as possible should be selected. Sometimes the anastomosis has to be done on the common iliac or end-to-end onto the internal iliac artery (Figures 8.10 and 8.11). This latter option has the disadvantage of disrupting distal pelvic blood supply in patients who often already have peripheral vascular disease. Care should be taken to ligate the lymphatics in the connective tissue sheath of the vessels to prevent the subsequent formation of a lymphocele.

If there are problems of space or extensive scarring because of a prior surgery, the renal vessels can also be anastomosed directly to the lower aorta and vena cava as is commonly done in paediatric transplantation.

The venous anastomosis should be done first and should be wide to prevent outflow obstruction. A 4–0 or 5–0 monofilament suture (e.g. Prolene) is used after clamping the iliac vein with a Satinsky clamp, opening it with a scalpel and flushing it with a heparinized solution of physiological saline. Similarly, the arterial anastomosis is done with a 5–0 or 6–0 suture after spatulating the renal artery. The vessels are flushed with heparinized saline to expel the air before the sutures are tied.

When there is more than one renal artery, it is preferable to have them on one aortic patch for a single anastomosis as this reduces anastomotic time, which is crucial.

### Table 8.6 Possible causes and differential diagnosis of delayed graft function.

<table>
<thead>
<tr>
<th>Dehydration</th>
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<tbody>
<tr>
<td>Arterial stenosis</td>
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<tr>
<td>Venous thrombosis</td>
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<tr>
<td>Urine leak</td>
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<tr>
<td>Ureteral obstruction</td>
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<td>Catheter obstruction</td>
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<td>Acute rejection</td>
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<tr>
<td>Acute tubular necrosis</td>
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<tr>
<td>Nephrotoxicity of immunosuppression</td>
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</tbody>
</table>

Figure 8.7 The donor kidney is irrigated with ice-cold preserving fluid until the fluid emerging from the renal vein is seen to be clear.

Figure 8.8 Extraperitoneal exposure of the common and internal iliac vessels.

Figure 8.8.1 Extraperitoneal exposure of the common and internal iliac vessels.
8.2 Technique of Removal of Donor Kidneys

because it represents warm ischemia (Figure 8.12). However, this is not always possible in which case it is necessary to anastomose each renal artery separately. If the recipient artery is found to be very atheromatous, endarterectomy can be done or a prosthetic vascular replacement may need to be inserted.

When the vascular anastomoses have been done, bulldog clamps are put on the renal vessels before the clamps are taken off the iliac vessels. Only when both anastomoses are satisfactory are the bulldog clamps removed; the venous before the arterial clamp and graft reperfusion begun (Figure 8.13). The pulse of the renal artery should be clearly palpable and the filling of the renal vein visible. With good perfusion, the colour of the transplant turns from white to a healthy pink quickly.

For the ureterovesical anastomosis, standard techniques such that of Lich-Gregoire can be used can be used. Because postoperative ureteral problems are more often those of stenosis rather than reflux, it is preferable to do a simple anastomosis with only a short submucosal tunnel on the anterior part of the bladder (Figure 8.14).

The ureter should be spatulated and a short double-J stent inserted.

8.2.2.3 Postoperative Complications

Graft function depends on good perfusion; therefore, a duplex ultrasound within the first 24 hours is done. If there are problems either with inadequate arterial perfusion or obstructed venous outflow, an early reoperation to correct the problem may be necessary. Venous obstruction often leads to renal vein thrombosis and graft loss. Problems with arterial perfusion can be the result of intimal lesions, dislodged atherosclerotic plaques, or more commonly, kinking of the renal artery. Kinking requires
surgical revision and placing the kidney medially without re-anastomosis. Anastomotic arterial stenosis can be managed by interventional dilatation [11].

Secondary bleeding with hematoma or urinoma or a lymphocele formation may occur. More often than in nontransplant surgery, these require revision surgery because the risk of infection is greater, but conservative treatment is preferable. Lymphoceles can compress vessels or the ureter. Ureteral anastomotic stenosis needs stenting, dilatation, or reimplantation.

Spontaneous rupture of the graft is a life-threatening complication leading to massive haemorrhage but has become rare with modern immunosuppression. Acute rejection can occur precipitated by failure to take the medication, infection or a blood transfusion.

8.2.2.4 Delayed Graft Function

Early anuria of the transplanted kidney is a common complication in cadaver kidneys and is usually due to acute tubular necrosis (ATN) resulting from severe ischemic damage [5]. It is, however, necessary to exclude all other correctable causes (Table 8.7).

The patient may be dehydrated. After years on dialysis, many patients find it difficult to change from a restricted fluid intake to copious intake. Intravenous infusions may need to be given.

There may be complications causing urinary obstruction. The simplest problem is a misplaced or obstructed bladder catheter. There may be ureteral anastomotic stenosis or insufficiency. Ultrasound will show a full or an empty bladder, hydronephrosis of the transplant kidney, or a perivesical fluid collection (urinoma). Transplant

Figure 8.12 Where there is more than one renal artery, both should be left on one aortic patch, which is sewn onto the side of the external iliac artery.

Figure 8.13 The vascular anastomoses are completed, and the submucosal tunnel is then prepared in the bladder for the ureter.

Figure 8.14 (a and b) A wide elliptical anastomosis is made between the ureter and bladder mucosa. (c) The terminal 5 cm of ureter are buried in a loose tunnel of bladder muscle.
hydronephrosis and urinoma will need a double-J catheter or a percutaneous nephrostomy before revision surgery.

Doppler ultrasound will show impaired graft perfusion by arterial stenosis or venous thrombosis. For arterial stenosis, interventional angiography may be required. Venous thrombosis leads to graft loss. Doppler sonography will also show the resistance index which if increased (>0.8) indicates rejection [12]. Blood levels of nephrotoxic immunosuppressants may be too high, requiring dose adjustments.

If these causes have been excluded, a biopsy will show either rejection or ATN. ATN is a completely reversible process and patience is needed.

8.3 Immunology of Organ Transplantation

An organ transplanted from an identical twin is not rejected as demonstrated by the first kidney transplantation performed in Boston in 1955 [13]. All other organ transplantations from one individual to another of the same species (an allograft) undergo recognition and rejection by the recipient’s immune system. Unless the immune response is effectively suppressed, the recipient’s immune system will destroy the graft.

8.3.1 The Major Histocompatibility Complex

Recognition of a transplanted organ as ‘non-self’ is caused by the recipient’s immune system recognising antigens on the cell surface of donor cells. These antigens are found in vertebrates on most nucleated cells and are determined by a set of genes on chromosome 6, called the ‘major histocompatibility complex’ (MHC). There are also minor histocompatibility (miH) factors, which can lead to graft rejection between siblings, even when all the known antigens of the MHC have been correctly matched.

The genes of the MHC system are divided into classes I, II, and III. MHC class I proteins are cell surface glycoproteins consisting of two chains; the heavy chain activates CD8 T-cells, and the light chain CD4 T-cells. MHC class II proteins are expressed only on B-cells, dendritic cells (DCs), and some endothelial cells. MHC class III genes encode for mediators such as tumour necrosis factors (TNF-α and -β).

One-half of the MHC genes come from the father, and the other half from the mother. Siblings and parents, therefore, have half their MHC antigens in common (Figure 8.15). With two alleles at each MHC locus, most individuals can express six different MHC class I proteins and eight different MHC class II proteins. Combined with the polymorphism at this locus, this means for unrelated individuals that MHC-identical donors and recipients are extremely rare. Even if they are found, miH antigens are invariably different. Complete identity is only possible with monozygotic twins.

Patients who have been exposed to MHC antigens through previous transplantation, transfusions, or pregnancy often develop antibodies against those MHC antigens (preformed antibodies).

8.3.2 The Human Leucocyte Antigen System

In humans, the MHC is called the ‘HLA system’ because it was first studied on white blood cells.

The HLA system is a complex multigene family of more than 10 loci. The genes and their products are classified into two types: HLA class I and HLA class II. HLA class I genes are situated at the telomeric end of the 6p21.3 region of chromosome 6 (Figure 8.16). This region encodes the classic transplantation antigens HLA-A, HLA-B, and HLA-C, which are expressed on nucleated cells. There are many other class I HLA loci.

The HLA class II region consists of three main loci (i.e. HLA-DR, HLA-DQ, and HLA-DP). The gene products are expressed on cells with immune functions (i.e. B-cells, activated T-cells, and antigen-presenting cells) and is induced during inflammatory processes.

Graft survival correlates with the number of HLA haplotypes shared by the donor and recipient. Therefore, HLA matching is done for organ allocation. However, there is large polymorphism of HLA proteins expressed because of variations of several or even single amino acids. This means that HLA specificities can be further subclassified by serological methods and even more so by DNA-based typing methods.

8.3.3 The ABO Blood Group System

With cadaver donor transplantation, donor and recipient must have the same ABO blood group. Antibodies to the ABO blood group antigens are preformed or natural antibodies. ABO incompatibility between donor and recipient leads to hyperacute rejection.

According to the frequency of the different ABO blood groups in the population, there is a shortage of A donors, and patients with this blood group on average have a longer waiting time for a kidney, especially if they are rhesus negative.

In ABO-incompatible live-donor transplantation, the recipient’s ABO antibodies can be removed by repeated
immunoadsorption and the use of B-cell depleting drugs (rituximab) before transplantation. The later reappearance of these antibodies is generally not associated with rejection (i.e. accommodation) [14].

8.3.4 HLA-Typing in Renal Transplantation

The number of HLA-specificities that can be routinely tested is limited. These are the three class I antigens HLA-A, HLA-B, and HLA-C and three class II types HLA-DR, HLA-DQ, and HLA-DP. Because of the polymorphism of HLA-antigens, this typing with broad specificity may result in ‘good matching’ but at a more specific level, several mismatches may actually be present [15].

More specific matching is not feasible for several reasons. The logistics of matching for such a diverse polymorphic antigenic system are complex; the increased ischemia time associated with an extensive matching process would lead to poorer outcomes, and there is a diminishing effect of HLA matching on transplantation outcome with modern more potent immunosuppressive regimens.
However, even with limited matching, the chance of finding an HLA identical recipient is small. It is higher if there is a large pool of recipients with their HLA status kept on a central register. The kidneys are sent to the best matched available recipient. Complete identity of the six HLA loci tested (a ‘full house’ organ) is desirable. In practice, for most renal transplantations, there are between one and three mismatches.

### 8.3.5 Cross-Matching and Preformed Antibodies

Patients with donor-specific sensitising have a high risk of hyperacute rejection, but this has been virtually eliminated by routine cross-matching. This consists of testing donor lymphocytes and recipient serum for preformed antibodies. There are different techniques of cross-matching, and there is an ongoing debate about which preformed antibodies are damaging and which are not. In most cases, IgG HLA class I and class II-specific antibodies represent a contraindication to transplantation.

Highly sensitised patients are those with more than 85% of preformed antibodies. To find acceptable donors for such patients, ‘acceptable mismatch programs’ have been instituted by many programs defining minimal criteria (e.g. for the HLA-DR locus). Another approach is allowing for paired live donor transplantation [16].

### 8.4 Graft Rejection

The response to a transplantation occurs in a series of relatively well-defined stages.

#### 8.4.1 Reperfusion Injury

The first stage results from the severe physical assault that the organ is subjected to during harvest from the donor including the haemodynamic and neuroendocrine responses to brainstem death and transplantation into the recipient including many hours of preservation under artificial conditions. All these events sensitise the organ to ‘reperfusion injury’ when it is warmed rapidly on revascularization in the recipient.

During and shortly after the ischemia and reperfusion periods, a variety of genes become activated and inflammatory cells begin to infiltrate the graft. The effectors of this first nonadaptive and not antigen-specific response are part of the innate immune system (i.e. activated endothelial cells, macrophages, and interleukins [IL-1, IL-6]) as well as complement factors. The inflammatory response also triggers the migration of bone-marrow derived donor DCs out of the graft.

This early response does not constitute graft rejection, but the severity of the initial injury and the subsequent inflammatory reaction are central in the stimulation of antigen-specific immunity later. A much damaged organ generates a strong ‘danger signal’, which initiates stronger responses when donor and recipient are antigenically different.

#### 8.4.2 Adaptive Immunity

The next phase is characterised by presentation of donor antigens to infiltrating recipient T-cells which then become activated, proliferate, and differentiate to a variety of other cells, which infiltrate the graft and destroy it unless effectively suppressed (Figure 8.17). The antigens that stimulate graft rejection are cell surface MHC (HLA) antigens and numerous mH systems. Incompatibility for either MHC or mH antigens lead to an immune response, but rejection is stronger with MHC incompatibilities [17].

#### 8.4.3 Antigen Presentation

For a strong immune response, MHC antigens need to be presented to the recipient. Bone-marrow derived DCs, which migrate from the graft into the recipient, are essential (direct antigen presentation). They present MHC class I and class II antigens, produce various costimulators and cytokines, and stimulate T cells, especially CD4+ and CD8+ cells. Recipient DCs, which infiltrate the graft, are also capable of recognising donor MHC antigens and presenting this antigenic information to immune system effectors (indirect antigen presentation).

#### 8.4.4 Types of Immune Response

Activation of T-cells requires several costimulatory signals for downstream intracellular activation, such as CD28. Following this, B-cells, DCs, and monocytes are activated. A response develops, which is either predominantly cell-mediated or humoral. Which of the two happens is largely cytokine-regulated.

Interferon-γ (IFN-γ) is the prototypical cytokine, and if it dominates, the rejection will be cell-mediated leading to the appearance of activated macrophages and specific circulating T-cells. If IL-4, -5, and -6 predominate, this will lead to humoral rejection. Thus, the local cytokine milieu seems to be important for determining which type of rejection occurs.

#### 8.4.5 Migration of Activated Cells

Activated leucocytes migrate into the graft by adhering to the graft endothelium. This requires complex leucocyte-endothelial interactions involving specific proteins (i.e. selectins, integrins, and immunoglobulins). Selectins control the first loose attachment of leucocytes (‘rolling’
along endothelial surfaces, which leads to the endothelial cells expressing IL-8 and platelet-activating factor. These lead to stronger leucocyte adhesion and arrest of the rolling process. L-selectin and other proteins produced by the leucocytes enables extravasation.

Chemokines from the graft such as α-chemokines (which attract neutrophils and T-cells) and β-chemokines (which attract monocytes/macrophages, DCs, and natural killer [NK] cells) support graft infiltration.

8.4.6 Graft Destruction

The immune response mounted depends on antibodies, unspecific cellular reactions as well as specific cytotoxic cells and cytokines. Antibodies can fix complement, especially complement component 4d (C4d), which recruits macrophages and activates endothelial cells. The point of entry, and therefore, the site of the most severe inflammatory reaction and destruction is the endothelial structure of the graft. Destruction of the small vessels of the graft occurs primarily and can be seen histologically while parenchymal changes are secondary to destruction of the vasculature.

8.4.7 Clinical Types of Rejection

There are three types of rejection: hyperacute, acute, and chronic.

8.4.8 Hyperacute Rejection

Hyperacute rejection is due to preformed antibodies (donor-specific HLA class I antibodies) and can occur intraoperatively or within hours postoperatively. With hyperacute rejection, the graft kidney swells, takes on a dark colour, and infarcts within minutes of its circulation being restored.

Recipient antibodies against donor HLA antigens bind to the vascular endothelium of the graft, disrupt intercellular junctions, and induce the release of mediators leading to rapid uncontrollable activation of intravascular thrombotic and complement activation [18]. This results in intravascular coagulation and interstitial haemorrhage and destruction of the graft within minutes.

8.4.9 Acute Rejection

Acute rejection occurs any time after about one week up to three months. It is a result of cell-mediated immunity in the majority of cases, whereby the graft is infiltrated by large numbers of activated T-cells (cellular rejection). Clinically, the kidney swells, becomes tender, and its function declines. There may be systemic symptoms such as fever, malaise, or hypertension. Acute rejection can also, less commonly, be predominantly mediated by antibodies (humoral rejection).

Acute rejection can be initiated by failure to take the drugs, infection, or a blood transfusion. Transplant biopsy is required, showing dense cellular infiltration and oedema and can determine the type of rejection and its severity (i.e. Banff classification) [19].

8.4.10 Chronic Rejection

Chronic rejection can occur any at any time after transplantation and is a gradual deterioration in renal function which does not improve when the dose of immunosuppressants is increased. Biopsy shows interstitial
fibrosis and tubular atrophy, which are the hallmarks of chronic rejection; there is also intimal fibrosis of arteries with hyalinization of glomeruli. Chronic rejection is a slow process which seems to occur in many renal transplants over the years and is held responsible for the slow but steady decline of transplant function starting many months or years after successful transplantation. It underlies the late graft loss seen in many patients [20].

8.5 Immunosuppression

Immunosuppressive treatment is always a combination of several drugs to maximise immune suppression; however, it increases the likelihood of side effects.

8.5.1 Corticosteroids

Steroids reduce T-cell proliferation and inhibit the production of IL-2 and of IL-1 and IL-6 in macrophages. They also inhibit the migration of monocytes to areas of inflammation such as acute rejection. Prednisone and prednisolone are metabolised in the liver where prednisone is converted to prednisolone. Their half-lives are increased in hepatic disease and shortened if taken together with drugs that induce hepatic enzymes. The sensitivity of lymphocytes to steroids can vary individually as well as under the influence of other immunosuppressants, accounting for the so-called ‘steroid resistance’ seen in some patients.

Side effects of steroids are numerous, and considerable and most protocols today aim at tapering the steroid dose shortly after transplantation or using a steroid-free maintenance protocol. Large-dose steroid treatment is used in acute rejection.

8.5.2 Azathioprine

Azathioprine was used until cyclosporine became available. It is a derivative of mercaptopurine, is activated by hepatic metabolism, and inhibits purine synthesis, blocking DNA and RNA synthesis in lymphocytes and IL-2 production. It is catabolised by xanthine oxidase, and thus, there is an interaction with allopurinol. Azathioprine has been largely replaced by mycophenolate, but it is an inexpensive drug still used in many countries.

8.5.3 Calcineurin Inhibitors: Cyclosporine and Tacrolimus

8.5.3.1 Cyclosporine

Cyclosporine became available in the 1980s and revolutionised renal transplantation by markedly improving graft survival. It is a fungal product and inhibits CD4+ T-helper cells, preventing IL-2 and cytotoxic T-cell induction. Cyclosporine binds to an intracellular protein (i.e. cyclophilin A), which inhibits a Ca2+-dependent phosphatase (i.e. calcineurin). Calcineurin is part of an intracellular signalling pathway leading to the expression of IL-2.

8.5.3.2 Tacrolimus

Tacrolimus also binds to an intracellular protein (FK BP-12), which inhibits calcineurin, blocking T-cell activation and IL-2 production. It is 10–100 times more potent than cyclosporine. Oral bioavailability is limited (25–30%) and 99% is plasma protein-bound. Long-term graft survival with tacrolimus is better than with cyclosporine [21].

Both calcineurin inhibitors are given orally, and drug levels have to be controlled. Hepatic clearance (cytochrome P450) leads to numerous drug interactions. Calcineurin inhibitors are nephrotoxic. This can occur early in kidneys with marked ischemic damage or within weeks associated with high serum levels, or there can be late, chronic nephrotoxicity, leading to progressive loss interstitial graft fibrosis.

8.5.4 Mycophenolate Mofetil (MMF)

Mycophenolic acid (MPA), also a fungal product, inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH) and thereby the synthesis of guanosine nucleotides in T- and B-cells. A synthetic analogue of MPA, mycophenolate mofetil (MMF), has better oral bioavailability. MMF is rapidly metabolised to an inactive glucuronide, but has a long half-life (17 hours), but plasma levels need to be monitored. Gastrointestinal side effects (diarrhoea, indigestion, and reflux) and bone marrow toxicity occur. With MMF, viral infections are more common.

8.5.5 mTOR Inhibitors

Sirolimus and everolimus block T-cell proliferation by inhibiting the mammalian target of rapamycin (mTOR) [22]. Sirolimus (rapamycin) is the product of a microorganism first isolated from soil from the Easter Island (Rapa Nui), giving it its name, and everolimus is a synthetic analogue. Both bind to an intracellular immunophilin (FK506-binding protein) which forms a complex with a serine-threonine kinase (mTOR). This is a key point in the cell cycle regulatory pathway. Both drugs block lymphocyte proliferation and IL-2 transcription and inhibit tumour cell growth. The incidence of post-transplant malignancy is reduced. Specific side effects are changes in lipid metabolism, delayed graft function, bone marrow suppression, and disturbed wound healing [23].

Sirolimus has a long half-life (60 hours), but everolimus has a short half-life (16–18 hours). Both drugs are
given orally. Dosing should be concentration controlled and metabolism is also by cytochrome P450 (CYP3A4).

8.5.6 Antibodies

Antibodies are used for the treatment of rejection. By immunising animals with human lymphocytes, heterogenous polyclonal sera can be obtained, which contain many antibodies with largely undefined specificities (i.e. antithymocyte globulin [ATG]). Polyclonal antibodies react with many different antigens and the animal proteins can cause allergic or anaphylactic responses. Fever, urticaria, rash, and headaches occur. The physiological half-life of these antibodies is several weeks.

With cell hybridization, monoclonal antibodies (mAb), which suppress T-cells and their subsets, are available. MAb preparations contain a single specific antibody and their action is more predictable. OKT3 (muromumab, murine anti-CD3) is an IgG2a mouse antibody binding human CD3. It mediates complement-dependent cell lysis and rapidly clears T-cells from the circulation.

Polyclonal and monoclonal preparations with anti-T-cell antibodies are used for the treatment of steroid-resistant rejection. Other specific mAbs are anti-CD25 (daclizumab, basiliximab), anti-CD25 (alemtuzumab), and anti-CD20 (rituximab) which can be used for induction and rescue treatment. The B-cell depleting effect of rituximab is used for ABO-incompatible transplantation and for the treatment of humoral rejection.

8.5.7 Belatacept

Belatacept is a fusion protein and acts as a selective blocker of T-cell-costimulation. It binds to CD80 and CD86 on antigen-presenting cells. This blocks the CD28-costimulation of T-cell activation [24]. It is given as an induction treatment and during the first weeks after transplantation. Ebstein-Barr virus infections and posttransplantation lymphoproliferative disorder (PTLD) seem to occur more frequently with belatacept.

8.5.8 Side Effects of Immunosuppression

All immunosuppressive agents have side effects which occur with time even after years of treatment. Azathioprine causes bone marrow depression. Corticosteroids induce diabetes, osteoporosis, obesity, and other unwanted effects. MMF can cause leucopenia and thrombocytopenia. Tacrolimus is diabetogenic. Calcineurin inhibitors can provoke hypertension and are nephrotoxic. mTOR inhibitors cause gastrointestinal problems and disturbances in wound healing.

Infections and the development of malignancies are more common with immunosuppression. Infections with ubiquitous viruses (i.e. cytomegaly, herpes simplex, zoster, and BK virus) are common after renal transplantation, especially with MMF treatment. Urinary tract infections can lead to pyelonephritis and graft dysfunction. Infectious agents not dangerous to immunocompetent hosts can be life-threatening in transplant recipients (e.g. pneumocystis).

The incidence of de novo malignancies is increased about 10-fold with immunosuppression, the most common being skin cancers. The risk of malignancy is proportional to the immunosuppressive potency but lowest with mTOR inhibitors. A specific malignant disorder due to immunosuppression is the PTLD.

8.5.9 Immunosuppressive Treatment Regimens

Immunosuppressive treatment used can be characterised as induction, maintenance, or rescue therapies. Induction immunosuppression is intensive treatment used to suppress immune responsiveness at the time of transplantation. Maintenance treatment is less potent but is tolerable for long-term use in a steady state. Rescue therapy is used with acute rejection and is – like induction therapy – intense and fairly toxic so that it cannot be given for prolonged periods of time.

8.5.9.1 Induction Treatment

Induction treatment is started before the transplantation procedure and continued for the first week. It is used in patients at high risk of rejection (e.g. second transplantations, preformed antibodies, high number of HLA mismatches). Monoclonal or polyclonal antibodies can be used. Induction treatment should be an individualised decision because side effects can be severe.

8.5.9.2 Maintenance Treatment

This consists of a combination with the early use of steroids tapered to a long-term low-dose or steroid-free regimen. Combinations of two or three drugs of different classes are used. Most centres have their preferred maintenance regimen based on experience which is adjusted to individual circumstances (Table 8.6).

8.5.10 Treatment of Rejection

The treatment of rejection requires biopsy, which will determine which type of rejection is present. First-line treatment is by high dose steroids for three days. Failing this, humoral rejection requires plasmapheresis and perhaps rituximab. Second-line treatment for cellular rejection is by antibodies (i.e. ATG, OKT3). In addition, the maintenance immunosuppressant may need to be changed [25].
8.5.11 Pregnancy after Renal Transplantation

Successful renal transplantation restores fertility and successful pregnancy is possible. Conception is possible after the first transplant year, provided immunosuppression is stable, and there have been no rejections. Hypertension during pregnancy is a common problem in transplant patients. Delivery can be vaginal, but obstetricians usually prefer caesarean section. There are very few data on any effects of immunosuppression on intrauterine development or during breast feeding.

8.5.12 Long-Term Treatment of the Recipient after Renal Transplantation

Patients who have had a transplant need close medical care. Immunosuppression and compliance with treatment, especially in children and adolescents, need to be supervised. Complications such as infections need early treatment. Bladder function is critical especially in patients who are older. Patients need to be regularly screened for de novo malignancies. Urothelial upper tract tumours of the native kidneys are relatively common. Maintenance immunosuppression requires blood level measurements at defined intervals.

References


9

Kidney and Ureter

Congenital and Acquired Anomalies

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Abstract

Understanding the pathophysiology of congenital and acquired renal and ureteric anomalies is vital to be able to appropriate overall management. We describe the most common types of these anomalies.

Keywords renal duplication; duplex; ectopia; horseshoe kidney; cyst; ureterocele; megaureter; pelviureteric junction (PUJ) obstruction

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9.1 Introduction

In this chapter we will discuss the various congenital anomalies of kidneys and ureters. The tumours involving the upper renal tracts are described in separate chapter.

9.2 Congenital Abnormalities of the Kidney

9.2.1 Embryology

Renal anomalies are amongst the most common of all organ systems. When an ultrasound is used as screening test in healthy infants, around 3.2% are found to have genitourinary tract anomalies, half of these requiring surgery [1]. During the fourth and fifth weeks of gestation, the ureteral bud begins to develop from the distal portion of the mesonephric duct. The cranial end of the ureteric bud meets the metanephrons and continues in its cephalic migration. During this process, it forms the pelvis, calyces, and part of the collecting ducts. At the same time, the metanephros differentiates into organised renal parenchyma around the collecting system. The kidneys assume their final position at the eighth week of gestation. During ascent, they rotate 90° on the axial plane, starting with the hilum facing forward and ending with it facing medially. The blood supply changes during the migration; initially the kidneys are supplied by the middle sacral artery, then by the common iliac, and finally by the aorta [2].

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9.2.2 Anomalies in Number

9.2.2.1 Supernumerary Kidney
This is a very rare anomaly due to duplication of the ureteric bud and a split mesonephric blastema. The supernumerary kidney is caudal to the ipsilateral kidney in 60% of cases. If a complete ureteric duplication occurs (around 50% of cases), the supernumerary kidney is likely to be cranial. There is usually one extra kidney, but cases of multiple extra kidneys have been reported. The supernumerary kidney has its own blood supply and capsule, is usually smaller, less functioning, and in a third of cases, is associated with other pathological changes (e.g. hydronephrosis, pyelonephritis). Many cases remain asymptomatic throughout life and are picked up incidentally on ultrasound. When complications occur, these are generally correlated with obstruction or infections and presents with typical symptoms of pain, abdominal mass, or fever [3].

9.2.2.2 Unilateral Renal Agenesis
Renal agenesis results from a failure of induction of the metanephric blastema by the ureteric bud [4]. Unilateral renal agenesis incidence is around 1:1100–1500 and occurs in similar sex ratios with a left-sided preponderance (Figure 9.1) [5, 6]. However, foetal ultrasound series have found a much lower frequency of this anomaly, postulating that many reported adult cases of unilateral renal agenesis probably represented involuted multicystic or dysplastic kidneys (Figure 9.2) [7].

9.2.2.2.1 Associated Anomalies
The ipsilateral ureter is absent in 50–87% of cases [8]. In case of complete ureteric agenesis, a hemi-trigone is seen on cystoscopy. The other kidney may be affected by vesicoureteric reflux (VUR), vesicoureteric junction (VUJ) obstructions, and pelviureteric junction (PUJ) obstructions [9]. The most common associated anomalies are those of the female genitalia, with an overall incidence of 20–60% and are a result of müllerian duct anomalies [5, 10]. Most of those are asymptomatic, but hydrocolpos or hematocolpos due to a blind vagina might develop at puberty with a pelvic mass or cyclical pain or cryptomenorrhoea. The uterus is often unicorne or bicornuate, and the ipsilateral Fallopian tube may be rudimentary or absent [11]. Vas deferens, seminal vesicle, and ejaculatory duct are absent in 50% of males with unilateral renal agenesis [11]. Around 25–40% of patients with unilateral renal agenesis have other abnormalities, most commonly within the cardiovascular and gastrointestinal systems.

9.2.2.2.2 Diagnosis
Ultrasound is the initial investigation; however renal ectopia or a hypertrophic adrenal gland can give the false-positive presence of a small kidney. Dimercaptosuccinic acid (DMSA) renogram should be performed in all the cases of suspected agenesis. If the child is potty-trained, a MAG3-IRC can be useful in demonstrating possible contralateral VUR. Ultrasound of parents and siblings is recommended because a 9% incidence of asymptomatic renal malformations has been reported [12].

9.2.2.2.3 Prognosis
Hypertrophy of the single contralateral kidney occurs. Although hyperfiltration may have an adverse effect on renal function, the risk of significant renal disease is low [13]. Annual urinalysis for proteinuria and blood pressure check is reasonable.

9.2.2.3 Bilateral Renal Agenesis (Potter Syndrome)
The incidence of bilateral renal agenesis was originally reported by Potter as 1 in 4800 births [14]; however, more recently the incidence is lower and estimated at 3.5 per 100 000 [8]. The risk of recurrent Potter syndrome in subsequent pregnancies is 2–5% [15]. Oligo- and anhydramniosis at 14–16 weeks of gestation, non-visualisation of kidneys and non-visualisation of urinary bladder is
9.2 Congenital Abnormalities of the Kidney

Diagnostic on foetal ultrasound. Around 40% of the infants are stillborn and in the remaining, along with absent renal function, oligohydramnios has caused severe pulmonary hypoplasia. A characteristic fascial deformity occurs because of the lack of growth and development (Figure 9.3). The prognosis is poor, and the majority will die within 24 hours of being born. In cases of early antenatal diagnosis, termination of pregnancy is recommended.

9.2.3 Anomalies of Rotation

The foetal kidney faces its hilum and pelvis anteriorly, and during ascent, undergoes a 90° rotation to achieve its final normal position where hilum and pelvis face medially. Different types of anomalies of rotation are described:

- Incomplete rotation: the most common, hilum faces anteriorly;
- Hyper-rotation: with hilum dorsal or lateral;
- Reverse rotation: hilum faces lateral and renal vessels cross the kidney anteriorly; and
- Malrotation is more frequently associated with ectopic or fused kidney and is incomplete in its commonest form. Usually it is an asymptomatic condition, and when symptoms occur, those are generally correlated with a degree of obstruction and hydronephrosis.

9.2.4 Anomalies of Ascent

Anomalies of renal ascent and fusion occur at six to nine weeks of gestation as the kidneys seem to ascend when in fact the embryo is growing caudally. The kidney is generally abnormal in position because of insufficient or contralateral ascent (classic form of renal ectopia and crossed kidney) or because of excessive ascent (thoracic kidney, much rarer).
9.2.4.1 Renal Ectopia
Renal ectopy refers to a kidney outside its renal fossa. The ectopic kidney can be ipsilateral or can have crossed the midline when malrotation is often associated. The condition is bilateral in 10% of cases. The ipsilateral ectopic kidney is more often within the pelvis (usually below aortic bifurcation), but it can also be lumbar (above the iliac crest but below L-2/L-3) (Figure 9.4) [16]. Pelvic kidneys occur in 1 in 2000–3000, and the left kidney is affected more often than the right (see Chapter 3). The renal pelvis is positioned anteriorly, and there is a short ureter to the level of the sacrum. Ptotic kidney maintains a normal ureteric length and ureter can be redundant, whereas the ureter of an ectopic kidney is shorter in relation to the degree of ectopia. During ascent the blood supply changes (from middle sacral artery to iliac artery and later aorta), the final blood supply is invariably anomalous with blood vessels, which are usually short, making surgical mobilisation difficult.

The majority of pelvic kidneys are diagnosed incidentally, but they can be complicated by obstruction, hydronephrosis, infection, or symptoms from the presence of an ectopic ureter.

9.2.4.1.1 Diagnosis
Ectopic kidneys can be completely asymptomatic or can give symptoms due to concomitant PUJ obstruction, VUJ obstruction, and VUR. PUJ obstruction in ectopic kidneys is the result of a high ureteral insertion, malrotation, or anomalous vessels. A certain degree of slow drainage accounts for the possibility of urolithiasis. Amongst clinically significant ectopic kidneys, around 30% present with urinary tract infections (UTIs). Ultrasound can detect the ectopic kidney antenatally and postnatally. The failure to detect renal parenchyma on one side should lead to a renogram before making the diagnosis of unilateral renal agenesis. Micturating cystourethrogram (MCUG), MAG-3, and magnetic resonance urography (MRU) should be taken into consideration in specific cases.

9.2.4.1.2 Associated Anomalies
VUR is found in 70–85% of children with an ectopic kidney [17], and the contralateral kidney is abnormal in up to 50% of patients. Contralateral renal agenesis has been found in 10% of ectopic kidneys. Genital anomalies are frequent in both sexes; in male, the most common are hypospadias and cryptorchidism. Other organs might have anomalies as well; in particular, skeletal anomalies are found in up to 50% of children.

9.2.4.1.3 Management
The most common clinical problem is PUJ obstruction. Urolithiasis might be difficult to treat because the kidney can be more distant from the skin surface, and there can be bowel interposition. Ureterorenoscopy (URS) can also be challenging if the insertion of the ureter is high in the pelvis of the ectopic kidney.

9.2.4.2 Thoracic Kidney
In a thoracic kidney, part or all of the affected renal tissue must sit above the diaphragm. This anomaly represents <5% of renal ectopy and has an incidence on autopsy of 1:13 000 (Figure 9.5) [2]. The thoracic kidney may result from an accelerated ascent process before the closure of the diaphragm or a delay in the diaphragmatic closure. It is usually completely rotated with the vascular supply

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**Figure 9.4** DMSA (posterior view) of a three-month-old girl with asymptomatic, well-functioning, left pelvic kidney: a case of simple renal ectopia.

**Figure 9.5** When there is a herniation of the diaphragm, the kidney may be seen in the chest, but it is not truly an ectopic kidney.
arising from the abdominal aorta, and the kidney is usually well functioning. The ureter is long to compensate the distance to the bladder and PUJ obstruction has been reported [18]. Again, as generally asymptomatic, the diagnosis may be suspected at chest X-ray for other reasons, which identify a possible mass or raised hemidiaphragm. MRU can confirm the diagnosis.

9.2.5 Anomalies of Fusion

9.2.5.1 Horseshoe Kidney

In a horseshoe kidney (HSK), the two lower poles of the kidney are joined in the midline by tissue called the ‘isthmus’. The result is the horseshoe kidney lies lower at L3/L4 compared to the normal anatomical position because the isthmus is unable to ascend past the inferior mesenteric artery. The calyces are normal in number; however, they are abnormal in position with calyces pointing posteriorly. The blood supply is often abnormal. The HSK is the most common fusion anomaly with an incidence of around 0.25% of the population (1:700) (see Chapter 3) [19].

Embryologically many theories have been postulated; certainly, there is an early medial contact between the two metanephric blastema, which can be due to a narrow passage through the space in between the umbilical arteries (arterial fork) during the ascent. The theory of ectopic metanephric blastema has also been postulated.

9.2.5.1.1 Anatomy

In 90% of the cases, the isthmus connects the lower poles of the two kidneys, and the renal units usually lie lower than normal probably because the inferior mesenteric artery stops the ascent of the HSK at the level of its origin from the aorta. However, the HSK can be anywhere from the true pelvis to the normal location. The isthmus can be functional or fibrotic. In the vast majority, the isthmus maintains some function. It is commonly in front of the great vessels but can be behind the aorta or inferior vena cava. Its blood supply is very variable. The arterial supply has been investigated deeply considering its importance in case of abdominal aortic aneurism.

It appears clear that, although renal arteries arising in a normal location are common (around 80%), extra arterial branches should be expected from the infrarenal aorta or from the iliac arteries. Other origins (e.g. medial sacral artery) are rare. The multitudes of vessels, which can supply the HSK, explain its lack of mobility.

The two renal units are usually malrotated, with the pelvis anteriorly faced because fusion happens before the completion of the rotation. The two halves of HSK can be simplex or duplex in configuration. Extrarenal calyces ending directly into the ureter with rudimentary or absent pelvis might be encountered. The ureters cross the isthmus anteriorly in the vast majority of cases. Ureters behind the isthmus are extremely rare. Moreover, the isthmus can be drained by its own calyces and independent ureter. VUJ is usually orthotopic.

9.2.5.1.2 Diagnosis

Ultrasound can identify the isthmus and make the diagnosis of horseshoe kidney even if magnetic resonance (MR) and computed tomography (CT) scans are more detailed. Radionuclide images (i.e. DMSA, MAG-3) will delineate the functional anatomy as often the isthmus has residual function.

9.2.5.1.3 Associated Anomalies

Many associated genitourinary anomalies have been reported: VUR and PUJ obstruction are the most common anomalies in symptomatic HSK in children with an incidence, together of around 50% [20]. HSK is found with increased frequency in well-known syndromes including Trisomy 18, Turner syndrome, and neural tube defects. Half of the HSKs are associated with extrarenal anomalies or syndromes with defects of the gastrointestinal tract and vertebral anomalies being the most common [21].

Around one-third of HSKs remain undiagnosed throughout life [22]. PUJ obstruction is the most common pathological cause of hydronephrosis; this can be due to high ureteric insertion, anomalous blood vessels, or ureteral kinking when the ureter passes across the isthmus [23]. Urolithiasis has been found in 20% of patients with HSK, not only correlated with slow drainage but also with metabolic abnormalities [24]. Patients with HSK are at increased risk of renal carcinoid and Wilms tumour [25]. These tumours tend to arise from the isthmus, probably reflecting the abnormal migration of nephrogenic cells that occurs in this region. Renal cell carcinoma (RCC) is the most common cancer found in HSKs, but its incidence is the same of normal population [26]. Because it anatomical configuration and position, in particular the fixed position of the isthmus, the HSK is believed to be more susceptible to rupture during abdominal blunt trauma.

9.2.5.1.4 Management

Sixty percent of patients remained asymptomatic for 10 years after discovery of HSK [27]. The most common operation required for HSKs is pyeloplasty for PUJ obstruction. This can be difficult if the renal units have not completed the ascent. Both extraperitoneal and transperitoneal approaches are feasible depending on specific anatomical characteristics. The laparoscopic approach is used in adult as well as in children [28].

9.2.5.2 Crossed Renal Ectopia

In crossed renal ectopia, the kidney crosses the midline while its ureter maintains a normal ipsilateral insertion
into the bladder. The incidence is around 1:7000 in autopsies [29] and the left-to-right crossing is more frequent. In almost all cases, the crossed kidney is fused with their mate, as the upper pole of the ectopic kidney joins the lower pole of the normal kidney.

9.2.5.2.1 Associated Anomalies
Malformations affecting other organs occur with increased frequency. VUR is common in the ectopic kidney, while ureterocele and PUJ obstruction are less frequent. Rarely, multicystic dysplasia can affect the crossed ectopic kidney. The incidence of renal tumours in crossed renal ectopia is uncertain; RCC, mesoblastic nephroma, Wilms tumour, and primary synovial sarcoma, with RCC being the most frequent.

9.2.5.2.2 Prognosis
Thirty percent of the patients with crossed renal ectopia develop pyelonephritis or urolithiasis and 25% have hydronephrosis.

9.2.5.3 Cystic Renal Disease
Simple cysts are fluid-filled sacs which may be single or multiple and range in size representing 70% of asymptomatic renal masses. They are mainly found in the renal cortex and do not communicate with the nephron or renal pelvis (Figure 9.6). This is in contrast to parapelvic cysts, which are simple parenchymal cysts found adjacent to the renal pelvis or hilum. Cysts may be bilateral and are increasingly prevalent with increasing age [30]. There is no definitive aetiology; however, congenital and acquired causes have been proposed, with chronic dialysis a factor in increasing formation of new simple cysts [31].

The most common means of presentation is incidental diagnosis on imaging for another purpose. Acute presentations of severe pain can occur with bleeding into a cyst as a result of the increased pressure from distension of the cystic wall. The differential diagnosis includes RCC, early autosomal dominant polycystic kidney disease (ADPKD), or complex renal cysts (i.e. containing blood, pus or calcification.)

On ultrasound, simple cysts are defined by being anechoic, round, or spherical in shape with a smooth outline. Where there are septations, calcification, or clusters of cyst, there is indication for further investigation with contrast CT or magnetic resonance imaging (MRI) to exclude concomitant malignancy. On CT, simple cysts have no enhancement after contrast injection and have homogenous fluid density within the cyst cavity (typically −10 to +20 Hounsfield Units [HU]). Hyperdense cysts have a higher density (20–90 HU); however, they are not enhanced with contrast. The Bosniak classification is based on CT appearance of simple and complex cysts and is useful as a predictor of malignant potential with increasingly complex features [32].

A simple cyst requires no further treatment or follow up. In the rare situations where flank pain thought to be the cause, options include percutaneous aspiration with or without sclerosing agent or surgical excision of the cyst wall (Figures 9.7–9.9).

Figure 9.6 (a) It was once believed that cysts were the result of failure of a tubule to join a glomerulus. (b) In fact, Potter et al. found that in cystic disease, the nephrons were always dilated throughout their entire length.
Medullary sponge kidney (MSK) is an acquired cystic condition of the kidneys whereby there is dilatation of the distal collecting ducts with multiple cysts and diverticulum within the medulla.

Pathologically, the kidney in cross section looks like a sponge due to dilated collecting ducts and the presence of numerous cysts, which are the result of urinary stasis precipitates calculi within the cysts (Figure 9.10) [33]. As the majority of people are asymptomatic, the diagnosis is an incidental finding, and in 75%, both kidneys are affected.

CT urogram shows dilatation of the distal portion of the collecting ducts with cysts resembling ‘bristles on a brush’ or ‘bunch of grapes’ if they become filled with calcifications. Hypercalciuria may be present in a third to half of patients and advice regarding fluid and diet should be tried before considering thiazide diuretics [34]. Whilst asymptomatic MSK disease necessitates no treatment, presentations with renal colic, haematuria, and recurrent
9.2.5.5 Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inheritable form of renal cystic disease and tends to become apparent in the third decade of life. It is an autosomal dominant–inherited disorder that results in multiple expanding renal cysts. The majority of affected individuals have a mutation either of PKD1 gene on the short arm of chromosome 16 (85%), or less often, PKD2 gene on the long arm of chromosome 4. The products of PKD1 and PKD2 are polycystin-1 (PC1) and polycystin-2 (PC2), and they normally act to inhibit cell proliferation. Generally, there will be sonographic evidence in all affected individuals of cysts before the age of 20. Those with PKD1 mutations tend to progress quicker than those with PKD2 mutations [36].

Because of the 50% positive family history, the presentation may be known before symptoms arise. Symptoms of palpable abdominal masses, flank pain, or macroscopic haematuria tend to present by the fourth decade of life [37]. Hypertension is present in virtually all patients [38], and rarely patients may have renal failure symptoms of lethargy, nausea, and anaemia.

With increasing age, there is in association with liver cysts, which are present endemically by the age of 50; however, these remain largely asymptomatic [39]. ADPKD contributes to 10% of all cases of renal failure [36]. The expansion cysts and resultant ischemic atrophy of surrounding renal tissue leads to end-stage renal failure (ESRF), inevitably by the fifth decade of life. Associated extrarenal conditions include Circle of Willis berry aneurysm (10–30%), which can lead to subarachnoid haemorrhage and death in 9% [40]. The incidence of RCC in patients with ADPKD is no higher than that of the general population but is often diagnosed at a younger age. Treatment of ADPKD aims to maintain renal function and is directed at controlling hypertension with ACE inhibitors and angiotensin receptor blockers and preventing UTIs.

9.2.5.6 Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD) is the result of a mutation of the PKHD1 gene on chromosome 6 and is rarer than the dominant variety at 1 in 5000–40 000. When severe it manifests in utero, whilst milder cases can emerge in children up to 20 years old. Between 30 and 50% of patients can die within several days because of uraemia or respiratory compromise [41]. The early form of the disease is associated with symmetrically large kidneys that are homogeneously hyperechogetic, and then these may appear as more discrete cysts with age. Hypertension and renal insufficiency are the major manifestations in surviving children; however, liver disease from invariable congenital hepatic fibrosis, becomes more evident with age.

9.2.5.7 Acquired Renal Cystic Disease

Acquired renal cystic disease (ARCD) is associated with chronic renal failure and is most commonly seen in patients on long-term haemodialysis and peritoneal dialysis. In contrast to simple cysts, they are in continuity with the renal tubules and are usually multiple, bilateral, and within the cortex of contracted kidneys. The
cysts are hyperplastic and frequently adenomas, either of which may progress to RCC. The incidence of RCC in the dialysis population is 5–50 times that of the general population and is increased with length of time on dialysis [42]. Even if the cysts regress with transplantation, then the risk of RCC persists, albeit at a much lower level [43].

Investigation is focused on the presenting symptom. If haematuria is persistent as it may be in patients on heparinised dialysis, then the options of transfer to peritoneal dialysis, renal embolization, or nephrectomy of non-functioning kidneys should be considered. Where malignancy is suspected, the options of nephrectomy or surveillance should be based on symptoms and likelihood of malignancy. Due to the high risk of development of RCC, there is indication for surveillance ultrasound or CT of patients with ARCD on dialysis.

9.3 Congenital Abnormalities of the PUJ

9.3.1 Hydronephrosis

Hydronephrosis is defined as an abnormal dilatation of the pelvis with or without associated calyceal dilatation. Hydronephrosis is found in around 1% of pregnancies and is caused by PUJ obstruction in 10–30% of cases.

9.3.2 PUJ Obstruction

PUJ obstruction is generally the result of a primary intrinsic defect of the ureteric muscular layers where there is an aperistaltic segment of ureter. Crossing vessels have been noted in up to 63% of adult with PUJ obstruction and only in 20% of patients with normal kidneys [44]. However, historically it is thought that it is truly an intrinsic lesion defect and the crossing vessel may be incidental [45].

Symptoms vary from UTIs and flank pain, even if the diagnosis is currently made very early by ultrasound and usually during pregnancy. Generally, the typical diagnosis shows decreasing differential renal function and increasing hydronephrosis with or without symptoms. In adults, the classical presentation is of flank pain precipitated by a diuresis but may also be associated with a flank mass or recurrent UTI. However, many PUJ obstructions lack to manifest all the typical features.

Renal ultrasound shows a dilated renal pelvis in the absence of a dilated ureter. CT urogram demonstrates a delay in excretion of contrast and a dilated renal pelvis. MAG 3 renogram with diuretic is the gold standard for showing radioisotope accumulation in the pelvis, and following furosemide, there continues to be a rising curve as contrast remains in the renal pelvis.

<table>
<thead>
<tr>
<th>SFU-grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No hydronephrosis</td>
</tr>
<tr>
<td>1</td>
<td>Only renal pelvis visualised</td>
</tr>
<tr>
<td>2</td>
<td>Dilatation of pelvis</td>
</tr>
<tr>
<td>3</td>
<td>Grade II + minor calyces</td>
</tr>
<tr>
<td>4</td>
<td>Grade III + thinning of parenchyma</td>
</tr>
</tbody>
</table>

Indications for intervention include symptoms associated with obstruction, impairment of overall renal function or progressive impairment of ipsilateral function, and development of stones or infection. Only a third of children with PUJ obstruction will require intervention [46]. Pelvic AP dilatation >3 cm is also a strong indicator of intervention for PUJ obstruction. Poor drainage after the administration of furosemide, increased anteroposterior diameter on the ultrasound, and grades III and IV dilatation as defined by the Society for Foetal Urology (Table 9.1) are also strong indicators. PUJ obstructions with a residual function <10% should be approached carefully because successful repair for poor functioning kidneys is more difficult to achieve, and nephrectomy should be considered. The diagnosis is completed confirmed with ultrasound and MAG3 (Figure 9.11) [46].

9.3.2.1 Surgical Correction

The armamentarium for the surgeon is wide and effective as different techniques and approaches have been described. The generally adopted technique is the Anderson-Hynes dismembered pyeloplasty, described in 1949, with success rates currently consistently >90% [47]. This operation can be completed using open (i.e. flank, posterior lumbotomy, subcostal), laparoscopic (i.e. transabdominal, retroperitoneal), or robotic approaches [48]. Minimally invasive approaches, including robotic, have shown a low perioperative complication rate, a short hospital stay, and success rates of >95% [49]. As yet there is no randomised trial comparing open to laparoscopic and robotic pyeloplasty. Other techniques for pyeloplasty, like the Foley Y-V plasty or the Davis intubated ureterotomy, have declined in popularity. Endoscopic incision or dilatation of the PUJ (either antegrade or retrograde) have been reported with overall less successful rates compared to dismembered pyeloplasty and are now prevailing in cases of recurrent PUJ obstructions after failed pyeloplasty [50]. Endopyelotomy might be challenging in failed pyeloplasty, if the length of the stricture is >1 cm. For children, redo laparoscopic...
pyeloplasty has been used effectively but may be a difficult operation because of scarring [51].

In children, the debate exists regarding the need of a transanastomotic stent (nephrostomy or double-J) in the postoperative period after pyeloplasty, given another anaesthetic is required for removal. However, a longer hospital stay because of the management of complications like urine leak and clot obstruction has been reported when the stent was avoided [52]. In adults, a stent is generally placed for four to six weeks postoperatively, and subsequent MAG3 renogram is used to demonstrate improved obstruction. Most failures of surgery, either of symptom persistence or lack of radiographic improvement occur within two years of surgery although 30% of failures occur later [53]. Failed pyeloplasty refers to either persistent obstruction or its recurrence due to anastomotic stricture and it occurs in 2–6% of cases. The laparoscopic approach has shown high effectiveness for redo pyeloplasty [53].

### 9.3.3 Congenital Abnormalities of the Ureter

The ureter may fail to develop or can partly develop or can abnormally develop. Also, failure of developing duplication ureters may lead to blinded-ending ducts with ureteric orifices or an aberrant ureter (Figures 9.12–9.14).

#### 9.3.3.1 Duplex System

A duplex system refers to a single kidney functionally divided into two moieties (upper and lower) draining independently into two pelvicalyceal systems. Those systems can join together before the PUJ (bifid system) (Figure 9.15) or beyond it but above the bladder (incomplete duplex) or be completely separated with two distinctive ureters with two separate ureteric openings (complete duplex).
The Wiegert–Meyer rule dictates that the upper pole ureter opens onto the bladder medially and distally to the upper pole moiety ureter which opens laterally and proximally (Figure 9.16) [54]. Therefore, the upper pole moiety ureter with its long intramural course is predisposed to obstruction, whilst the lower pole moiety with reduced intramural ureteric length is susceptible to reflux in 85% of cases.

Unilateral cases of renal duplication are more common than bilateral with a higher female to male ratio of 2:1. The overall incidence is 1 in 125 and both sides are affected equally. The presentation may be an incidental finding, UTI symptoms or recurrent, flank pain (Figure 9.17).

Investigation with ultrasound shows ureteric duplication with the possibility of dilatation. The CT urogram findings of a ‘drooping lily’ arise due to decreased contrast excretion from an obstructed renal upper pole, displacing the lower pole downwards and laterally. The definitive test of reflux is a micturating cysto-urethrogram and a $^{99m}$Tc- DMSA renogram assesses renal function.

Treatment depends on symptoms and whether reflux or obstruction is the main issue.

9.3.3.1.1 Embryology
The ureteric bud which arises from the mesonephric duct meets the metanephrons to form the kidney as the result of the bidirectional induction between the two
structures. To develop normally, the ureteric bud needs to arise and reach the metanephrons in the correct area. The farther the ureteric bud joins the metanephrons from the normal region, the more significant the degree of renal dysplasia will be. The ureteric bud will originate the entire collecting system. If it branches before to reach the metanephrons, the result will be an incomplete duplex or a bifid system. If two ureteric buds arise from the mesonephric duct, there will be a complete duplex; initially, the proximal ureteric bud will meet the metanephrons above the other to form the upper moiety, but then, during the process of rotation to establish the final junction between ureters and bladder, the proximal ureter will move more caudal compared to the ureter draining the lower moiety. The result is that, in a complete duplex, the caudal ureteric orifice (UO) drains the upper moiety as explained by the Weigert-Meyer rule. The ureter draining the upper moiety can insert within the bladder or more caudally, into structures derived from the mesonephric duct; whatever the level of insertion is, those ureters are called ‘ectopic.’ Clinically, the main difference between ectopic ureter in men male and women female is that for the former the UO of an ectopic ureter is always above the urethral sphincter, providing the maintenance of urinary continence. In females, the ectopic ureter can insert below the urethral sphincter, leading to various degree of incontinence. The ureter draining the lower moiety tends to insert more laterally, with a shorter intramural tunnel and hence more prone to reflux.

**9.3.3.2 Ectopic Ureter**

The ureteric orifice arises below the normal insertion point of the trigone of the bladder. The majority of cases have associated with a duplex collecting system and are caused by the ureteric bud arising from an abnormal position on the mesonephric duct. As the upper pole as previously described always enters distal and medial to the lower pole ureter, upper pole ureters are predisposed to ectopic placement (Weigert-Meyer rule.) The sites of ectopic ureters vary in females from bladder neck, urethra, and vagina and in males from posterior urethra, seminal vesicles, ejaculatory duct, vas deferens, or bladder neck (Figure 9.18). It is three times more common in females than males. The presentation is usually in both sexes with acute or recurrent UTI. In females when the opening lies below the urethral sphincter, girls present with persistent vaginal discharge or incontinence. In males, the ureter always sits above the external urethral sphincter; therefore, there is no incontinence.

The farther is the UO form the orthotopic position, the higher is the degree of dysplasia affecting the renal moiety drained by that ureter [57]. Recognising an ectopic ureter might be very difficult, and a high index of suspicion is required. In suspected cases of ectopia, it is not unusual and requiring an MRU to have the best anatomical details. Even with this, poor functioning and small upper-pole moieties can be difficult to visualise (cryptic duplex). MCUG and cysto-vaginoscopy may or may not help to identify the ectopic ureter or UO, respectively. Once the diagnosis is established, the surgical treatment depends on the functional contribution of the upper-pole moiety and symptoms. If poor functioning, upper-pole hemi-nephrectomy is indicated. If a reasonable function is preserved, then ureteric reimplantation (of both the duplex system ureters) or uretero-ureterostomy can be performed.

Bilateral ectopic ureters affect girls, and the challenge is not only to correct the insertion of the ureters with
ureteric reimplantation, but mostly to manage the small bladder and poor sphincteric mechanism that the bilateral ectopia has induced.

### 9.3.3 Ureterocele

Ureterocele represents a cystic dilatation of the terminal ureter into the bladder. The most adopted classification distinguishes the ureterocele into two types: orthotopic and ectopic. An orthotopic ureterocele arises entirely from the normal location of its UO; it is contained within the bladder, but it can prolapse at the bladder neck or beyond. The ectopic ureterocele has part of its wall arising from an abnormal location, usually the bladder neck. The ectopic type is most commonly associated with the upper moiety of a duplex kidney and may cause obstruction (Figure 9.19). The diagnosis is reached by

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**Figure 9.18** The ureter from the upper half-kidney may open into the vagina below the sphincter and cause incontinence.

**Figure 9.19** (a and b) A ureterocele may prolapse through the urethra and cause obstruction.
9.3.3.4 Megaureter

Megaureter refers to an abnormal dilatation of the ureter, with or without hydronephrosis. Any dilatation of the retrovesical ureter ≥7 mm from the 30th week of gestation onward is considered abnormal [60]. Megaureter can be classified pathophysiologically into four categories: obstructive, refluxing, reflux with obstruction, and non-refluxing and non-obstructing.

9.3.3.4.1 Diagnosis and Work-Up

A predictive value of a megaureter detected antenatally has not been established yet [61]. The only current recommendation is to monitor it postnatally if ≥7 mm. As the hydroureteronephrosis carries an increased risk of UTI; antibiotic prophylaxis is advisable [62]. Postnatally, the first investigation should be ultrasound followed by MCUG in all the cases of ureteric dilatation. Irrespective of bilateral or unilateral hydroureteronephrosis in a male infant, the MCUG should be done early (around 14% of males with unilateral hydroureteronephrosis have posterior urethral valves) [63]. The possible obstructive component of a megaureter is the most dangerous for the kidney; therefore, prompt diuretic renogram is indicated in case of isolated ureteric dilatation >10 mm. Interpretation of the MAG3 can be difficult because delays in drainage might be seen in the absence of obstruction due to the nature of the redundant ureter or capacious pelvis. The result should be therefore interpreted based on both clinical and radiological data. In an asymptomatic patient, an initial differential renal function of 40% or a drop by 5% on serial scans should indicate an element of obstruction. Contrariwise, delayed drainage at MAG3 with stable or improving dilatation on ultrasound and normal differential renal function in an asymptomatic patient do not indicate the need of urgent intervention.

Conservative management of primary obstructing megaureter (POM) is well established in the literature with more than 70% of patients not requiring surgery at long term follow-up [64]. Indications for intervention are drop or reduced differential renal function, breakthrough UTI, pain, or worsening dilatation. Ureteric reimplantation (with or without tapering) is the definitive treatment. In experienced hands, the reimplant can be performed before the first year of age [65]. Otherwise it can be postponed and a temporising procedure can be undertaken such as double-J stenting, cutaneous ureterostomy, endoureterotomy, or endoscopic balloon dilatation. Late complications of conservatively treated POMs have been reported during the adult life, suggesting that follow-up is still needed after childhood [66].

9.3.3.5 Retrocaval Ureter

Retrocaval ureter is a rare entity where the course of the ureter becomes posterior to the inferior vena cava at the level of L3–L4 (Figure 9.21). It is the result of the
inferior vena cava developing from the subcardinal system (which lies anteriorly to the ureter during the foetal life) instead of the supracardinal system (which lies posteriorly). Its prevalence is around 1:100 live births and is more common in males. It occurs as a result of the persistence of the cardinal veins. Usually it presents in the third to fourth decades of life with flank pain, haematuria, UTI, or urolithiasis. The ultrasound shows hydronephrosis along with proximal ureteric dilatation. MAG3 renogram confirms the degree of obstruction and MRU defines the anatomy and suggests the diagnosis. Based on previous intravenous urogram (IVU) series, there may be an ‘S Shaped’ or ‘sickle shaped’ curve of the ureter, with the point of obstruction coinciding with the lateral margin of the inferior vena cava [67].

1) Moderate to severe hydronephrosis with ‘S’ or ‘fishhook’ deformity of the ureter at the point of obstruction. The point of obstruction has some distance from the lateral margin of the IVC.

2) Mild hydronephrosis with ‘sickle-shaped’ curve of the ureter at the point of obstruction. The obstruction coincides with the lateral margin of the inferior vena cava.

Retrocaval ureters requiring surgery are mostly treated by uretero-ureterostomy either approached open or laparoscopically (Figure 9.22).

### 9.3.3.6 Congenital Abnormalities of VUJ

VUJ obstruction, even if anatomically belonging to the junction itself, has been described in the paragraphs dedicated to megareuter, which represents the radiological and clinical manifestation guiding the management.

#### 9.3.3.6.1 VUR

VUR refers to the retrograde flow of urine from the bladder up to the ureter or kidney. The incidence in children is around 10%, with higher rates in younger, Caucasian, and females. Because an affected child has a 40% of a sibling being affected as well, screening of siblings is recommended. Amongst children presenting with UTI, around 30% are found to have reflux [68]. When the ureter passes through the bladder wall the muscular attachments prevent reflux. Therefore, when the intramural ureter is short (ratio of intramural ureter length to diameter of ureter <5:1) reflux occurs. VUR when associated with UTI can result in reflux nephropathy, hypertension, and progressive renal failure. In adults, 25% of patients requiring renal replacement therapy do so because of reflux nephropathy. The presentation is generally with symptoms of UTI but can be more general with abdominal pain, failure to thrive, or vomiting. In adults, VUR may be asymptomatic, a cause of loin pain associated with a full bladder, or recurrent UTI.

VUR can be classically divided into two main subtypes: primary, due to a shorter intravesical tunnel at the VUJ, and secondary, due to other pathological conditions (e.g. posterior urethral valves, neurogenic bladder, detrusor sphincter dysynergia) which increase the intravesical pressures. In adults, secondary VUR may occur iatrogenically following ureteric meatotomy for the removal of ureteric stones at the VUJ. It also arises in duplex systems where the lower pole moiety with a shorter intramural course is predisposed to VUR.

VUR has been classified, based on the degree of the retrograde flow of urine, into five grades [69]:

- **Grade I**: reflux into the ureter only
- **Grade II**: reflux into a nondilated pelvi-calyceal system
- **Grade III**: dilatation of the collecting system
- **Grade IV**: more dilation with blunting of the calyces and tortuosity of the ureter
- **Grade V**: massive dilation of the collecting system and severe tortuosity of the ureter

The grade of the VUR has been found the most important factor in determining the likelihood of spontaneous resolution, even if other variables can be put into the equation to finally estimate the specific risk for each patient (e.g. age, gender, laterality, bladder behaviour, renal scarring, and number of UTIs.)
Diagnosis  VUR is clinically suspected and subsequently confirmed with radiological investigations. The gold standard is the MCUG, on which the grading scale is based. After the age at which a child is toilet trained, an alternative to MCUG is the MAG3-IRC (MAG3 with indirect radionuclide cystography), where the captured images continue during the micturition, to detect the concurrent radionuclide activity back to the ureter or kidney. MAG3-IRC is less invasive but less sensitive. Ultrasound can identify reflux, especially if the difference between the ureteric dilatation before and after the micturition is evident. For the evaluation of renal scars, DMSA is historically adopted, even if MAG3 seems to have the same sensitivity [70].

Treatment  Large debate exists in regards to the need for and treatment modalities for VUR. Various treatment modalities like no active treatment, prophylactic antibiotic, endoscopic treatment, and reimplantation (i.e. open, laparoscopic, vesicoscopic) have all showed to be of value depending on the cohort of patients analysed.

VUR Treatments in Children  The rationale of any algorithm for the treatment of VUR is based on:

1) The formation of new renal scars is due to the presence of infected urine reaching the kidney [71].
2) VUR, especially low grade, has high chances of spontaneous resolution.
Undoubtedly, there is a subgroup of patients who could be observed safely even if the first presentation was UTI. The assumption that the VUR is always the cause of the UTI might be wrong in some cases as the likelihood of UTIs in the presence of a low-grade reflux without any stasis of urine in the upper tract is minimal.

The daily administration of antibiotic prophylaxis until the spontaneous resolution of the VUR is a widely used strategy. The RIVUR trial found a significant decreased number of recurrent UTI in patients with VUR who received prophylaxis compared to the placebo group, even if there was no difference in the risk of renal scarring [72]. Whilst the Swedish reflux trial, which included children aged 12–23 months with grades III–IV reflux, showed a benefit of prophylaxis in diminishing the incidence of UTI and renal scar formation only in girls [73]. Antibiotic prophylaxis needs good compliance from the family and regular follow-up from the clinician to catch breakthrough UTIs promptly.

**Surgical Treatment** Surgical treatment is generally indicated in case of breakthrough UTIs, development of new scars, or symptoms. If a VUR has not resolved spontaneously after conservative treatment the cut-off age for surgery is usually around five years, but the timing is absolutely individualised.

**Endoscopic Approach** The endoscopic injection of dextranomer/hyaluronic acid copolymer (Dx/HA) Deflux®, has achieved popularity with time as the VUR can be treated as a day case. The overall successful rate of endoscopic injection is about 70%. The procedure can be repeated if indicated, with improved efficacy however this is not replicated in a third injection. The two most widely adopted techniques are the STING (originally meaning ‘subureteral Teflon injection’) and the hydrodistention injection technique (HIT), with its modifications of double-HIT and triple-HIT. The main difference is that with the STING the injection is made just outside the ureteric orifice, usually at 6 o’clock, while with the HIT the injection is made into the ureter just beyond the ureteric orifice.

The rate of complications is low: ureteric obstruction occurs with an incidence of around 0.7%. The reflux can be resolve completely or step down to a lower degree; the long-term outcome is difficult to estimate as the distal ureter can improve its anatomy spontaneously, contributing to the long-term effect. The Dx/HA has shown less tendency to migrate with time compared to other materials previously used.

**Ureteric Reimplantation** Ureteric reimplantation surgery has reported successful rates of >95%. When done open, the approach is usually through a Pfannenstiel incision. Many techniques have been described to reimplant the ureter, and they can be divided into two types: extravesical (e.g. Lich-Gregoir) and intravesical (e.g. Cohen, Politano-Leadbetter) reimplantation. Specific complications include recurrence, UO stenosis, and bladder dysfunction (especially for extravesical bilateral reimplantation). The length of the new ureteric tunnel should be five times the diameter of the ureteric lumen [74].

**VUR Treatment in Adults** In adults with primary VUR and recurrent UTI who have no symptoms in between the infection, treatment should be directed at UTIs when they occur, with the added option of low-dose prophylaxis if the frequency of UTIs increases. If there is regular pyelonephritis or deterioration in renal function or progressive radiological signs of reflux, then reimplantation should be considered. When there is minimal function in the affected kidney (<10%), nephrectomy should be considered. For secondary reflux into a transplanted kidney no treatment is required.

### Expert Opinion

Congenital anomalies can lead to lifelong ailments and deterioration in both quality of life and life expectancy of patients. Therefore, it is crucial that adult urologists understand the basic science behind the development of the urinary tract and the pathophysiology of illness that accompany them because the management of the majority of these cases will continue to adulthood.

### References


10

Hydronephrosis

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Abstract

Hydronephrosis is a common urological finding of which the causes are numerous and its investigation can put significant demand on healthcare resources. The importance of correct investigations and diagnosis is imperative to elucidate appropriate treatments. Causes range from congenital to acquired and symptomatic to asymptomatic. Knowledge of the pathophysiology, diagnostic imaging, and management of hydronephrosis is vital for all urological practitioners.

Hydronephrosis needs appropriate early investigation with prompt treatment to enable renal preservation and prevent irreversible renal damage. An understanding of the pathophysiology of acute obstruction is important to fully appreciate the complex nature of the kidney in homeostasis. This chapter discusses the pathophysiology, investigation, and common causes of hydronephrosis.

Keywords ureteric obstruction; hydronephrosis; pelviureteric junction obstruction; megaureter; postobstructive diuresis; ectopic ureter; ureterocele; retrocaval ureter; perinatal hydronephrosis

Key Points

- Definition and pathophysiology of hydronephrosis.
- Investigations for hydronephrosis.
- Management of the more common causes of hydronephrosis and pelviureteric junction (PUJ) obstruction.

10.1 Definition

Hydronephrosis is the dilatation of the renal calyces and pelvis with urine. Hydroureter is defined as a dilatation of the ureter. Both phenomena can be unilateral or bilateral, acute or chronic, congenital or acquired, and physiological or pathological. Although these terminologies are used synonymously with obstruction, both can be present without it (i.e. vesicoureteric reflux [VUR]).

Superseded infection needs immediate intervention to prevent morbidity and mortality. A series of 59064 autopsies of patients of all ages identified a prevalence rate of hydronephrosis to be 3.1% [1]. Out of the 21587 women, the most common etiology for hydronephrosis was either pregnancy or gynaecological malignancies (mostly cervical or uterine cancer). This was found to be most prevalent between the ages of 20 and 60 years [1]. In contrast, out of the 37477 men, the most common etiology for hydronephrosis was prostatic disease (either benign prostatic hypertrophy or prostate cancer) with a peak prevalence of over 60 years [1].

Congenital hydronephrosis occurs in approximately 2–2.5% of children. Antenatal screening has led to early diagnosis with most obstructive conditions being detected prior to birth. An autopsy series of stillbirths, infants, and children found a higher prevalence in boys...
with the majority being younger than one year [2].

Table 10.1 outlines the causes of hydronephrosis.

<table>
<thead>
<tr>
<th>UNILATERAL</th>
<th>BILATERAL</th>
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<tbody>
<tr>
<td><strong>Congenital</strong></td>
<td><strong>Congenital</strong></td>
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<tr>
<td>Renal</td>
<td>Renal</td>
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<tr>
<td>Polycystic kidney</td>
<td>Polycystic kidney</td>
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<tr>
<td>Pelviureteric Junction (PUJ) obstruction</td>
<td>Lower urinary tract</td>
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<tr>
<td>Renal cyst</td>
<td>Posterior urethral valve</td>
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<td>Parapelvic cyst</td>
<td>Phimosis</td>
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<tr>
<td><strong>Acquired</strong></td>
<td><strong>Acquired</strong></td>
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<tr>
<td>Ureteric stenosis</td>
<td>Ureter</td>
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<tr>
<td>Obstructing megaureter</td>
<td>Retroperitoneal fibrosis</td>
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<td>Retrocaval ureter</td>
<td>Radiation therapy</td>
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<td><strong>Acquired</strong></td>
<td><strong>Acquired</strong></td>
</tr>
<tr>
<td>Renal</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Pelvic lipomatosis</td>
<td>Pregnancy</td>
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<tr>
<td>Sloughed papillae</td>
<td>Pelvic lipomatosis</td>
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<tr>
<td>Renal artery aneurysm</td>
<td>Proxidetia</td>
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<tr>
<td><strong>Acquired</strong></td>
<td><strong>Acquired</strong></td>
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<tr>
<td>Ureter</td>
<td>Bladder cancer</td>
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<tr>
<td>Ureteric cancer</td>
<td>Neurogenic bladder</td>
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<tr>
<td>Metastatic ureteric obstruction</td>
<td>Benign prostatic hypertrophy</td>
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<td><strong>Acquired</strong></td>
<td><strong>Acquired</strong></td>
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<td>Calculi</td>
<td>Prostate cancer</td>
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<tr>
<td>Clot</td>
<td>Urethral cancer</td>
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<td>Trauma</td>
<td>Urethral stricture</td>
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<tr>
<td>Ureteric stenosis</td>
<td>Penile cancer</td>
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<td>Tuberculosis</td>
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<td>Amyloidosis</td>
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<td>Endometriosis</td>
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<td>Ureteritis cystica</td>
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<td>Abscess</td>
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</table>

All causes of bilateral obstructive nephropathy can be unilateral in the early stages. Some causes of unilateral obstructive nephropathy can cause bilateral.

10.3 Pathophysiology

10.3.1 Macroscopic Changes in Upper Urinary Tract Obstruction

A combination of urinary pooling and reduced ureteric contractility following obstruction gives rise to back pressure to the proximal kidney. This subsequently causes dilatation of the collecting system resulting in hydronephrosis. The kidney eventually swells and increases in weight because of the urinary pooling, causing flattening of the renal papilla and back filling of the collecting system with eventual parenchymal oedema seven days following the obstruction. The renal cortex is compressed, resulting in the characteristic cortical and medullary thinning seen with obstruction, usually by days 21–28 [3].

10.3.2 Microscopic Changes in Upper Urinary Tract Obstruction

With prolonged obstructive nephropathy, the tubular swelling extends to the more proximal aspect of the nephron. The primary histological derangements are localised to the tubulointerstitial compartment of the kidney. The mechanical changes cause massive tubular dilatation and are associated with renal tubular cell stress leading to eventual apoptotic cell death and progressive tubulointerstitial atrophy and fibrosis with resultant renal injury. This is mediated by an influx of proinflammatory mediators, such as macrophages and suppressor T-lymphocytes, which trigger proinflammatory cytokines and growth factors (tumour necrosis factor-α, transforming growth factor-β1, interleukin-18, monocyte chemotactic protein-1, and macrophage inflammatory protein-1 and 1β) that stimulate fibroblastic proliferation and activation of the extra cellular matrix. The tubular epithelial stress response also leads to oxidative stress by increase in superoxide radical production with a reduction in catalase enzymes, which metabolises hydrogen peroxide. These changes destabilise the mitochondria and promote the release of cytochrome C, which in turn activates Caspase (cysteine aspartate specific protease)-mediated apoptosis.

In early onset urinary tract obstruction, the glomeruli are relatively preserved; however, long-standing obstruction leads to extensive glomerulosclerosis.

10.3.3 Ureteric Function in Upper Urinary Tract Obstruction

Ureteric peristalsis enables a coordinated contraction of the renal pelvis and ureter to propel urine into the urinary bladder. The central control mechanism of this phenomenon is still poorly understood, but the primary oscillator of ureteric peristalsis is thought to be renal pelvis urine volume.

Studies of sheep and human ureters in an obstructed state found that stretch dramatically increased contraction amplitude in both renal pelvis and distal ureter, but only increased contraction frequency in the renal pelvis [4]. In canine studies, after prolonged complete obstruction of four weeks, both canine renal pelvis and ureter...
were aperistaltic [5]. However, with the same duration of partial obstruction, peristalsis continued with roughly half the frequency but up to fivefold increase in contraction amplitude. In eight weeks following relief of complete obstruction, the contraction amplitude, and frequency returned to baseline. In partial obstruction however, contractile amplitude remained elevated.

10.3.4 Renal Haemodynamics, Glomerular Filtration Rate and Intrarenal Pressure in Upper Urinary Tract Obstruction

The normal resting pressures of the renal pelvis and ureter are approximately 0–10 cm H$_2$O. Normal pressure change during peristalsis varies between 20 and 60 cm H$_2$O. As mentioned previously, there is a dramatic rise in both intrarenal and intra-ureteric pressure in acute obstruction. The rise in pressure is transient and is followed by a prolonged gradual decline. This is secondary to an increasing renal pelvis dilatation in proportion to the compliance of the system, reduced renal blood flow and glomerular filtration rate (GFR), and pyelolymphatic and pyelovenous backflow [6].

Obstructive nephropathy leads to haemodynamic changes of the kidney with resultant alterations in the glomerular filtration rate. These changes differ between subjects with unilateral or bilateral ureteral obstruction.

Animal studies have identified that changes in renal blood flow and ureteral pressures occur in three separate phases in unilateral ureteral obstruction (Table 10.2) [7, 8].

1) In the initial phase, which lasts 90 minutes, there is an increase in renal tubule pressures from 6 to 7 mm Hg up to 50–70 mm Hg leading to a decrease in GFR. This pressure change leads to a compensatory nitric oxide and prostaglandin E$_2$-mediated decrease in afferent arteriolar resistance, which raises glomerular capillary pressure and maintains GFR at 80% of normal despite the raised renal tubular pressure.

2) The second phase, lasting 1.5–4 hours, exhibits a decline in renal blood flow with a persistently elevated ureteral pressure secondary to afferent and efferent arteriolar vasoconstriction in response to substances including thromboxane A2 and endothelin. GFR is therefore reduced to roughly 20% of normal.

3) In the final phase, which is mediated by an increase in afferent arteriolar resistance, there is a decline in both ureteral pressure (though reduced, but 50% higher than normal pressure) and renal blood flow resulting in loss of kidney function.

Bilateral obstruction differs as ureteral pressures remain elevated for greater than 24 hours, and by causing only a small initial rise of renal blood flow, lasting 90 minutes, followed by a decline in renal blood flow in both kidneys (or solitary kidney) [9].

All these experiments were conducted on animals with unicalyceal renal system (i.e. dogs, rats) and have not been consistently reproduced in animals with multicalyceal systems similar to humans.

10.3.5 Effect on Tubular Function

Sodium and potassium handling via opposing active transport mechanisms at the basolateral membrane of the proximal tubules, the ascending loop of Henle, distal tubule, and the countercurrent mechanism is crucial for controlling the extracellular fluid volume. In unilateral obstruction, down-regulation of apical sodium antiporters and catalytic units of the basolateral Na-K-ATPase has been demonstrated. The disruption in sodium reabsorption leads to failure of the countercurrent multiplier because of the interruption of the corticomedullary gradient. Evidence

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time</th>
<th>Promotor</th>
<th>Effect on intrarenal pressure</th>
<th>Effect on eGFR</th>
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<tr>
<td>Unilateral Obstruction</td>
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<tr>
<td>1</td>
<td>Up to 90 min</td>
<td>Increase NO and PGE2 causing afferent arteriole dilation</td>
<td>Increase</td>
<td>Increase</td>
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<tr>
<td>2</td>
<td>90min–5hours</td>
<td>Thromboxane A2 and endothelin cause efferent arteriole vasoconstriction</td>
<td>Increase</td>
<td>Decrease</td>
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<tr>
<td>3</td>
<td>&gt;5 hours</td>
<td>ACE and angiotensin II cause afferent arteriole vasoconstriction</td>
<td>Decrease</td>
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<tr>
<td>Bilateral Obstruction</td>
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<td>3</td>
<td>&gt;5 hours</td>
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ACE, angiotensin-converting enzyme; NO, nitrous oxide; PGE2, prostaglandin E2.
from rat-based studies has shown some reduction in sodium expression in the contralateral kidney leading to early natriuresis [10, 11]. There is a similar down-regulation of sodium transporters in bilateral ureteral obstruction. Potassium excretion is also reduced, but compensatory mechanisms for the contralateral kidney prevent hyperkalaemia.

Urinary tract obstruction causes an alkalization of urine in both animal and human studies. This is due to the dependence of hydrogen ions on sodium transporters, which is impaired in the context of obstruction, to be in the urinary filtrate. The main acidification defect is thought to be in the distal tubule [12].

10.3.6 Effects of Obstruction on the Kidney

Obstruction leads to atrophy of the renal parenchyma. The principal effect of this atrophy is borne by the papillae, relatively more tubules being destroyed than glomeruli. Because there are fewer tubules to render the urine concentrated, the hydronephrotic kidney makes a larger volume of dilute urine and the effect of any obstruction is exaggerated.

Ultimately, entire nephrons are lost, and there is a deterioration in the creatinine clearance from the obstructed kidney, but for a considerable time, the obstructed kidney or idiopathic hydronephrosis remains a useful dialyser, and even when very thin, is still capable of sustaining life.

If infection supervenes at any time, then the devastating effect of inflammatory scarring – reflux nephropathy – are added to the slow atrophy caused by obstruction. This means that the presence of infection lends a measure of urgency to the need to relieve the obstruction.

10.3.7 Postobstructive Renal Recovery and Diuresis

Following relief of the ureteral obstruction, functional renal recovery is significantly dependent on the degree and duration of obstruction. In rat models, return of GFR following obstruction has been found to have an inverse relationship to duration of obstruction [13].

In canine studies, in unilateral ureteral obstruction of less than seven days, full recovery of GFR was achieved. After 14 days of obstruction 70% of GFR returned, after three weeks only 30%, and after six weeks there was no GFR recovery at all. Despite renal function recovery, interstitial fibrosis and apoptosis persists [14].

Following relief of obstruction, the kidney produces hypotonic urine. This is only clinically significant in subjects with bilateral ureteral obstruction due to the compensatory mechanisms of the unobstructed contralateral kidney in unilateral cases. After 24 hours of bilateral obstruction, there is a significant reduction in aquaporin 2 expression in the kidney. This protein channel is the predominant vasopressin-regulated water channel in the collecting tubules and ducts. This results in impaired ability of the kidney to reabsorb water. Studies have shown that aquaporin 2 expression returns to only at 50% after seven days following relief of obstruction and can remain down-regulated long term, contributing to chronic polyuria in obstructive nephropathy [15].

Bilateral ureteral obstruction also causes a postobstructive diuresis secondary to accumulation and retention of water, sodium, urea, as well as increased atrial natriuretic peptide (ANP) production. These factors lead to a diuresis, potassium excretion, and natriuresis, which does not occur to a significant extent in unilateral obstruction. The osmolality of urine has been shown to take up to 1 month to return to normal in rat models with only 24 hours of urinary tract obstruction [16].

In more than 90%, the diuresis is physiological (i.e. natural consequence to remove excess water, electrolytes, and metabolism by-products). However, 10% is pathological, mainly because of the loss of the cortico-medullary concentration gradient with excess ANP production, which lead to exaggerated loss of water and electrolytes.

10.3.8 General Clinical Features

There are five easily recognisable syndromes.

1) Pain with diuresis. Young people, usually men, boasting of their prowess at drinking beer, give a characteristic history of pain in the loin, followed by vomiting, after drinking several pints of beer. It is all too easy to jump to the diagnosis of a duodenal ulcer.

2) Loin pain and fever may be caused by an infection in the hydronephrotic sac. Curiously, this is often almost silent, even though the urine in the kidney may look like pea soup. Occasionally, the pyonephrosis makes the patient desperately ill with septicemia, and its relief by percutaneous nephrostomy is an emergency.

3) A mass. Many patients notice a lump in the loin, even though it may not be clinically palpable. The patient who feels a lump in the loin is often right, and it deserves investigating.

4) Gastrointestinal symptoms. In later life, the patient may not associate the consumption of fluid with the onset of pain. Commonly, a hydronephrosis is detected by chance in the course of investigating other abdominal pains. If the hydronephrosis is on the right side, distension of tissues behind the duodenum may give rise to dyspepsia closely resembling the pain of a peptic ulcer, and patients have often undergone prolonged treatment for a nonexistent duodenal ulcer before their hydronephrosis is discovered.
Similarly, a left-sided hydronephrosis may cause disturbance of bowel function. Many of these unfortunate patients are labelled as having colonic dysfunction or are even dismissed as valetudinarians, especially when they get relief by inexplicable manoeuvres such as lying face down or bending over the side of the bed.

5) Hypertension. The routine investigation of a young person with hypertension sometimes reveals hydronephrosis. The dilated cortical tissue is secreting renin.

10.4 Diagnostic Imaging

10.4.1 Ultrasound

The first-line imaging modality in the majority of cases is renal tract ultrasonography. It is safe, lacks ionising radiation, low cost, and easily available. Ultrasonography can detect the foetal kidney by 15 weeks of gestation and can easily detect anomalies by 20 weeks; therefore, it is the investigation of choice in the antenatal period. It provides the anatomical finding of hydronephrosis but offers limited functional information and therefore cannot exclusively diagnosis urinary tract obstruction.

Conversely, 50% of patients with acute urinary tract obstruction have normal ultrasound appearances in the immediate setting [17]. An extrarenal pelvis or a parapelvic cysts can give a false-positive impression of hydronephrosis.

10.4.2 Nuclear Medicine Isotopic Renograms

Diuretic renography can provide noninvasive information about dynamic renal function. Either a dynamic scan using mercaptoacetyl triglycine (MAG3) or a static scan dimercaptosuccinic acid (DMSA) scans. Both are readily labelled by 99 m technetium (99 mTc), which emits gamma radiation detectable by a gamma camera. MAG3 undergoes tubular (90%) and glomerular (10%) excretion, while DMSA binds to the proximal renal tubules. Therefore, MAG3 renograms play an important role in differentiating a nonobstructed dilated system from an obstructed system as well as providing an approximate split functionality of the kidneys. A DMSA scan provides a better deferential split functioning. The scans also provide details of cortical defects like scars and delineation of duplex kidney deferential function between upper and lower moieties.

Furosemide is given either 15 minutes before the isotopic injection (F-15), at the time of injection (F0) or 20 minutes after the injection (F + 20).

MAG3 renograms have three phases:
- A vascular phase (first 10 seconds): reflecting renal blood flow
- Uptake phase (10 seconds to 5 minutes): the uptake of the radio-tracer, this reflects the parenchymal function, and a ‘static’ image can be taken at this stage to estimate the differential function.
- Excretory phase (after five minutes): excretion of the radio-tracer

Images are taken and plotted to give resulting curves (Figure 10.1):
- Type I curve: normal renal uptake and drainage
- Type II curve: Obstruction, continues to rise, with no response to a diuretic
- Type IIIa curve: normal drainage from a hypotonic (stretched/bagged) renal pelvis
- Type IIIb curve: equivocal, the curve very slowly falls and does not rise
- Type IV curve (Homsy sign): A short-lived response to the diuretic is followed by a rise in the curve. It repre−ents obstruction, a F-15 eliminates the transient effect, showing a continual rising curve.

In all these renographic tests, infection may give false results because oedema of the kidney may reduce its blood flow. Hence, if the kidney is infected, the renograms should be repeated after a period of drainage and antibiotics.

10.4.3 Computer Tomography Urography (CTU)

CTU is the modality of choice for a complete evaluation of the urinary tract obstruction. It has by in large replaced intravenous urography (IVU). It offers greater anatomical definition as well as provides functional information to aid with the diagnosis of the underlying cause of obstruction.

10.4.4 Magnetic Resonance Urography (MRU)

MRU can integrate anatomical and functional information without the radiation; however, it is poor at detecting urinary tract stones with a sensitivity of 68.9–81% [18, 19].

10.4.5 Pyelography (Either Retrograde or Antegrade)

Pyelography can accurately define ureteral and collecting system anatomy and can aid in the locality of upper urinary tract obstruction. It is useful in subjects where other imaging modalities have not accurately defined the anatomy of the collecting system.
10.4.6 The Whitaker Test

An objective method of detecting obstruction is to measure the pressure inside the renal pelvis during diuresis. Pressure flow studies are applied using percutaneous nephrostomy and bladder catheter. It carries a slight risk of introducing infection into the closed obstructed system.

In practice, there are some cases where it is obvious that the kidney is reduced to nothing more than a thin bag of scarred tissue which ought to be removed, and others in which there is a substantial thickness of renal tissue worth saving. When dynamic diuresis renogram results are equivocal, and investigations do not give a clear picture of the clinical symptoms of obstruction, a Whitaker test might come in handy.

With the patient lying on the urodynamics bed, a mix of saline with contrast is infused through the nephrostomy at a rate of $10 \text{ ml min}^{-1}$ and the pressure difference between the kidney and bladder is measure.

10.4.6.1 Results

Results indicate whether there is an obstruction.
- $<15 \text{ cm H}_2\text{O}$: unobstructed
- $15–22 \text{ cm H}_2\text{O}$: equivocal; might need repeating
- $>22 \text{ cm H}_2\text{O}$: obstructed

Figure 10.1 (a) MAG3 curves. (b) As the dilated renal pelvis bulges out between the two lower anterior segmental arteries, it carries the obstruction segment outside, giving the misleading impression that it is the lower pole artery which is causing the obstruction. (a) View from behind and (b) View from in front.
10.5 Complications of Hydronephrosis

10.5.1 Infection
After the progressive diminution of renal function, infection is the most important complication. In the presence of obstruction, urine in the renal pelvis is leading freely into the renal lymphatics, and if the urine is infected, organisms readily enter the bloodstream. Septicaemia is an ever-present risk. The curious thing is how often patients seem to remain well despite having a kidney full of purulent urine.

When pyonephrosis is encountered, the first step should be to drain it by means of a percutaneous nephrostomy. For the first few days, thick pus will drain away but will soon be followed by the production of a useful quantity of urine. The creatinine concentration in this urine should be measured from time to time until it becomes stable before making a decision as to whether to try to save the kidney or perform a nephrectomy.

10.5.2 Stones
Stones readily form in the pool of stagnant urine in hydronephrosis. They are multiple and rounded like pebbles from the seashore in contrast to those stones which arise within the kidney and give rise to secondary obstruction and hydronephrosis. The latter are not smooth, and they retain the shape of the renal pelvis and its calices. When it is not easy to be sure whether the obstruction or the stone came first, a version of the Whitaker test may be used at operation or after percutaneous nephrolithotomy to see if there is an idiopathic obstruction at the pelviureteric junction.

10.5.3 Trauma
It is easier to burst a balloon when it is blown up, and for the same reason, a distended hydronephrosis is apt to be ruptured by external injury. The urogram performed as an emergency soon after the patient is admitted with suspected closed renal injury may show the unexpected coexistence of a hydronephrosis and extravasation of urine, but more often the renal function is too poor to display the anatomy of the kidney. A CT scan will show the thinned out parenchyma. This sometimes raises a medicolegal question; did the injury cause the hydronephrosis? This may be easy to answer if the renal parenchyma is already severely atrophied at the time of injury. In other cases, it is impossible to be sure that the injury was not responsible for the obstruction.

10.5.4 Hypertension
Hypertension associated with a hydronephrosis may resolve with cure of the obstruction. In former days, the lower pole artery used to be divided because it was believed to be causing the obstruction (Figure 10.1b), and in these cases, hypertension was a common sequel to the infarction of the lower pole.

10.6 Management (General Principles)
The generic principles of managing a patient with urinary tract obstruction are twofold:
- identification and prompt treatment of the causative factor.
- preservation or removal of the affected kidney, depending on the degree of reversibility of its function.

If acute urinary obstruction is presenting with pain then administration of analgesia is important. Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line treatment and superior to opioids in the case of renal colic. NSAIDs inhibit cyclo-oxygenase (COX) enzyme, which regulates prostaglandin synthesis. Prostaglandins increase glomerular afferent arteriolar vasodilatation, which lead to increase in GFR. NSAIDs inhibit prostaglandin synthesis, thereby preventing glomerular afferent arteriolar vasodilatation. This reduces glomerular filtration by up to one-third, therefore, reducing renal pelvic pressure and stimulation of stretch receptors and leading to alleviation of the pain. Prostaglandin inhibition also reduces ureteric inflammation.

Immediate drainage of the obstructed kidney, particularly if there is superseded infection or in the presence of a solitary kidney or bilateral ureteral obstruction, is essential. This is not only potentially lifesaving but will also prevent further functional decline.

If the obstruction were from the lower urinary tract, then urinary bladder catheterization would be the immediate treatment. In cases of upper urinary tract obstruction, interventional radiological techniques such as percutaneous nephrostomy, or endourological procedures such as ureteric stents, would allow temporary or permanent drainage depending on the situation. Both these techniques have been equally effective in relieving an obstructed collecting system with similar morbidity [20].

10.7 Perinatal Hydronephrosis
Routine screening foetal sonography, at approximately 18–20 weeks gestational age, has dramatically increased the detection of urinary anomalies over the last 25 years. It identifies antenatal hydronephrosis (ANH) in 1–3% of all pregnancies (Table 10.3) [21, 22]. In the past, only symptomatic patients with a palpable mass, haematuria,
or urinary tract infections (UTIs) would mandate further investigations.

There is a lack of correlation between the final urological diagnosis and prenatal and postnatal ultrasound findings. This dilemma has led to many different grading systems, for ANH, with no global consensus as to the most consistent method. However, a collaborative unified grading system was developed to guide the diagnosis and management of perinatal urinary tract dilatation with risk stratification and proposed a standardised protocol for follow up [22, 23].

The parameters used in this grading classification were antero-posterior renal pelvis diameter (APRPD), calyceal dilatation, parenchymal thickness, parenchymal appearance, ureter, and bladder (Table 10.4). Management is determined by initial risk stratification and is split into pre- and postnatal presentation (Figures 10.2 and 10.3).

High-grade obstruction that may warrant antenatal surgical intervention accounts for less than 5% of all detected urinary tract abnormalities. The rationale for treatment is to maximise the development of pulmonary and renal function. There has to be a thorough analysis of risk–benefit ratio prior to embarking on any form of invasive intervention. Unilateral hydronephrosis does not usually require in-uretero intervention. The most common indication for intervention is evidence of bladder outflow obstruction (BOO) with dilated bladder and bilateral hydroureteronephrosis. By and large, the most common form of intervention is in-uterine vesicoamniotic shunt placement under ultrasound guidance.

### 10.8 Pelviureteric Junction Obstruction

Pelviureteric junction (PUJ) obstruction causes impediment to the flow of urine from the renal pelvis to the ureter. The exact aetiology is unknown but there are several

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Incidence (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological/Transient</td>
<td>50–70</td>
<td></td>
</tr>
<tr>
<td>Pelviureteric junction (PUJ) obstruction</td>
<td>10–30</td>
<td></td>
</tr>
<tr>
<td>Vesicoureteric reflux (VUR)</td>
<td>10–40</td>
<td></td>
</tr>
<tr>
<td>Vesicoureteric junction</td>
<td>5–15</td>
<td>Megaureter</td>
</tr>
<tr>
<td>Multicystic dysplastic kidney disease (MDCK)</td>
<td>2–5</td>
<td></td>
</tr>
<tr>
<td>Posterior urethral valves</td>
<td>1–5</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Rare</td>
<td>Ectopic ureter, Duplex system, Polycystic kidney disease, Ureterocele, Prune belly syndrome</td>
</tr>
</tbody>
</table>

### Table 10.4 Normal values for urinary tract dilation classification system.

<table>
<thead>
<tr>
<th>Ultrasound findings</th>
<th>Time at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior–posterior renal pelvis diameter (APRPD)</td>
<td></td>
</tr>
<tr>
<td>Calyceal dilation</td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>&lt;4 mm</td>
</tr>
<tr>
<td>Peripheral</td>
<td>&lt;7 mm</td>
</tr>
<tr>
<td>Paenchymal thickness</td>
<td>&lt;10 mm</td>
</tr>
<tr>
<td>Parenchymal appearance</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Ureters</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Bladder</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Unexplained oligohyramnios</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>N/A</td>
</tr>
</tbody>
</table>
plausible theories described (Table 10.5). There are many acquired causes of obstruction including renal calculi, traumatic stricture, urothelial neoplasm, postinflammatory scarring, and fibro-epithelial polyps. This chapter will focus on congenital PUJ obstruction.

Congenital PUJ obstruction affects between 1 in every 1000–2000 live births. It has a gender ratio of 1:1 and can present at any age of life. Two-thirds of the subjects have a left sided PUJ obstruction, but between 10 and 46% have bilateral disease [24, 25].

10.8.1 Pathogenesis

PUJ obstruction can be congenital or acquired. In congenital, the causes are more likely intrinsic; however, extrinsic crossing vessels may contribute. PUJ obstruction the common pathology is of intrinsic luminal disease. Under normal physiology, the pacemakers of urine propagation, which lie in the minor renal calices, contract to direct urine down to the renal pelvis and ureters. The proximal ureter is open and accommodates the urine by
Figure 10.3 Postnatal diagnosis, risk stratification, and management of hydronephrosis. Source: Adapted from Nguyen et al. [22].

Table 10.5 Causes of extrinsic and intrinsic pelviureteric junction obstructing.

<table>
<thead>
<tr>
<th>Type</th>
<th>Congenital</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrinsic obstruction</td>
<td>Horseshoe kidney</td>
<td>Iatrogenic (postinstrumentation)</td>
</tr>
<tr>
<td></td>
<td>Crossing vessels</td>
<td>polyps</td>
</tr>
<tr>
<td></td>
<td>Duplex collecting system</td>
<td></td>
</tr>
<tr>
<td>Intrinsic obstruction</td>
<td>Noncontractile segment</td>
<td>Urothelial malignancy</td>
</tr>
<tr>
<td></td>
<td>Fibrosis of vales</td>
<td>Renal collecting system calculi</td>
</tr>
<tr>
<td></td>
<td>Kinking of ureter</td>
<td>Traumatic stricture formation</td>
</tr>
</tbody>
</table>
stretch, which subsequently stimulates downstream flow by peristalsis. In PUJ obstruction, the proximal ureter is not receptive to the urine load, thus raising the pressures required to allow urine delivery into the ureter to above normal. This leads to the contraction dissociation of both the distal renal pelvis from the proximal ureter, as well as the proximal renal pelvis from the distal pelvis. As a consequence, the renal pelvis becomes increasingly dilated as pacemaker-induced contractions become more ineffective. This dilatation is accelerated by the inefficient urine transport secondary to the reduced peristaltic transmission as well as reduced urinary bolus volumes.

A frequently found defect is an aperistaltic ureteric segment with abnormal fibrous tissue and longitudinal muscle fibres replacing the normal spiral musculature. Less frequently, the subject can have a primary ureteric stricture, due to excessive collagen deposition, which can occur anywhere throughout the lumbar ureter but most frequently are situated at the PUJ (Figure 10.4).

Abnormal folds of ureteral mucosa and musculature, retained from foetal development, can lead to kinks or valves. In some, a complete adventitial bridge can be retained leading to ureteral bands and adhesions. These congenitally retained folds can occasionally produce an angle of entry of the ureter to the distal renal pelvis in such a manner that the pelvis dilates inferiorly and anteriorly, with a resultant proximal ureteric insertion. This leads to inadequate drainage of the most dependent part of the renal pelvis. Although commonly a secondary phenomenon, high ureteric insertion can rarely be a primary congenital pathology.

The role of aberrant crossing vessels in causing extrinsic PUJ obstruction is still debatable (Figure 10.1). Studies have shown that 63% of patients with PUJ obstruction have aberrant crossing vessels on cross-sectional imaging [26]. However, many of these patients with evidence of crossing vessels also have intrinsic luminal pathology causing renal pelvis dilatation, which subsequently balloons and impinges on to the crossing vessels [27]. Nonetheless, studies have found improvement in obstruction with ligation of aberrant vessels alone, suggesting this is the primary cause [28].

Acquired causes are more commonly caused by intrinsic causes rather than extrinsic compression. Intrinsic causes include trauma from a stone or endoluminal procedures (ureteroscopy), and urothelial tumours at the PUJ (polyps or malignancy). Extrinsic causes include retroperitoneal fibrosis, malignancy, or iatrogenic injury.

### 10.8.2 Natural History and Presentation

Puji obstruction most commonly is a congenital problem; however, it can present at any stage of life. It has a variable natural history. Due to the widespread use of antenatal sonography, there has been a dramatic rise in the diagnosis of asymptomatic hydronephrosis in newborns. Obstruction can resolve spontaneously in some cases, whereas with others it increases in severity with deterioration in renal function. It can also remain stable for years in many patients (Table 10.6). It can occasionally present in a previously normal or mildly dilated kidney. A study of conservatively managed children with an antenatal diagnosis of PUJ

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>CLINICAL DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flank pain</td>
<td>Not uncommon. Usually after the age of 4. Persists for several hours or days. Usually in the loin but can be epigastrium. Pain following ingestion of fluid due to renal pelvic distension (Dietl crisis).</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Common before advent for prenatal screening. Presents with pyonephrosis with high fever and warrants immediate urinary drainage.</td>
</tr>
<tr>
<td>Haematuria</td>
<td>May be spontaneous or following minor trauma (i.e. exercise).</td>
</tr>
<tr>
<td>Palpable flank mass</td>
<td>Most common presentation of neonates prior to prenatal screening. In children, can mimic Wilms tumour but can be differentiated by radiological imaging.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Rarely a primary presentation.</td>
</tr>
<tr>
<td>Incidental</td>
<td>Incidental finding from imaging organised for other reasons is not uncommon.</td>
</tr>
</tbody>
</table>
obstruction showed 17% required surgical intervention due to worsening obstruction, 27% had spontaneously resolved obstruction, and 56% had stable disease with no deterioration in obstruction or renal function [29].

10.8.3 Investigations
Radiological modalities should be targeted at determining the anatomical site and functional significance of the suspected obstruction. Usually the first-line investigation in children is ultrasonography. This can visualise the dilated collecting system and can determine the level of obstruction. In adults, a CT scan is standard protocol for patients with loin pain, or contrast-enhanced CT urogram for patients with haematuria. Both modalities will accurately give you anatomical information regarding site of obstruction with CT urogram giving you functional data as well (Figure 10.5).

Diuretic renography, most commonly mercaptoacetyltriglycine-3 (MAG3) dynamic renogram, is used in the evaluation of PUJ obstruction (Figure 10.6). It gives functional information as well as quantitative data regarding split renal function and is a valuable tool to assess the success of surgical treatments. DMSA scan is useful in patients with poor renal function in determining whether a reconstructive procedure or nephrectomy would be the most appropriate surgical intervention.

10.8.4 Management
If patients with suspected PUJ obstruction do not fulfil the criteria for surgical intervention, then close monitoring with serial diuretic renography may be appropriate. The indications for intervention are:
- progressive decline in unilateral split function.
- impairment in overall renal function.
- obstruction associated symptoms (pain or haematuria).
- infection episodes (pyonephrosis).
- renal tract stone development.
- secondary hypertension.

Different endourological and open, laparoscopic, and robotic procedures have been described to treat PUJ obstruction. Age and comorbidities play a major role in decision making because a patient who is elderly and comorbid may be suitable for conservative monitoring or long-term ureteral stenting, whereas reconstructive surgery would be most appropriate for a paediatric patient to potentially reverse renal dysfunction.

10.8.5 Pyeloplasty
Laparoscopic or robotic pyeloplasty are the current gold standard of treating PUJ obstruction because they are associated with quicker recovery and discharge from hospital and less postoperative morbidity and a low risk of conversion [30]. Laparoscopy can be done either by the more common transperitoneal or retroperitoneal approach. Robotic pyeloplasty is usually done via a transperitoneal approach. The steps of the procedure are identical regardless of approach.

Though minimally invasive techniques have replaced open pyeloplasty, the techniques of the procedures are similar. Anderson and Hynes popularised their novel technique in the middle of the twentieth century. It can be used almost universally for different PUJ obstruction scenarios even when there is a high ureteric insertion into the renal pelvis as well as when it is already dependent. It is the sole procedure that completely excises the abnormal PUJ itself. Its use is more debatable in situations with a predominantly inaccessible intrarenal pelvis or long proximal ureteric stricture. Nonetheless, the key principle is the use of a wide, well-vascularized flap of renal pelvis to enlarge the narrow part of the ureter. Essential to success is absence of any tension and free drainage.
Figure 10.6 MAG 3 Renogram showing reduced clearance of radio-isotope form right kidney (a) and then post pyeloplasty improved drainage (b).
10.8.5.1 Procedure
The colon is reflected medially off the kidney and the dilated renal pelvis presents itself into view. Once the renal pelvis has been exposed, it is carefully freed from all its confusing coverings of connective tissue. When these have been swept aside, the relationship of the lower pole vessels if these are present becomes clear, and they are lifted up on a silicone sling (Figure 10.7).

If the lower pole vessels are in the way, a dismembered pyeloplasty will be performed, and this can be modified if there is a long narrow upper segment of ureter (Figure 10.8).

It helps to fill the renal pelvis with 30–40 ml of saline with a syringe before marking out the flap with fine stay-sutures (Figure 10.9). Unless this is performed while the pelvis is distended, it is easy to mark it wrongly. Cut through the ureter near the pelviureteric junction, and thread it behind the lower pole vessels, slit up, and spatulate in the lateral aspect. The redundant renal pelvis is excised. The apex of the spatulated ureter is brought to the inferior border of the renal pelvis (Figure 10.10). It is important to use only absorbable suture material for the anastomosis, but whether interrupted or continuous sutures are used is of little consequence. A ureteral stent inserted through the anastomosis.

Figure 10.7 (a and b) A sling is placed around the lower pole segmental vessels.

Figure 10.8 Dismembered pyeloplasty. A U-shaped flap is formed from the redundant renal pelvis.

Figure 10.9 The renal pelvis is distended.
If there is a long narrow segment of ureter, the flap can be made longer by using the Culp manoeuvre, carrying the flap in a spiral fashion round the pelvis (Figure 10.11). If there is no lower pole vessel, there is no need to detach the ureter and either a simple flap or the Culp spiral modification can be adapted. Using either method, the anastomosis is made in a long ellipse to prevent subsequent contraction, and there must be no tension.

Figure 10.10 (a–d) A long elliptical anastomosis is formed between the flap of the pelvis and the spatulated ureter.

Other pyeloplasty procedures include Foley Y-V Plasty and Scardino-Prince vertical flap.

10.8.5.2 Results
Stones have been seen to form on the suture material used to sew the ureter to the renal pelvis; they are almost inevitable if nonabsorbable suture has been used for the anastomosis, but they can occur on absorbable sutures as well.
Figure 10.11 (a–f) When there is a long narrow segment of ureter, Culp's spiral flap of renal pelvis is used.
Hypertension is an important late sequel of even a successful pyeloplasty, and it is wise for the patient to be closely followed by the general practitioner.

In a few patients, despite an apparently successful operation – as judged by a free runoff down the anastomosis and no hold-up of contrast or isotope in the renal pelvis – the patient continues to experience recurrent pain in the loin, sometimes accompanied by verified infection in the urine. To some extent this kind of result, which is fortunately rare, represents a failure of selection of candidates for an operation; in retrospect, it is easy to say that it would have been better to have advised a nephrectomy.

In the majority, the outcome is excellent in terms of the absence of symptoms, infection, stones, and deterioration of renal function, but when assessed by the appearance of the kidney in a urogram, the patient and the surgeon need to be warned that the kidney often continues to look disappointingly dilated. This does not mean that it is obstructed. An initial ultrasound or a MAG3 renogram can show whether there is worsening hydronephrosis. However, it does mean that once there has been a thinning of the renal parenchyma and a deterioration in the muscular capacity of the renal pelvis, then the pyelographic appearances are unlikely to return to normal. This need not matter; the important point is that the obstruction has been permanently overcome and things will not deteriorate any further.

### 10.8.6 Endopyelotomy

The basic principle of this technique is a full-thickness postero-lateral incision through the obstructed anatomy in the PUJ from lumen to periureteric and peripelvic fat with bridging ureteric stent placement to allow healing. Rarely offered as first-line treatment for PUJ obstruction, however, can be in recurrence of PUJ obstruction post pyeloplasty rather than a repeated pyeloplasty. Can also be offered in the symptomatic frail elderly patient.

Ramsey first described the technique in 1984 [31]. Multiple adaptations have been made since. The incision can be done by either an endopyelotomy knife or laser through either percutaneous or ureteroscopic approaches. Success rates do not approach that of laparoscopic or robotic pyeloplasty but have been shown to be as high as 87.5% in well-selected patients [32]. Antegrade (via percutaneous tract) and retrograde approaches have been described as well as retrograde cautery wire balloon endopyelotomy and balloon endodilatation. There is no convincing evidence that any of these methods have superior outcomes. The benefits include shorter operative time with reduced hospital stays and postoperative recovery.

### 10.8.7 Nephrectomy in Hydronephrosis

When the preoperative investigations show that the kidney has minimal function, or when at operation it is clear that the cortex is but a paperthin shell, nephrectomy is the correct operation.

### 10.9 Retrocaval Ureter

Retrocaval ureter results from the persistence of the posterior cardinal veins during embryologic development. This is a rare anomaly where the ureter surrounds the vein at the level of the third and fourth lumbar vertebra. It almost invariably affects the right ureter, and its presence should be suspected with a S-shaped ureter on imaging. Incidence rate is approximately 1 in each 1000 births [33]. Type I is more common (90%) and results in hydronephrosis due to compression of the ureter between the inferior vena cava and the vertebra. Type II presents with no obstruction. Management of obstruction is surgical with either open or laparoscopic pyelopyelostomy with transposition of the ureter anterior to the inferior vena cava.

### 10.10 Duplication Anomalies, Ectopic Ureter, and Ureteroceles

#### 10.10.1 Definitions and Incidences

Duplication implies that there is an upper and a lower renal function moiety, each with its own pelvicalyceal system and ureter. The individual moiety’s ureter may join anywhere along its length. Nearly 1% of postmortem examinations have been found to show upper urinary tract duplication to varying degrees [34]. Roughly 40% of cases show bilateral abnormalities. Duplication anomalies show an incomplete penetrance and are an autosomal dominant trait affecting 8% of member of affected families. The majority of upper tract duplications unite above the ureteric orifice and usually have minimal clinical manifestations. On the contrary, complete duplications often cause symptoms and affect renal functionality. These are much rarer affecting less than 0.1% of individuals, with the majority being female. Twenty-five percent of complete duplications present bilaterally.

In incomplete ureteric duplication, the ureteric bud arises normally from the mesonephric duct but then undergoes variable degrees of bifurcation. Complete duplication occurs when two separate ureteric buds arise separately from the mesonephric duct. In complete duplication systems, inevitably the accessory ureteric bud drains the upper pole moiety and enters the bladder in a distal location more medially placed location than
Hydronephrosis

10.10.2 Management

Treatment of ectopic ureter or ureterocele, whether of a single or duplex system, is based on anatomical and functional investigations.

Anatomical assessment involves an ultrasound. It will easily identify upper tract dilatation in both a single and duplex system, as well as help differentiate a dilated upper moiety ureter (the Meyer-Weigart law). This can lead the upper moiety to ectopic insertion, which may the urethra or the urogenital sinus. The ectopic ureter is prone to obstruction because of its long intramural course through the bladder wall, which can cause severe hydronephrosis. Upper moiety ureters are usually associated with dysplastic nonfunctioning upper renal moiety. In contrast, due to the insertion into the bladder with a shorter submucosal tunnel, VUR occurs predominantly in the lower moiety ureteric orifice (Figures 10.12–10.14).

Ectopic ureter is any ureter, single or duplex, that does not enter the trigonal area of the bladder. In females, the ectopic ureter may be suprasphincteric, at the level of the striated sphincter, or distal either at distal vagina or introitus. In contrast, male ectopic ureters are always suprasphincteric, connecting to the seminal vesicles, ejaculatory ducts, or the vas deferens, causing pain and infection rather than urinary incontinence clinically.

Ureteroceles are cystic dilatations of the distal ureter that are located either within the bladder or involving the bladder neck and urethra (Figure 10.15). These can also be single or duplex systems (usually in the ureter draining the upper pole moiety). There are several classifications of ureteroceles with the most clinically useful being intravesical (entire ureterocele above bladder neck) or extravesical (some part of ureterocele permanently at bladder neck or urethra).

Figure 10.12. Computed tomography (CT) axial and coronal images showing left duplex renal collecting system with dilated upper moiety. B, bladder; LM, lower moiety; UM, upper moiety.

Figure 10.13. Computer tomography showing left kidney atrophic upper moiety with hydronephrosis to the bladder. Source: Photographs courtesy of Dr. Mark Robinson Aneurin Bevan UHB Hospital.
ectopic ureter from a ureterocele (Figure 10.15). A CTU or MRU can provide the most detailed imaging of an affected urinary tract.

Functional assessment of renal function can be made by DMSA scan or to investigate obstruction form upper moiety (Figure 10.14) and bladder assessment by voiding cystourethrogram (VCUG) (Figure 10.16). Endoscopic evaluation is essential. The goals of therapy are preservation of renal function, elimination of obstruction, infection and reflux, and maintenance of urinary continence.

Uncomplicated, asymptomatic duplex does not need treatment. Obstructed upper moiety will need a ureteric reimplantation. However, if the renal moiety is poorly functioning, a hemi-nephrectomy and ureterectomy would be the treatment choice.

### 10.11 VUR

As the name implies, VUR is retrograde flow of urine from the bladder back up the ureters with or without hydronephrosis. Normally a physiological sphincter is formed by the ureters passing obliquely through the bladder wall for about 2 cm. When the bladder contracts...
Hydronephrosis during micturition, the intramural ureter is compressed by the bladder wall and prevents urine from passing back up the ureters.

10.11.1 Aetiology

Primary anatomical VUR is a defect in the intramural ureteric length to ureteric diameter ratio (ILUD ratio), whereby the intramural ureteric length is too short to allow successfully complete compression to prevent reflux. Normal ratio is 5:1. See mainly in duplexed lower moiety ureters, but this can happen in single ureters.

Secondary VUR is due to disease or conditions not related to the intramural ureter:

- Most common cause is iatrogenic: during TURP or TURBT whereby the ureteric orifice is resected, reducing the ILUD ratio. Other causes include ureteric reimplantation without antireflux techniques or incising a ureterocoele open.
- High bladder pressure leading to significantly high bladder pressures, overcoming the physiological sphincter mechanism (e.g. bladder outflow obstruction [i.e. prostatic obstruction or urethral strictures] or poor bladder compliance [i.e. neuropathic bladders]).

VUR is more commonly asymptomatic detected incidentally; however, patients can present with loin pain occurring with a full bladder or after micturition or recurrent UTIs.

Investigation of choice to demonstrate VUR is a voiding cystourethrogram. Voiding cystogram can establish the grade of VUR, which can help guide management (Table 10.7).

Urodynamics can be done to assess bladder pressures. CTU can be useful to establish anatomy. DMSA scan can be done to assess renal function and demonstrate renal scarring.

10.11.2 Management

Generally, VUR is not a dangerous or harmful condition; however, in the presence of high bladder pressure or infection, VUR can slowly kill the kidney. Ergo, treatment is tailored around the symptoms, renal functionality, as well as degree of VUR. VUR grades I–II resolve spontaneously in 80–90% of patients, whereas grade III in 50% and in 20% of grades IV and 10% of grade V [35].

10.11.3 Primary VUR

Conservative measures: with increased hydration and bladder toilet training, with the use of prophylactic antibiotics if there is a history of recurrent UTIs.
Endoscopic management: Deflux bulking agents can be injected intramurally with the distal ureter and ureteric orifice with high success rates. However, repeated injections might be required. Deflux is a hyaluronic acid/dextranomer copolymer.

10.11.4 Surgery

Ureteric reimplantation is indicated in higher grade VUR, or lower grade VUR failed to respond to endoscopic injections in a duplex renal system, or renal ectopia.

Nephroureterectomy if the kidney is nonfunctioning, or VUR is persistent and causing significant symptoms.

Treatment of secondary VUR is managing of the underlying pathology; if it fails, measures are similar to primary VUR managements.

10.12 Megaureter

Megaureter is a dilatation of the ureter irrespective of cause with or without associated renal pelvis dilatation. The upper normal limit diameter of the ureter in children up to 16 years old is 0.50–0.65 cm and 0.7 cm in adults. Megaureter refers to a ureteric diameter of 7 mm or greater [36].

Smith classified megaureters into four categories: obstructed, refluxing, refluxing with obstruction, and non-refluxing and non-obstructing [37]. It can also be classified into primary and secondary. The challenge with this condition is to promptly treat obstructing ureters and preventing unnecessary intervention in dilated nonobstructing stable ureters. For the purpose of this chapter we will focus on primary obstructive megaureter (POM).

POM is thought to be caused by an aperistaltic non-functioning segment of the distal ureter near the vesicoureteric junction leading to obstruction and proximal dilatation. Approximately 10–23% of antenatally detected upper tract dilatation is thought to be caused by POM [38]. It more commonly affects the left ureter and is more common in young boys.

The vast majority of the children are asymptomatic. Symptoms due include UTIs, abdominal pain, and haematuria.

Nonobstructive megaureters can be safely observed with serial sonography and the majority resolve spontaneously within the first two years. Studies have shown that ureters greater than 10 mm prove more difficult to manage and only 17% resolve with 21% of cases requiring surgical intervention [39]. These patients require close monitoring with functional (MAG3 renogram) and anatomical imaging (ultrasound) (Figure 10.17).

Surgery is indicated in cases of POM with recurrent UTIs, persistence of dilatation, differential renal function of less than 40% of affected renal unit, or deterioration of greater than 5% function on serial renograms [36].

The procedure of choice for babies older than one year old is ureteric reimplantation with or without ureteral tapering. In grossly dilated ureters in infantile bladders of babies younger than one, temporising methods such as ureteric stenting, endoscopic balloon dilatation, endouretostomy, cutaneous ureterostomy, and refluxing ureteral reimplantation is favoured.

10.13 Ureteral Strictures

Ureteral strictures can be either congenital (rare) or acquired. The acquired causes include ureteral calculi, traumatic surgical instrumentation, malignancy, radiation, ischaemia, infection, and periureteral fibrosis. More commonly, strictures are benign and iatrogenic, caused either by endoluminal surgery or during laparotomy for nonurological operations; these lead to ischaemic strictures.

**Table 10.7 International reflux classification and suggested management of vesicoureteral reflex (VUR).**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Contrast into a ureter only; no dilation</td>
<td>Asymptomatic: conservative management</td>
</tr>
<tr>
<td>II</td>
<td>Contrast into the whole collecting system, ureter, renal pelvis, and calyces; no dilation</td>
<td>Asymptomatic: conservative management</td>
</tr>
<tr>
<td>III</td>
<td>Mild dilation</td>
<td>Asymptomatic: conservative management</td>
</tr>
<tr>
<td>IV</td>
<td>Dilated ureter is slightly tortuous; moderate dilation of pelvis and blunting of calyces</td>
<td>Ureteric reimplantation</td>
</tr>
<tr>
<td>V</td>
<td>Severe ureteric dilation and tortuosity, gross dilation of pelvis and calyces</td>
<td>Ureteric reimplantation</td>
</tr>
</tbody>
</table>
Figure 10.17 Coronal computed tomography image with contrast showing delayed excretion showing right megaureter. U, ureter.
10.13.1 Pathophysiology

Ischaemic strictures are usually caused by injury at time of operation (i.e. colorectal, vascular, or gynaecological) or postradiotherapy. Ureteroscopic damage to the ureter causes a flap or perforation or ureteric anastomoses (i.e. urinary diversion or in transplanted kidneys) leads to urine extravasation and fibrosis formation causes a stricture.

Cross-sectional imaging with CT usually identifies a hydronephrotic kidney with hydrourerter up to a transition point. For exclusion of malignancy, retrograde pyelography and ureteroscopy with or without biopsy is commonly necessary.

Endourological treatments include:

- Conservative management if asymptomatic and malignancy ruled out.
- Ureteral stent placement: indicated in the symptomatic frail elderly patient
- Balloon dilatation or endoureterotomy

If these treatments are unsuccessful, or in carefully selected patients, ureteric reconstruction according to site and size of disease and patient factors can achieve good success rates. Nephrectomy is also an option if the renal function is poor (<15%)


11

Kidney and Ureter Trauma

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Abstract

Renal injuries are mostly managed conservatively. Operative intervention with view of kidney salvage is possible. However, nephrectomy may be the only option to control life-threatening haemorrhage. During the conservative period, it is extremely important to keep patients under close monitoring because this will allow early identification of patients who will require surgical intervention. Ureteral injuries are relatively rare and mostly iatrogenic. Management of the ureteral injuries depends level of injury, severity, and on time (early or late) of recognition of the injury. Careful assessment (cystoscopy with retrograde pyelogram) and appropriate imaging computed tomography urogram or intravenous pyelogram (IVP) are essential to select most suitable method of repair of ureteral injury.

Keywords kidney injury; trauma; ureter injury

Key Points

Renal Injury
- Eliciting a detailed history of the trauma
- Early imaging and diagnosis
- Conservative management unless the patient is unstable
- Awareness of complications

Ureteric Injury
- Early recognition with a high index of suspicion
- If early postoperative injury: early treatment is best
- Management depends on ureteral site of injury
- Principles of ureteral repair must be adhered to

11.1 Kidney Injuries

The kidney is the most commonly injured genitourinary organ. It is involved in about 1–5% of all trauma [1, 2]. The kidney is protected by the perinephric fat surrounding it, the abdominal muscles, vertebra, and ribs; therefore, isolated renal injuries are rare and will require a large degree of force and are usually seen in multisystem injuries. However, children have proportionately less fat padding and muscle bulk; therefore, lesser force can cause renal injury. The renal injury can cause considerable morbidity and mortality; however, advances in imaging and management strategies have resulted in a decreased need for surgery in majority of renal trauma cases [3–5].

11.1.1 Types of Injuries

1) Blunt trauma: a common (~90%) cause of renal injury
2) Penetrating injury: less common cause and could be;
   - High velocity, for example, rifle bullet (800–1000 m s⁻¹)
   - Medium velocity, for example, handheld guns (200–300 m s⁻¹)
   - Low velocity, for example, knife stab injury
3) Blast injury
It is important to note the type of injury because the majority of blunt injuries (>95%) can be managed conservatively, but half of stab injuries and >75% of gunshot injuries will require surgical exploration [4].

Blunt injuries to the kidney usually result from sport injuries, falling from heights, or road traffic accidents (RTAs).

Usual mechanism is a direct blow to the loin or kidney, compressing the kidney between the 12th rib and the lumbar vertebrae (Figure 11.1). Furthermore, in RTAs, the likely mechanism is rapid acceleration followed by rapid deceleration, which can cause renal pedicle injury (renal artery or vein disruption or tears or thrombosis or renal pedicle avulsions). The renal pedicle is more commonly injured this way because it is attached firmly to the retroperitoneal structures. Extent of deceleration is an important factor and should be enquired in the history. Mild trauma resulting in haematuria can be the result of occult pre-existing pathology (e.g. pelviureteric junction [PUJ] obstruction, renal tumour etc.) [6].

Penetrating injuries anterior to the anterior axillary line will most likely cause damage to the renal hilum (vessels or renal pelvis), whereas posterior to this will be in the parenchyma and injuries are less serious. Low-velocity weapons usually cause damage confined to the line of the wound track. Although high-velocity trauma causes greater injury and tissue loss as large energy is transmitted outside the path of the projectile. This results in temporary cavitation, deformity, shearing, and contamination of the affected site or organ. Blast injuries can have components of blunt and penetrating and invariably cause significantly more damage than either alone (Figure 11.2).

11.1.2 Classification of Kidney Injury

The extent of injury following blunt trauma can result in cortical laceration, collecting system injury, and in extreme cases, complete disruption of the renal pedicle. These will lead to blood loss with or without extravasation of urine (Figures 11.3–11.8) [7]. Degree of injury depends on force of impact. The American Association for the Surgery of Trauma (AAST) has developed a grading system for renal trauma (Table 11.1), which is commonly used both in clinical and research settings.

In most minor injuries, the renal parenchyma is split, there is usually microscopic haematuria, minimal loss of blood, and patient remains haemodynamically stable. These are referred as renal contusions, and their prognosis is so good and further investigation is usually not required [8]. However, in very severe injuries, usually resulting from rapid deceleration injuries, the renal artery and vein are torn across, resulting in immediate and immense loss of blood. One needs to bear in mind that, nearly 25% of the cardiac output goes through both kidneys in a minute (12.5% for each); therefore, bleeding can be significant if not contained.

11.1.3 Diagnosis and Investigations

11.1.3.1 History and Initial Assessment

Potential severity of renal damage is assessed from history, past medical history (single kidney, pre-existing renal pathology), and examination, with emphasis on the nature of injury, pain, and haematuria. Haematuria is a hallmark of renal trauma, but it does not always correlate with the degree of injury. Indeed, in more serious injuries, such as renal pedicle injuries, arterial thrombosis or disruption of the ureteropelvic junction can occur without any haematuria [9, 10]. In young adults and children with renal trauma, hypotension is a late sign or may not occur despite life-threatening blood loss, so vigilance is vital in management of the injured child.

Hemodynamic stability should be noted and used to guide future management. Blood pressure (BP), pulse, haemoglobin (Hgb), and haematocrit (Hct) are useful parameters.

Patients with shock (systolic blood pressure <90 mmHg) will need immediate resuscitation and close monitoring. In penetrating injuries, bullet entry and exit wounds should be identified and the trajectory of the bullet considered. Similarly stab injuries can appear small but may penetrate deep into the abdominal cavity.

A urine dipstick is a rapid and reliable test to screen for nonvisible haematuria; however, false-negative findings do occur in approximately 3–10% of cases [11]. If there is nonvisible haematuria with normal systolic BP (>90 mmHg), the likelihood of renal trauma is <0.5%, whereas in the presence of visible haematuria, the risk increases to nearly 10%.

Figure 11.1 Closed renal injury: the kidney is compressed between the 12th rib and the lumbar transverse processes. The lower ribs and the tips of the transverse processes are frequently fractured.
11.1 Kidney Injuries

11.1.3.2 Blood Tests

- Serial Hgb level and Hct are important markers of blood loss and guide management strategies. A low Hct, especially in the presence of shock, implies the need for rapid resuscitation.
- In a renal function test, an initially elevated creatinine level usually suggests pre-existing renal pathology.

11.1.3.3 Imaging

Computed tomography (CT) with intravenous contrast is the gold standard for the diagnosis of renal injuries in patients who are stable. CT can define the location and extent of renal injury; additionally, it allows identification of associated intra-abdominal injuries. A renal pedicle injury is suggested by a lack of contrast enhancement of the kidney or a central parahilar hematoma, whereas a large medial hematoma displacing the renal vasculature.
suggests a venous injury. Delay images taken at a 10–15 minute delay (after intravenous contrast) are important for visualisation of the renal collecting system and diagnosis of renal pelvis and ureteral injuries. In renal pelvis injuries, the contrast extravasation is usually seen medial to the renal hilum.

CT scans can be avoided in patients with blunt, nondeceleration trauma; microscopic haematuria; and no shock because incidence of renal injury is low [8]. Imaging is mandatory in:

- Children with nonvisible haematuria and any degree of renal trauma.
- Nonvisible haematuria with a BP <90 mm Hg.
- Visible haematuria.
- Rapid acceleration or deceleration injuries (to rule out renal pedicle injury or ureteric avulsion) [12].
- Penetrating trauma because imaging should be performed regardless of haematuria status [13].

A CT scan provides good information, showing the full extent of the laceration of the renal parenchyma with a collection of blood outside the kidney confined within Gerota fascia.

Ultrasound may be useful in determining which patients need further imaging with CT and may eliminate unnecessary scans. Additionally, ultrasound can be used for serial evaluation of stable injuries or after urinoma or retroperitoneal hematoma [14].

Intravenous pyelography (IVP) is no longer the preferred modality in patients with renal trauma. However, if CT is...
not available, IVP can establish the presence or absence of the kidneys, define the parenchyma, and outline the collecting system. Non-visualisation or non-function of a kidney usually indicates severe trauma to the kidney, such as pedicle injury or shattered kidney. The IVP may show distortion of the renal outline on one side, with extravasation of contrast medium, or it may show no secretion at all.

In patients who are not stable and have to immediately go to the operating theatre, a one-shot intra-operative IVP on the table can be performed. A single plain film is taken 10 minutes after the injection of $2 \text{ ml kg}^{-1}$ contrast medium. This can provide useful information on a suspected injury and can determine the functional status of the contralateral kidney [15].

Figure 11.5 Types of grade 4 injuries. (a) Laceration into the collecting system, (b) laceration into collecting system with segmental renal artery injury, (c) laceration of upper pole with associated segmental artery injury, and (d) laceration into collecting system with extravasation of urine and segmental renal artery injury.
Magnetic resonance imaging (MRI) and angiography are lesser used modalities in the initial evaluation of patient with renal trauma. However, MRI is used in patients with an iodine allergy, if CT is not available, or in rare cases, when CT findings are equivocal [16].

The most common indication for angiography is non-visualisation of the kidney. In such cases, renal angiogram may show damage to the renal artery or its segmental branches. It is also the test of choice for the evaluation of renal vascular injuries and selective embolisation can be performed in same setting (Figure 11.9a–d). CT angiogram is a preferred modality in present era.

**11.1.4 Management**

Patients who are haemodynamically stable can be treated conservatively, whereas patients who are unstable need surgical or radiological intervention.

**11.1.4.1 Nonsurgical Management**

Conservative management is the treatment of choice for the majority of patients with renal injuries. The conservative management has a low failure rate (1%) and may save kidneys that might otherwise be lost during attempted repair [3]. There is increasing trend for more severe injuries to be treated conservatively. Even patients with urinary
extravasation and solitary injuries can be managed expectantly, with a resolution rate of >90% [17]. However, during the conservative management, close monitoring is vital to recognise need for added intervention or surgery.

The conservative nonoperative management is favourable in [8, 18]:

- Patients who are haemodynamically stable or who remained stable after initial resuscitation.
- Absence of grade V vascular or ureteral injuries.
- Exploratory laparotomy for other abdominal injuries (in patients with renal injuries who do not require renal surgery) should not necessarily include retroperitoneal or renal exploration.

Some patients with penetrating renal trauma can be managed conservatively as well. The site of penetration is helpful to determine management decisions. For example, nearly 90% of patients with stab wounds posterior to the anterior axillary line can be managed...
conservatively [19]. Operative intervention should be performed if the injury involves the hilum, or if there is continued bleeding, ureteral injuries or pelvic lacerations are present [20]. Low-velocity gunshot and stab wounds in patients who are stable have good outcomes when managed with a nonoperative approach, but tissue damage resulting from high-velocity gunshot injuries may necessitate exploration and even nephrectomy [21].

Grade V vascular injuries are regarded as an absolute indication for exploration, but parenchymal grade V injuries in patients who are stable at presentation may be safely treated conservatively [22, 23]. However, intervention is predicted by the need for continued fluid and blood resuscitation, perirenal haematoma size >3.5 cm, and the presence of intravascular contrast extravasation [24].

Initial conservative approach is appropriate in patients who are stable with urinary extravasation or devitalised renal fragments [25]. But in cases of persistent extravasation or urinoma, management is usually successful with ureteral stenting or nephrostomy tube placement. Persistence of extravasation might necessitate exploration.

The need of follow-up CT in patients managed conservatively is controversial; however, relative indications include fever, increased pain, or persistent bleeding or dropping haemoglobin. Most injuries will heal with conservative approach, but there can be an increased rate of complications [26, 27].

### 11.1.5 Surgical Exploration: Options

Operative exploration to control haemorrhage and salvage or remove a kidney is required in a minority of patients with renal trauma [28].

Absolute indications for renal exploration are:

- Life-threatening renal haemorrhage with hemodynamic instability, irrespective of the mode of injury [28]
- An expanding or pulsatile perirenal hematoma identified intra-operatively [28, 29]. (This signifies a grade V vascular injury.)

Relative indications include:

- Persistent bleeding and suspected renal pelvis or ureteral injury.
- Penetrating renal trauma (isolated grades I–III stab and low-velocity wounds (e.g., low-velocity gunshot wounds in patients who are otherwise stable can be managed expectantly [19]).
- Inconclusive imaging and a pre-existing abnormality or an incidentally diagnosed tumour may require surgery even after minor renal injury [30].

The management of renal injury may also be influenced by the decision to explore or observe associated abdominal injuries [31]. For isolated renal trauma, surgery should be performed using a transperitoneal approach with early vascular control prior to opening the Gerota fascia [32, 33].
The renal vasculature is accessed through the posterior parietal peritoneum, incising over the aorta and medial to the inferior mesenteric vein (Figure 11.10).

Renorrhaphy is the preferred technique for renal reconstruction. General principles of renorrhaphy include:

- Early control of renal artery.
- Evacuation of haematoma.
- Examination of the lacerations, including repairing of the injured vessels and conserving as much of the parenchyma as possible.

If a polar injury occurs or if nonviable tissue is present, a partial nephrectomy may be necessary. Watertight closure of the collecting system is recommended. If it is not feasible, a simple closure of the parenchyma over the collecting system can be successful as well. An omental pedicle flap

Figure 11.9 Grade 4 injury with multiple segmental artery bleeds being embolised. (a) Computed tomography of grade 4 injury; (b) angiography showing bleeding points; (c) embolization; and (d) post embolization showing bleeding stopped.
or perirenal fat bolster can be used in the case of renal capsule injury. The use of haemostatic agents and sealants in reconstruction are helpful for effective haemostasis [34]. In all cases, a retroperitoneal drain is usually required.

Nephrectomy is necessary if the kidney is not salvageable. The overall rate of patients who undergo a nephrectomy during exploration is around 13%, usually in patients with penetrating injuries and higher rates of transfusion requirements, haemodynamic instability, and higher injury severity scores [35].

The nephrectomy is generally required in patients who have a penetrating injury, an increased need for transfusion, hemodynamic compromise, high-grade injury, and associated intra-abdominal injuries [36, 37]. Mortality rate is higher in patients requiring nephrectomy, but cause of deaths are usually the associated injuries rather than the renal trauma alone [38]. Grade V vascular injuries are generally treated with nephrectomy because repair is usually not successful [39]. However, repair should be attempted in patients with a solitary kidney or bilateral renal injuries [40], but it is not used in the presence of a functioning contralateral kidney [4]. Similarly, in gunshot injuries caused by a high-velocity bullet, reconstruction can be difficult, and nephrectomy is often required [41].

### 11.1.6 Role of Angiogram and Embolisation

Arteriography with selective embolisation’s role is increasing in renal injuries (Figure 11.9); however, the results can be poor in patients with grade V injuries [42]. However, initial or repeated embolisation for the higher-grade injuries can prevent a nephrectomy in more than 75% of patients. Segmental arterial injury can be managed non-operatively with good results [43].

Radiological embolisation is indicated in patients with active bleeding from renal injury but without any other indication for immediate surgical exploration. Patients who are obviously showing evidence of internal bleeding (e.g. dropping Hgb), but are in a stable state, should have a renal angiogram with embolisation of bleeding vessels [44] (Figure 11.11).

### 11.1.7 Renal Injury in the Patient with Polytrauma

Most patients with penetrating renal trauma have associated adjacent organ injuries, and hence, a multidisciplinary team approach is required for effective management. In the absence of an expanding haematoma with haemodynamic instability, associated multi-organ
injuries do not increase the risk of nephrectomy [35]. In patients with polytrauma and associated renal injuries, it is vital to determine the most significant injury. Each injury should be managed on its merit irrespective of conservative or surgical approach.

### 11.1.7.1 Iatrogenic Renal Injuries

Iatrogenic renal trauma is rare but can lead to significant morbidity, especially as the more common injuries are vascular. However, significant injury requiring intervention is rare. Patients with minor injuries should be treated conservatively. Severe or persistent injuries require intervention with embolisation. In patients who are stable, a second embolisation should be considered in case of failure [45]. Renal exploration might be required if bleeding continues or patient becomes unstable.

Haemorrhage is the most concerning complications after percutaneous nephrolithotomies (PCNLs), biopsies, or partial nephrectomy. Post-PCNL bleeds can be conservatively managed with clamping of the nephrostomy; however, embolisation might be required for persistent bleeds. Arteriovenous (A-V) fistula and pseudo-aneurysms can occur after partial nephrectomy or more commonly percutaneous renal biopsies. The majority are small and heal spontaneously, but they can persist to cause retroperitoneal bleeding or heavy haematuria. Angiography detects the fistula and can proceed to embolisation for treatment. Persistence will require either a partial or complete nephrectomy.

### 11.1.7.2 Complications of Renal Trauma

In all patients who are conservatively managed, a repeat CT scan should be done at least 48–86 hours after the trauma for re-evaluation of the trauma stage and to ensure no missed complications.

Early complications (within 30 days of the injury):

1) There is a small but real danger of delayed haemorrhage (i.e. secondary haemorrhage) in patients who have a major renal laceration. Delayed bleeding can occur within several weeks of the injury and is usually managed with selective angiographic embolisation [46]. Delayed onset of marked haematuria after penetrating trauma most often indicates the presence of an A-V fistula. Percutaneous embolisation is often successful in these instances, but surgery may be required to repair large fistulas. Nephrectomy might be required if bleeding persists.

2) Urinary extravasation usually resolves over time unless obstruction or infection is present (Figure 11.12). Persistent large volume extravasation usually responds well to stent placement or nephrostomy drainage [27]. Renal repair might be required if persistent urine leakage despite conservative measures.

3) Although pseudocysts and urinomas are uncommon, it is most important to recognise them (Figure 11.12). A collection of extravasated urine becomes walled-off by fibrous tissue but remains in communication with the renal pelvis [47]. The wall of the cavity becomes eventually more or less lined with urothelium, and in turn, this leads to calcification and heterotopic bone formation. In time, the urinoma takes on the appearance of an eggshell. The contents of the urinoma often become infected, but even if they do not, the absorption of urine from the granulation tissue lining the cavity leads to hyperchloraeic acidosis. Merely draining the cavity is seldom sufficient, and it is usually necessary to dissect out the lining of the cavity and repair the defect in the renal pelvis, which a difficult and time consuming operation.

4) Perinephric abscess formation can be managed with percutaneous drainage or open drainage. However, open drainage can pose an increased risk of renal loss [28].

5) The haematoma around the lacerated kidney may compress the ureter and lead to hydronephrosis, but it is rarely possible to be sure that a hydronephrosis was not present before the injury.

Late complications:

1) **Late onset hypertension**: Hypertension after renal trauma occurs in <5% of patients [48] and is caused by external compression from a perirenal hematoma on the renal artery (Page kidney) or chronically as a result of compressive scar formation. Other causes include renal artery or branch thrombosis, stenosis (Goldblatt kidney), or an A-V fistula. The reduced blood supply causes renal ischaemia, leading to excess renin excretion in an effort to increase the blood pressure to increase renal blood supply. The hypertension might develop over months to years after the initial trauma. Management is by pharmacological antihypertensive agents or by excision of the ischemic

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**Figure 11.11** Angiography may reveal a bleeding arterial branch which can be plugged with gel foam or a coils.
parenchyma, vascular reconstruction, or even nephrectomy [49].

2) Renal insufficiency: due to the devascularised segment(s).

11.2 Ureteral Injuries

Trauma to the ureters is relatively rare, and the most common cause is iatrogenic. Overall, ureteral trauma accounts for 1–2.5% of genitourinary tract trauma [50, 51].

11.2.1 Causes of Ureteric Injuries

1) Iatrogenic injuries to the ureter. The ureter can be injured during pelvic surgery (e.g. diathermy damage, caught in ligature, crushed in a clamp, divided by accident, or damage to the blood supply causing devascularisation and leading to ischaemic damage). Risk factors for iatrogenic ureteric trauma include advanced malignancy, prior abdominal or pelvic surgery or irradiation, inflammatory processes (e.g. diverticulitis, endometriosis, anatomical abnormalities, and major intra-operative haemorrhage [52]). A list of common procedures with associated risks of ureteric injury is listed in Table 11.2 [45].

2) Blunt trauma. About one-third of cases of trauma to the ureters are caused by blunt trauma, mostly RTAs or fall from heights [53].

3) Penetrating injuries (gunshot or stabbing). Penetrating ureteral trauma is the most prevalent after iatrogenic and is mainly caused by gunshot wounds [50, 51].

4) Deceleration injuries (e.g. PUJ shearing). The renal pelvis tears away from the ureter.

11.2.2 Classification of Ureteral Injuries

Severity of ureteral injury are based on degree of ureteral injury (Table 11.3; Figure 11.13) [54].

11.2.3 Clinical Features

The iatrogenic injury is usually not be recognised at time of surgery [44, 55]. More often, a delayed diagnosis is

<table>
<thead>
<tr>
<th>Table 11.2 Ureteral injury with various procedures.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
</tr>
<tr>
<td>Gynaecological</td>
</tr>
<tr>
<td>Vaginal hysterectomy</td>
</tr>
<tr>
<td>Abdominal hysterectomy</td>
</tr>
<tr>
<td>Laparoscopic hysterectomy</td>
</tr>
<tr>
<td>Urogynaecological (anti-incontinence/prolapse)</td>
</tr>
<tr>
<td>Colorectal</td>
</tr>
<tr>
<td>Ureteroscopy</td>
</tr>
<tr>
<td>Mucosal abrasion</td>
</tr>
<tr>
<td>Ureteral perforation</td>
</tr>
<tr>
<td>Intussusception or avulsion</td>
</tr>
</tbody>
</table>
made when leakage of urine from the wound drain or vagina is noted.
Nonspecific features include abdominal or flank pain, infection/sepsis, haematuria, ileus, vomiting, and signs of urinary obstruction (hydronephrosis and reduced renal function).

11.2.4 Investigations
Investigations should not be delayed in patients with suspected ureteric injuries, and one should have a low threshold for its consideration. If suspicion of injury was intra-operative, then direct inspection, injection of methylene blue into the ureter with observation of leakage, on-table IVU, or retrograde studies can be done. However, postoperative or trauma-related suspicion: a renal ultrasound can show variable degrees of hydronephrosis or a urinoma. Whereas a contrast CT scan with delayed images would show extravasation of contrast from the ureteral injury site or an obstruction at the site of injury (Figure 11.14). However, diagnostic retrogrades are the gold standard, especially if other images were not conclusive.

<table>
<thead>
<tr>
<th>Grade of ureteral injury</th>
<th>Description of injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Contusion or haematoma</td>
</tr>
<tr>
<td>II</td>
<td>&lt;50% transection</td>
</tr>
<tr>
<td>III</td>
<td>&gt;50% transection</td>
</tr>
<tr>
<td>IV</td>
<td>Complete transection with &lt;2-cm devascularisation</td>
</tr>
<tr>
<td>V</td>
<td>Avulsion with &gt;2-cm devascularisation</td>
</tr>
</tbody>
</table>

Table 11.3 Classification of ureteral injury.

Fluid (leaked urine) from drain or vagina can be tested for creatinine to confirm diagnosis, if the level is >300 umol L⁻¹ than serum creatinine, then it is urine.

11.2.5 Management of Ureteral Injuries
Patient should be managed as a whole; therefore, if the ureter is obstructed and patient is unwell (i.e. infection or sepsis), a percutaneous nephrostomy should be placed to decompress the drainage system and allow the

![Figure 11.13 Ureteric injuries with contrast extravasation, (a) Grade 2 (obtained from http://www.medscape.org/viewarticle/727952_3), (b) grade 3, and (c) grade 4.](image)

![Figure 11.14 Distal ureteral injury with urine extravasation. Source: Case courtesy of Dr. Chris O’Donnell, http://Radiopaedia.org, rID: 36562.](image)
infection to settle, followed by a delayed repair. Otherwise, early repair is the best option with more favourable outcomes.

11.2.5.1 Retrograde Study and JJ Stent Insertion

In all ureteral injuries, it is necessary to confirm the diagnosis by retrograde urography. Bilateral retrogrades should be done despite injury to one side because bilateral ureteric injury is not uncommon. Careful assessment should be made for a vesicovaginal fistula because these may well co-exist with the ureteral injury [56].

At the time of performing the retrograde urogram, an attempt may be made to pass a guidewire up the ureter from below, or if there is a percutaneous nephrostomy in position, from above (Figure 11.15). If the guidewire can be wriggled past the site of the obstruction, a JJ stent may be passed over it and left in situ for four to six weeks by which time the injured ureter may be found to heal completely without any stricture [57].

Partial ureteric injuries can be repaired immediately with a stent or urine diversion by a nephrostomy tube. Stenting is helpful because it provides canalization and may decrease the risk of ureteric stricture [52].

11.2.5.2 Other Operative Repair Options

Management of a ureteric trauma depends on many factors, including the location of the injury, timing of detection of the injury, and the nature and severity of the injury (e.g., previous radiotherapy can cause poor healing). The principles of ureteral repair should to be adhered to (Table 11.4).

Figure 11.15 If a guidewire can be made to pass the site of the injury a double-J stent may be passed over it.
Depending on location of injury various types of reconstruction are available:

**Upper Ureter:**
- Uretero-ureterostomy if the injured section is short (<3 cm)
- Transuretero-ureterostomy (TUU) for longer injuries (>3 cm)
- Uretero-calyceostomy if the either the TUU or the uretero-ureterostomy fails

**Mid Ureter:**
- Uretero-ureterostomy
- TUU
- Ureteric reimplantation (ureteroneocystostomy) with or without Boari flap

**Lower Ureter:**
- Ureteral reimplantation
- Ureteral reimplantation with or without psoas hitch

**Complete Ureteric loss:**
- Ileal interposition
- Autotransplantation
- Nephrectomy

Depending on the timing of the injury:

**Early recognition**
If a ureteral injury is suspected intra-operatively or in the first 14 days postoperatively, a retrograde pyelogram study followed by attempting a JJ stent insertion is a reasonable choice. However, if the ureter is accidently ligated with suture or transected, an open repair is required. Repair options are based on location.

**Later recognition**
Injuries that are diagnosed late are usually treated first by a nephrostomy tube with or without a stent [52]. Retrograde stenting is often unsuccessful in this setting. These patients can present with peritonitis and anuria, urinoma, sepsis, wound or vaginal leakage, and flank pain.

A careful management is required for this group of patients. This includes resuscitation, treatment of sepsis, and a percutaneous nephrostomy inserted to divert urine and relieve the obstruction. A CT urogram should be done to determine the location and severity of the ureteral injury. After the acute phase, a cystoscopy, examination under anaesthesia, and retrograde pyelogram study are required before definitive management.

If small fistula is detected, a JJ stent insertion is usually enough to allow spontaneous recovery. The endourological treatment of small ureteral fistulae and strictures is safe and effective in selected cases [58], but an open surgical repair is often necessary. For uretero- and vesicovaginal fistulas repair with interposition of intact layer of healthy tissue is important. Ureteral repair, otherwise, is similar to other management options.

### 11.2.6 Operative Repair Options for Ureteral Injury

There are four alternative methods of repairing an injured ureter:

- Boari-Ockerblad flap
- Psoas hitch
- Transureteroureteric anastomosis
- Ileal loop interposition

#### 11.2.6.1 Boari-Ockerblad Flap

This is the preferred and most reliable method of repairing an injured ureter [56, 59]. The original incision is reopened, unless the hysterectomy has been performed by the vaginal route, in which case a vertical midline incision gives marginally easier access than a Pfannenstiel incision especially in patients with high body mass index (BMI).

The injured ureter is followed down to the site of injury where it is seldom possible to see exactly how it has been injured; sometimes a distinct suture can be found but usually the site of injury is concealed in scar tissue and oedema (Figure 11.16). The ureter is divided at the site of blockage. It always retracts cranially for several centimetres, leaving a gap larger than first anticipated (Figure 11.17). The bladder is now filled, and a widely based flap is marked out with stay sutures before the wall of the bladder is incised (Figure 11.18). Careful haemostasis is obtained by suture ligature rather than diathermy. The opposite ureter is marked and protected by passing a catheter into it.

A long submucosal tunnel is made in the Boari flap, and the ureter is drawn down this into the bladder. The end of the ureter is spatulated, everted, and sewn to the Boari–Ockerblad flap with interrupted fine absorbable sutures (Figure 11.19). The flap is intubated using a JJ stent. The flap is closed in the line of the opening in the bladder using two layers of fine absorbable suture. It is sometimes helpful to attach...
Figure 11.17 The ureter is divided above the site of the injury: it always retracts. The bladder is filled and the $\cap$-shaped Boari flap marked out with stay sutures.

Figure 11.18 The $\cap$-shaped Boari flap is raised and a submucosal tunnel formed with scissors.

Figure 11.16 The ureter is followed down to the site of the injury.

Figure 11.19 The ureter is drawn through the submucosal tunnel, spatulated, and sutured to the mucosa of the bladder over a suitable splinting catheter.
the flap to adjacent fibrous tissue to make sure it lies correctly and that there is no tension at all on the anastomosis (Figure 11.20).

The bladder is drained with a suitable urethral catheter and the wound closed with absorbable sutures with a drain to the retropubic space.

The JJ stent is usually removed after six weeks followed by CT urogram or IVP three months' after surgery.

11.2.6.2 Psoas Hitch
This is an alternative method for ureteral repair [60]. Having found the injured ureter and divided it at the site of injury, the bladder is mobilised by dividing the superior vesical vessels on the opposite side. The bladder is then incised at right angles to the line of the ureter (Figure 11.21), drawn up, and attached with two or three stout sutures of absorbable material to the tendon of psoas minor (when present) or to some adjacent strong fibrous tissue in those patients without this tendon. The implantation of the ureter is performed using an antireflux tunnel (Figure 11.22).

11.2.6.3 Transureteroureteric Anastomosis
The injured ureter is led behind the mesosigmoid to the good side, and there it is spatulated and anastomosed...
end-to-side onto the good ureter using very fine absorbable sutures (Figure 11.23).

Of these three methods, the Boari–Ockerblad technique is the most reliable and versatile [61, 62]. It can even be brought right up to the kidney in some cases [63]. There is a temptation with the psoas hitch to allow a little tension on the anastomosis, and with transureteroureteric anastomosis, there is a risk that the good ureter will be damaged [60].

11.2.6.4 Ileal Loop Interposition
For very high injuries of the ureter where it is not possible to effect an end-to-end anastomosis, it is usually safer to make an ileal conduit in the usual way, and anastomose one end to the ureter and the other to the bladder (Figure 11.24).

References


12

Kidney and Ureter Inflammation

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Abstract

Inflammatory condition of the kidneys and ureter are common place in modern practice. These conditions can present the urologists with patients who are extremely unwell and suffering with life-threatening sepsis. Prompt assessment of such patient is vital, and basic resuscitation skills need to be coupled with an extensive knowledge of the possible underlying pathologies along with their medical and surgical management options. Although rare in Western countries, chronic infections such as tuberculosis (TB) and parasitic infections should always be part of a differential diagnosis. For trainees in urology, it is important to have a board range of differential diagnoses at your disposal and knowledge of how to investigate these effectively – both on the wards and in an examination setting.

Keywords  pyelonephritis; emphysematous pyelonephritis (EPN); xanthogranulomatous pyelonephritis (XPN); renal abscess; renal tuberculosis; schistosomiasis; glomerulonephritis

Key Points

- Acute inflammatory conditions of the kidney can present in a patient who is systemically compromised and should be assess as a matter of urgency.
- Sepsis carries a high risk of mortality.
- Radiologically guided percutaneous nephrostomy (PCN) has superseded many open surgical options for drainage of an infected renal collecting system or abscess.
- Renal tuberculosis is the most common extrapulmonary site of infection.
- Retroperitoneal fibrosis is not inflammation of the ureter parse but is a result of an inflammatory process in the surrounding tissues.
- Consider early involvement of a nephrologist if no urological cause can be found.

12.1 Medical Inflammatory Conditions of the Kidney

There are a number of medical inflammatory conditions of the kidney that the urologist should have a familiarity with because they may present to the acute urology on-call situation.

The classification of these conditions is dependent upon the site and is broadly divided into glomerulonephritides (inflammation of the glomeruli) and tubulointerstitial [1].

12.1.1 Glomerulonephritis (Table 12.1)

Commonly this group of disorders are immunologically mediated and respond to immunosuppressive therapy. Histopathology, via renal biopsy, is required to make the diagnosis [1].

12.1.2 Tubulointerstitial (Table 12.2)

This is a disease of the renal tubules. It presents with proteinuria, electrolyte disturbance, and varying degrees
Table 12.1 Summary of glomerulonephritides.

<table>
<thead>
<tr>
<th>Type</th>
<th>Histology</th>
<th>Causes</th>
<th>Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal Change</td>
<td>Unknown pathogenesis</td>
<td>Atopy, HLA-DR7, Drugs</td>
<td>Commonly idiopathic, presents with severe nephrotic syndrome</td>
<td>Good response to corticosteroids</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis (FSGS)</td>
<td>Non-specific immune deposits; segmental scars in glomeruli</td>
<td>HIV infection, obesity, heroin use, previous local glomerular injury</td>
<td>Primary disease: Idiopathic nephrotic syndrome</td>
<td>Less responsive to treatment</td>
</tr>
<tr>
<td>Focal segmental glomerulonephritis</td>
<td>Small-vessel vasculitis segmental inflammation and necrosis</td>
<td>Primary or secondary small vessel vasculitis; Occurs in systemic disease</td>
<td>Secondary disease: proteinuria</td>
<td>Good response to corticosteroid</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td>Podocyte injury due to surface antigen antibodies Glomerulosclerosis secondary to thickening of basement membrane Granular subepithelial IgG immune deposits noted</td>
<td>HLA-DR3, drugs, hepatitis B, heavy metals, malignancy</td>
<td>Idiopathic Common cause in adults</td>
<td>Immunosuppressants and corticosteroids</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Unknown pathogenesis Segmental nephritis and increased mesangial matrix and cells IgA immune complexes seen</td>
<td>Commonly idiopathic, liver disease</td>
<td>Wide spectrum of presentation, haematuria (early sign), hypertension</td>
<td>Supportive Poor response to immunosuppressive therapy Poor evidence for steroid use</td>
</tr>
<tr>
<td>After infection</td>
<td>Infiltration by neutrophils and macrophages combined with diffuse Subendothelial immune deposits</td>
<td>Any infection (commonly streptococcal)</td>
<td>Haematuria, hypertension, sodium with fluid retention and oliguria</td>
<td>Spontaneous resolution</td>
</tr>
<tr>
<td>Mesangio-capillary glomerulonephritis</td>
<td>Immunoglobulin type: Circulating immune complexes deposition Complement type: Caused by complement abnormalities (Immune deposits Crescentic nephritis)</td>
<td>Infections, autoimmunity, complement gene mutation</td>
<td>Haematuria, proteinuria</td>
<td>Treat underlying disease, immunosuppressive therapy</td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td>Autoantibodies to α3 chain of type IV collagen in basement membrane. Linear IgG immune deposits Crescentic nephritis</td>
<td>HLA-DR15</td>
<td>Rapid loss of renal function over days and weeks. Lung haemorrhage</td>
<td>Cyclophosphamide, corticosteroids, and plasma exchange therapy</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>Anti-DNA antibodies. Immune deposits always seen depending on type. Non-specific</td>
<td>Complement consumption, complement deficiencies</td>
<td>Can present with alone with no extrarenal manifestations</td>
<td>Prednisolone and cytotoxic therapy</td>
</tr>
</tbody>
</table>

Source: Adapted from [1].

HIV, human immunodeficiency virus; HLA, human leucocyte antigen; IgA, immunoglobulin A; IgG, immunoglobulin G.
of renal failure. Tubulointerstitial disease is further split into acute and chronic [1].

### 12.2 Acute Surgical Inflammatory Conditions of the Kidney

#### 12.2.1 Pyelonephritis

Pyelonephritis is inflammation of the kidney and renal pelvis. In the presence of no complicating factors (e.g. congenital malformations, instrumentation of the urinary tract, or states of reduced immunity such as diabetes) this condition can be termed uncomplicated pyelonephritis.

##### 12.2.1.1 Aetiology and Risk Factors

Gram-negative bacteria are common causative organisms of upper urinary tract infections because they are in lower urinary tract infections. *Escherichia coli* (*E. coli*) is responsible for the majority of pyelonephritis cases (80%), but other organisms such as *Klebsiella pneumoniae*, *Proteus mirabilis*, *Streptococcus faecalis*, and *Pseudomonas* should be considered when choosing antibiotic therapy. Factors affecting bacterial virulence are key to infections. See Chapter 20 for more details. Although pyelonephritis can affect any population or age group, there are certain groups of patients at higher risk (Table 12.3).

##### 12.2.1.2 Clinical Presentation

Acute pyelonephritis is a clinical diagnosis. Classically, it presents with symptoms of systemic upset (i.e. pyrexia, nausea, vomiting, anorexia, and lethargy) and more specifically with unilateral loin pain, worse over the renal or costovertebral angle.

Patients might complain of lower urinary tract infection symptoms (L-UTI): frequency, urgency, dysuria, and offensive smelling urine.

Care must be taken in the initial assessment of patients with sepsis (Table 12.4). Severe sepsis has a reported mortality of 20–42% [4]. Severe sepsis has a reported mortality of 20–42% [4].

#### 12.2.1.3 Pathophysiology of Sepsis

Inflammation caused by chemical, mechanical, or infective stimuli occurs and precedes healing. This is usually localised to the area of the stimuli; however, activation of inflammatory cascades on a systematic level can give rise to systemic inflammatory response syndrome (SIRS). For example, this can be initiated by the out membrane of gram-negative organisms, the lipopolysaccharide layer or their endotoxins, or in gram-positive organisms, the lipoteichoic acid, or peptidoglycan.

These triggers activate receptors on immune cells (neutrophils, macrophages, lymphocytes, and plasma cells) leading to production of pro-inflammatory cytokines, tumour necrosis factor α (TNF-α), interleukins (IL-2, -6, and -8) and activation of the kinin, complement, and fibrinolytic system cascades. The cytokines, TNF-α, and IL lead to the production of prostaglandins, leukotrienes, platelet-activating factor, and phospholipase A2; these cause endothelial damage, which in turn causes capillary leakage. In addition, the activated neutrophils release nitric oxide, which leads to vasodilation (Figure 12.1). The

---

**Table 12.2 Causes of acute and chronic tubulointerstitial renal disease [1].**

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs: Penicillin, NSAIDs, Mesalazine, PPI</td>
<td>Drugs: Tenofovir, analgesia, lithium, cyclosporine, tacrolimus, drugs causing AIN</td>
</tr>
<tr>
<td>Infection: Pyelonephritis, TB, Leptospirosis, Hantavirus</td>
<td>Infection: Pyelonephritis</td>
</tr>
<tr>
<td>Immune: Autoimmune nephritis, transplant rejection</td>
<td>Immune: Sarcoidosis, Sjögren syndrome, SLE, chronic transplant rejection</td>
</tr>
<tr>
<td>Toxic: Myeloma light chains, mushrooms (<em>Cortinarius</em>)</td>
<td>Toxic: Lead, mushrooms (<em>Cortinarius</em>), Herbal medicines</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>AIN</td>
</tr>
<tr>
<td>Metabolic: Excessive phosphate administration, hypokalaemia, hyperoxaluria</td>
<td>Congenital: VUR, inherited, Wilson disease, MSK, sickle-cell disease, renal dysplasia</td>
</tr>
</tbody>
</table>

AIN, acute interstitial nephritis; MSK, medullary sponge kidney; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor; SLE, systemic lupus erythematosus; TB, tuberculosis; VUR, vesicoureteral reflux.

**Table 12.3 Risk factors for pyelonephritis in adults.**

- Female
- Vesicoureteric reflux (VUR)
- Urinary tract obstruction
- Urinary tract calculi
- Neuropathic bladder
- Diabetes mellitus
- Congenital malformations
- Pregnancy
- Indwelling catheters
- Instrumentation of the urinary tract
activation of the coagulation systems leads to microthrombi formation leading to dysfunctional tissue perfusion.

These effects result in widespread microvascular injury, tissue ischaemia, and clinical manifestation of hypotension.

### Investigation

Initial investigations should include urine analysis with bedside urine dipsticks to check for the pH, white blood cells, nitrites, and red blood cells.

Perform urine microscopy and culture to identify causative organisms and provide antibiotic sensitivities.
Send blood for full blood count (FBC) and urea and electrolytes (UE) as well as inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Blood cultures must be sent for all pyrexic patients before antibiotic use. For those patients who present with septic shock lactate levels must be obtained via arterial blood gas measurement.

X-ray of the kidneys, ureter, and bladder (KUB) should be carried out to assess for obvious renal stone disease or gas around the kidney (the later finding could suggest emphysematous pyelonephritis [EPN]). Renal tract ultrasound must be performed to rule out renal collecting system obstruction, stone disease, or malformations which may alter further investigations and management. Computed tomography (CT) scans, however, are becoming the standard imaging modality in the acute setting and should be considered if symptoms are >72 hours to exclude abscesses (Figure 12.2) [5].

12.2.1.5 Management
Management is determined by how unwell the patient is. Patients who are clinically well can be deemed as mild to moderate but those who require hospital admission can be defined as severe. In hospital settings, sepsis should be treated along an agreed protocol, such as the Surviving Sepsis campaign bundles [2]. In most cases, if the infection is severe enough to require hospitalisation, then management should be a multidisciplinary approach and must include local high-dependency unit (HDU) and intensive-therapy unit (ITU) teams.

Until antibiotic sensitivities can be established, initial management is with broad-spectrum antibiotic therapy targeted at gram-negative organisms. Local antibiotic resistance is an important factor in deciding on antibiotic cover for patients. In mild to moderate cases of acute pyelonephritis, oral antibiotics may suffice. However, intravenous antibiotics will be required for severe infections, and once the pyrexia has settled, the intravenous antibiotics can be switched to oral antibiotics. Fluoroquinolone such as ciprofloxacin can be used as a first-line therapy because most organisms are sensitive to them; however, local antibiotic guidelines should dictate appropriate antibiotic use [5].

12.2.2 Renal Abscess
Previously known as a ‘renal carbuncle’, this rare infection is a collection of pus within the renal parenchyma.

12.2.2.1 Aetiology and Risk Factors
Any condition that reduces host defences or leads to abnormal drainage of the renal collection system predisposes one to renal abscess formation (i.e. diabetes mellitus, nephrolithiasis, or ureteric obstruction) [6].

Before the widespread use of antibiotics, renal abscesses were due to haematogenous spread of gram-positive bacteria such as staphylococci. Today the most common organisms are gram-negative uro-pathogens such as E. coli, Klebsiella spp., and Proteus spp.

12.2.2.2 Clinical Presentation
Symptoms are similar to any upper tract urinary infection (i.e. pyrexia, loin pain, and malaise). Symptoms may be acute over days and weeks or become chronic over months, which eludes to the likelihood of abscess formation. Very rarely the abscess may be ‘pointing’ (Figure 12.3).

12.2.2.3 Investigation
CT is the gold standard diagnostic investigation, with a renogram to assess kidney functionality.

12.2.2.4 Management
Abscess >5 cm are commonly drained percutaneously or with open surgery. Small abscesses (≤3 cm) are treated with antibiotics and expectant management. Abscesses of 3–5 cm can be treated with either modalities (i.e. drainage or conservatively with reportedly similar results) [6–8].

12.2.3 Pyonephrosis or Infected Hydronephrosis
Pyonephrosis is the accumulation of pus within the renal collecting system. It is associated with irreversible damage to the renal parenchyma resulting in permanent loss of function.

12.2.3.1 Aetiology and Risk Factors
Risk factors to development of pyonephrosis are attributed to any factor that causes hydronephrosis (e.g. ureteric obstruction by stones or cancer) with subsequent development of infection (i.e. infected obstructed system).

12.2.3.2 Clinical Presentation
Patients present with pyrexia, renal or costovertebral angle tenderness, and are acutely unwell with systemic toxicity. History might be eluding to aetiology and usually symptoms present for a few days or weeks prior to the worsening sepsis.

12.2.3.3 Investigation
Assessment of a patient who is acutely unwell should follow that of acute pyelonephritis. CT scans are the gold standard and will establish the diagnosis and aetiology as well as aid determination of the extent of the disease. CTs can show the presence of air in the system, stone burden, and degree of hydronephrosis, oedema, and thickening of the urinary tract as well as perinephric fat stranding. Isotope scans can assess kidney functionality. If not available, then X-ray of the KUB could demonstrate air in the
collecting system and ultrasound can identify hydronephrosis and echogenic material within the collecting system, as well as perinephric fat stranding.

12.2.3.4 Management
Initial management should include resuscitation and intravenous broad-spectrum antibiotics. Urgent decompression of the affected renal collecting system is the priority. Until decompression of the system is achieved, the patient will continue to deteriorate, hence, the need for urgent decompression. This can be achieved by either percutaneous drainage with a nephrostomy insertion or ureteric drainage with a ureteric stent.

12.2.4 Perinephric Abscess
Extension of infection outside the renal parenchyma into Gerota fascia can result in perinephric abscess formation. Usually resultant from rupture of a cortical abscess or an obstructed infected renal system. Rarely,
Examination of the flanks may reveal a palpable mass, and there may be erythema of the overlying skin. Extension of the hip may elicit severe pain in the back due to psoas spasm and inflammation.

Initial management should include resuscitation and intravenous broad-spectrum antibiotics followed by urgent percutaneous drainage. In severe cases or in those with persistent or loculated collections, open surgical drainage may be required. Potentially, although rarely, a nephrectomy is needed, especially if the kidney is non-functioning.

### 12.2.5 Emphysematous Pyelonephritis (EPN)

First described in 1898 by Kelly and MacCallum, emphysematous pyelonephritis (EPN) is a rare necrotizing infection of the renal parenchyma or perirenal tissue caused by gas-forming uro-pathogens [9].

#### 12.2.5.1 Aetiology and Risk Factors

The majority (85%) of patients presenting with EPN have diabetes mellitus with 34% caused by an obstructive uropathy. Other risk factors include: obstructive uropathy, immunosuppression, alcoholism, drug abuse, and neurogenic bladder; anatomical abnormalities have also been associated [10–12].

EPN affects women more than men 4:1 [12]. This is thought to be due to the increased risk of urinary tract infections (UTIs) in women [11, 13, 14].

*E. coli* is the most common organism followed by *Klebsiella*, *Proteus*, and *Pseudomonas* species; coagulase-negative *Staphylococcus* and Group D *Streptococcus* have also been implicated [11, 12, 15, 16].

#### 12.2.5.2 Clinical Presentation

EPN is a life-threatening condition with a high mortality rate. Patients present with pyrexia (75%), renal angle pain and tenderness (70%), haematuria (30%), pyuria (78%), and are profoundly unwell and exhibit signs of severe sepsis with 25% presenting in septic shock [12]. Patients are sometimes treated as pyelonephritis until they fail to respond to management. Nearly 45% present with associated acute kidney injury (AKI). Rarely crepitus may be felt in the region of the renal angle.

#### 12.2.5.3 Investigation

All patients who are acutely unwell must first be resuscitated before specific investigation can be carried out. Initial work up should include a full history and clinical examination. Particular attention should be noted to rule out a new diagnosis of diabetes mellitus or previously known history of the disease. Further investigations follow that of acute pyelonephritis (bloods and urine analysis).

Once the patient is stable, then prompt imaging of the renal collecting system must be undertaken. X-ray can
be used to identify gas pattern shadowing within the region of the renal collecting system, but this can be non-specific and only accurate in diagnosing EPN in 53% of patients [12]. Ultrasound again can demonstrate gas in or around the renal collecting system and should be considered if no other imaging modalities are available, with an accuracy of about 68% [12].

A CT urogram is the gold standard with a 100% accuracy in diagnosing EPN (Figure 12.4). There are two CT-based scoring systems (Table 12.5).

12.2.5.4 Management
Initial management should include resuscitation, intravenous broad-spectrum antibiotics, and adequate control of blood sugar levels. As the majority of causative organisms are gram-negative bacteria, antibiotic therapy should target these until specific cultures and sensitivities are available.

Historically, antibiotic therapy coupled with open nephrectomy or surgical drainage was the treatment of choice. However, advances in the last decade have established image-guided, percutaneous drainage under local anaesthetic as the intervention of choice for EPN. Figure 12.5 depicts a flow diagram of EPN management.

Once the patient is stable, then a MAG-3 or dimercaptosuccinic acid (DMSA) can be performed to establish renal functionality.

12.2.5.5 Prognosis
In the past, mortality rates were quoted to be as high as 50%; however, with percutaneous drainage, meticulous medical management, and close support with the intensive care unit, survival rates have increased, with current predicted mortality rates of about 18% [12]. Although, the cause of the majority of cases, the presence of diabetes mellitus or nephrolithiasis play no role in increasing mortality rates, but septic shock was the greatest predictor with >50% attributed mortality.

12.2.6 Xanthogranulomatous pyelonephritis (XPN)
Xanthogranulomatous pyelonephritis (XPN) is a rare acute and chronic kidney infection, leading to destruction of renal tissue and permanent loss of renal function. It is associated with underlying renal stone disease or renal obstruction.

12.2.6.1 Pathophysiology, Aetiology, and Risk Factors
Infections and urinary obstruction lead to engorgement and destruction of the renal parenchyma leading to suppuration, haemorrhage, and necrosis. This leads to abscess formation with deposition of granulomatous tissue with granular histiocytes and ‘foamy’ lipid-laden macrophages. There is also fibrohistiocytoma-like or plasma cell granuloma-like patterns, and possible myofibroblast metaplasia. The affected kidney or section of kidney becomes grossly enlarged.

XPN is more commonly diffused, affecting the entire kidney; however, focal cortical or even segmental forms can occur.

Table 12.6 lists risk factors that can predispose to XPN; however, invariably stones are the culprit. E. coli and Proteus are the more common organisms; however, any of the uro-pathogens can lead to XPN.

12.2.6.2 Clinical Presentation
Patients present in a similar manner to those with pyonephrosis or acute pyelonephritis. Symptoms include flank or loin pain, pyrexia, haematuria, and systemic upset. On clinical examination, it may be possible to ballot a renal mass on the affected side.

12.2.6.3 Investigation
Urine and blood cultures may be positive for common uro-pathogens. Blood test may show renal dysfunction, anaemia, or leucocytosis. Inflammatory markers such as CRP and ESR will be elevated.

US imaging of the renal tract may demonstrate a dilated collecting system and an enlarged kidney containing echogenic material. CT scanning may show renal stones within the renal mass. Due to indistinct radiological appearance, XPN is indistinguishable from renal cell carcinoma. However, occasionally the ‘Bear Paw’ sign can be picked up on the cross-sectional appearance of the kidney. The renal pelvis is contracted, whereas the calyces are dilated, mimicking the toe pads of the bear paw. The role of magnetic resonance imaging (MRI) is not well established in the context of XPN, and so is not routinely used. Radioisotope imaging will demonstrate a poorly or nonfunctioning kidney.

Definitive diagnosis can only be made with tissue analysis. Microscopic examination shows yellow nodules of pus, necrosis, and haemorrhage within the calyces.

12.2.6.4 Management
Most patients will initially be treated with antibiotics until their acute infection has settled. After diagnostic imaging, patients will proceed to a nephrectomy to rule out malignancy after which, the confirmation the diagnosis of XPN is usually made. Intraoperatively, XPN can be technically challenging due to the severe inflammation, which results in obliteration of tissue planes as they become fused together and become difficult to dissect.

12.2.6.5 Complications and Prognosis
Within the literature, there have been cases noted of sinus and fistula formation because of chronic infection. These can be to adjacent organs or structures
Figure 12.4 (a–d) Transverse and coronal computed tomography (CT) images showing gas within the renal collecting system (white arrow) consistent with emphysematous pyelonephritis (EPN). Source: Photographs courtesy of Dr. Mark Robinson Aneurin Bevan UHB Hospital.
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(i.e. psoas abscess or even cutaneous) but are considered extremely rare [17, 18].

### 12.3 Chronic Surgical Inflammatory Conditions of the Kidney

#### 12.3.1 Tuberculosis

**Introduction**

Tuberculosis (TB) commonly manifests as a respiratory infection. Extrapulmonary TB can affect any part of the body with the kidney being the most common. Table 12.7 shows other genitourinary manifestation of TB.

![Figure 12.5 Recommendations for treating emphysematous pyelonephritis (EPN). Source: Adapted from [12].](image)
Table 12.7 Manifestations of genitourinary TB infection and common routes of infection.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestation</th>
</tr>
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<tbody>
<tr>
<td>Renal</td>
<td>Abscess formation</td>
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<tr>
<td></td>
<td>Fistula formation</td>
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<tr>
<td></td>
<td>Auto-nephrectomy</td>
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<tr>
<td></td>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Ureteric (secondary to renal TB infection)</td>
<td>Fibrosis with stricture formation: leading to obstruction</td>
</tr>
<tr>
<td></td>
<td>Ureteric orifice dysfunction: leading to reflux</td>
</tr>
<tr>
<td>Bladder (secondary to renal TB infection)</td>
<td>Chronic ulcerations (worm-eaten edges)</td>
</tr>
<tr>
<td></td>
<td>Reduced capacity bladder and poor compliance</td>
</tr>
<tr>
<td>Prostate (haematogenous spread)</td>
<td>Chronic prostatitis</td>
</tr>
<tr>
<td></td>
<td>Fistula formation</td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
</tr>
<tr>
<td>Urethra or penis (secondary to bladder TB infection)</td>
<td>Stricture disease</td>
</tr>
<tr>
<td></td>
<td>Penile lesions</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
</tr>
</tbody>
</table>

TB, tuberculosis.

12.3.1.2 Aetiology and Risk Factors

Tubercle bacilli reach the urinary tract via the bloodstream from a primary focus in the lung or bowel. There can also be tertiary spread from bone lesions. The bloodstream brings the mycobacteria to the kidney where they form multiple minute abscesses in the parenchyma (Figure 12.6), which later invade the tubule, erode into a calix, spread to other calices and the pelvis, and finally progress down the ureter into the bladder. Caseating granulomas are formed, which are Langhans giant cells surrounded by lymphocytes and fibroblasts. With the chronic infection, there is healing by fibrosis and calcification. The fibrous tissue contracts, leading to obstruction of one or more calices. The fibrosis eventually leads to destruction of the renal tissue, resulting in atrophic kidneys, ultimately leading to loss of functionality and autonephrectomy.

Ureteric involvement leads to stricture formation at the vesicoureteric junction (VUJ) more commonly, followed by pelviureteric junction (PUJ) and mid-ureter [19–22] (Figure 12.7). Involvement of the ureteric orifice leads to distortion, the ‘golf-hole’ appearance, and may give rise to reflux.

The earliest lesions cannot be detected in the kidney until a small tuberculous abscess ruptures into the calix, giving rise to irritating symptoms and pyuria. Untreated, these abscesses enlarge, coalesce, and calcify until the entire kidney may be converted into a calcified mass, previously known as a ‘cement kidney’.

As the mycobacteria spread down the ureter, they cause patches of granuloma in its wall, and on reaching the bladder, similar granulomas form in the vicinity of the ureteric orifice. Sometimes these are so oedematous that they resemble a papillary tumour. Later in the disease, there is ulceration which may become confluent throughout the bladder.

12.3.1.3 Clinical Presentation

Initial symptoms include fever, night sweats, weight loss, lethargy, and failure of treatment for a persistent UTI. Late symptoms can include haematuria and loin pain. Patients may present with lower urinary tract infections that mimic cystitis or prostatitis.

A detailed history should be sought to illustrate previous TB infections or contact with persons infected with TB. A detailed travel history of the patient and their most recent contacts is also important.

12.3.1.4 Investigation

Examination may be unremarkable for these patients. Urine testing usually shows sterile pyuria and negative cultures. If TB is suspected, then three early morning urine samples (EMUs) should be sent for Ziehl-Neelsen staining to confirm the presence of acid-fast bacilli. Three samples are needed because the TB bacterium is excreted only intermittently in the urine; hence, multiple samples of urine that have been in the bladder overnight allow for a greater chance of detection. The specimen is cultured on Lowenstein-Jensen medium; however, cultures can take up to four weeks because the TB bacterium's doubling time is exceedingly slow (15–20 hours). Therefore, polymerase chain reaction (PCR) testing can also be carried out.

CT urogram and intravenous pyelogram (IVP) could show moth-eaten calyces, renal calcification, cavitation of the renal parenchyma, hydronephrosis or hydroureter due to stricture, infundibular stenosis, and small shrunken kidney (autonephrectomy) [23] (Figures 12.8 and 12.9). Pelvic calcification may be seen due to vas, seminal vesicle or prostatic involvement.

Cystoscopy, retrograde studies, ureterorenoscopy, and biopsy can also be performed to assist in the diagnosis. Renograms can establish kidney functionality.

12.3.1.5 Management

Before the advent of effective anti-tuberculosis drugs, nephrectomy and cavernotomy was the treatment of choice in such patients. Today, prompt diagnosis and initiation of appropriate antibiotic therapy is the cornerstone of management.

Six months of multidrug anti-TB regimens are effective for urinary TB infections [24, 25]. Aggressive antibiotic use is to allow achievement of prompt eradication, decrease therapy duration as with individual medication, and the likelihood of drug-resistance developing.
The regime consists of two months of isoniazid, ethambutol, rifampicin, and pyrazinamide followed by four months isoniazid and rifampicin alone. Almost half of patients will require a surgical intervention if the disease process is not treated early. Surgical management plays a part in treating complications such as abscess formation and ureteric stricture. Nephrectomy for nonfunctioning kidneys and bladder augmentation or diversion or cystectomy for the small capacity, scarred ‘thimble’ bladder maybe required.

### 12.3.2 Ureteric TB

During this first few months of treatment, the urinary tract is kept under very close surveillance, by ultrasound supplemented where appropriate by CT urogram, because unnoticed tuberculous lesions heal quickly, and obstruction may develop silently in the ureter and lead to loss of a kidney.

For short strictures with an accessible lumen, good kidney function (>25%) and a good bladder capacity, endourological procedures can be attempted. Alternative complex strictures (e.g. long segment, bilateral, inaccessible lumen, poor kidney function) require more invasive surgical procedures.

Ureteric stents can be attempted with good outcomes [26]. Endoscopic balloon dilation may be attempted; however, it is rarely definitive and repeated procedures are often required [27]. Endoureterotomy incision can be done; however, care must be taken to site of incision, depending on the level of the ureter involved. Lower ureteral strictures are incised in an anteromedial direction, taking care to stay away from the iliac vessels, whereas upper ureteral strictures are incised laterally or posterolaterally. The ureterotomy incision can be made using a cold knife, a cutting electrode, or laser. The incision should be made from the ureteral lumen out to periureteral fat in its full thickness [27].

Short defects of the upper or mid-ureter can be treated by uretero-ureterostomy with ureteric anastomosis principles applied (Table 12.8).

---

**Figure 12.6** The pathogenesis of renal tuberculosis: (a) haematogenous infection produces multiple small abscesses, most of which resolve completely, leaving one or two foci in the papillae. (b) These erode into the lumen of the calix, (c) carrying infection into other calices in which caseation (d) and cavitation (e) take place.
A stricture at the upper end of the ureter will require a pyeloplasty or ureterocalicostomy (Figure 12.10); however, because the renal destruction is so severe in such cases that usually reconstruction is not possible.

At the lower end, it may be necessary to re-implant the ureter by means of a Boari flap (Figure 12.11) or a Psoas hitch.

Obstruction in the middle-third of the ureter is more difficult to deal with; on the right side, the appendix may lend itself as an ideal substitute for the stenosed segment (Figure 12.12), but on the left side, it may be necessary to bridge the gap with ileum or colon (Figure 12.13).

Alternatively, if the ureter can be mobilised sufficiently, a transureteroureterostomy can be done. However, caution for bilateral ureteric involvement.

For long ureteric strictures, or multiple or whole ureteric involvement, an ileal replacement will be required; alternately autotransplantation is an option, especially if other methods of repair fail or are not feasible.

In the bladder, the healing process may shrink so much that it needs to be enlarged by enterocystoplasty to restore its reservoir function. The traditional solution has been to use the caecum, but this may generate high pressures and threaten the upper tract; many surgeons now prefer a detubularised segment of bowel, even if the patient has to catheterize to empty it.

12.3.2.1 Complications and Prognosis
Complications arise from infection spreading to adjacent genitourinary structures (Table 12.6).

12.3.3 Chronic Pyelonephritis
12.3.3.1 Introduction
Chronic pyelonephritis is the end product of recurrent or continuous inflammation of the kidney. It leads to scarring of renal tissue and permanent loss of renal function. The inflammation can be related to an infective cause such as recurrent UTIs or, as in the case of children, due to a noninfective aetiology such as vesicoureteric reflux (VUR), which leads to more marked scarring. In adults, noninfective causes are those such as high pressure retention of urine due to benign prostatic
12.3.2 Clinical Presentation
Most patients are asymptomatic unless they show signs of recurrent UTI. Due to the insidious nature of the disease, patients may present with symptoms of end-stage renal failure.

12.3.3 Investigations
The diagnosis can be made from radiological appearances and also pathological analysis. Baseline renal function must be performed followed by radiological investigations to confirm the diagnosis. Ultrasound, CT, intravenous urogram (IVU), or radioisotope imaging (DMSA) will show renal scarring, deformed calyces, and thinning of the renal cortex. Scars are typically in the upper or lower poles because these are more prone to reflux. The affected kidney may also look atrophic or shrunken on scanning.

12.3.4 Management
Treating the underlying cause may help prevent loss of further renal function. Optimization of renal function is imperative, and a nephrologist is required to monitor these patients. Patients with end-stage renal failure

Figure 12.8 (a–c) Tuberculosis of left kidney.

hyperplasia (BPH) or detrusor-sphincter dysnergia in spinal cord injury, while infected causes are seen with obstructed infected uropathy (e.g. obstructive stone).
should be considered for renal transplant or dialysis. In children, prompt assessment of VUR is required.

12.3.3.5 Complications and Prognosis

End-stage renal failure is the only associated complication if bilateral disease.

12.3.4 Papillary Necrosis

Papillary necrosis (PN) originates from impairment of the vascular supply and from subsequent focal or diffuse ischemic necrosis of the distal segments of the renal pyramids. Common causes of PN include, pyelonephritis, obstructive uropathy, sickle-cell disease, TB, cirrhosis and chronic alcoholism, analgesics (NSAIDs specifically), renal vein thrombosis, diabetes, and systemic vasculitis (i.e. mnemonic: POSTCARDS). The arterial supply to the renal papilla comes partly from the vasa recta and partly from arteries at the fornix of the calix. Either vessel may become occluded when the papilla becomes oedematous or injected with urine, and the papilla becomes ischaemic and sloughs off. A line of demarcation forms, and the dead papilla may pass down the ureter to cause obstruction or remain in the renal pelvis to act as the nucleus for stone formation. The presence of the ischaemic papilla exacerbates existing inflammation and obstructive changes in the collecting tubules in the medullary rays. The process culminates with healing by epithelializing the papilla; however, there is usually ensuing scarring and atrophy of the kidney.

Patients present acutely with an AKI with deteriorated renal function, gross haematuria, flank pain, and occasionally tissue fragments in the urine.

Treatment is conservative starting with removal of the underlying cause. Broad-spectrum intravenous antibiotics if infection is present; maintain hydration, glycaemic control, urinary alkalinisation, and cessation of analgesics; and patients with sickle cell disease may require exchange transfusions.

12.4 Other Inflammatory Conditions of the Kidney

12.4.1 Malakoplakia

This is a rare inflammatory condition that can affect any area of the body, but most commonly presents within renal collecting system. It was first described by Michaelis and Gutmann who described extra and intracytoplasmic histiocytes that they termed ‘Michaelis-Gutmann bodies’ [28].

It can affect any age group but is predominantly seen in patients older than the age of 50. Any form of immunosuppression or recurrent gram-negative UTIs puts people at greater risk (Table 12.9) [29, 30].

Patients present with symptoms of a renal mass or renal failure. There may be a history of recurrent UTIs. Radiological scanning can show an enlarged, nonfunctioning kidney with multiple poorly differentiated lesions which can mimic renal cell carcinoma. Differential diagnosis include XPN, lymphoma, renal cell carcinoma, or renal abscess [29].

Most patients undergo nephrectomy because of the suspicion of malignancy, and at histological analysis, the diagnosis is made. Renal biopsy could be considered to aid in preoperative diagnosis. Some authors have theorised that antibiotic treatment only may suffice if the diagnosis can be made in this way [31, 32].
Figure 12.10 A tuberculosis stricture of the upper end of the ureter may be relieved by pyeloplasty (a–d) or by ureterocalicostomy (e–g).

Figure 12.11 A tuberculosis stricture of the lower end of the ureter may be relieved by reimplantaing the ureter into the bladder with a Boari flap, so long as the bladder is not too contracted. When the bladder is contracted, it may be necessary to add on a piece of bowel.
12.4 Other Inflammatory Conditions of the Kidney

12.4.2 Hydatid Disease

This rare parasitic infection only affects the kidney in 3–4% of cases [33]. It is caused by ingestion of a dog parasite known as Echinococcus granulosus (a type of tapeworm). Dogs are the definitive host other farm animals, and humans act as an intermediate host. Infection in humans is due to contact with dog or animal faeces (Figure 12.12).

Patients can be asymptomatic and the diagnosis can be made incidentally. Others may develop haematuria or chronic loin pain [34]. There is no one definitive test, but eosinophilia is noted in up to 50% of cases. Indirect haemagglutination and enzyme-linked immunosorbent assays are the most sensitive tests. Immuno-electrophoresis against arc-5 antigens is also widely used [34–36]. Ultrasound and CT scans will show a thick-walled, fluid-filled spherical cysts with calcified walls. Differential diagnosis could be renal cell carcinoma.

Medical management uses albendazole, which is an anti-helminthic agent that causes degenerative changes in the intestinal cells of the worm by binding to the colchicine-sensitive site of tubulin, thus inhibiting microtubule production, leading to impaired uptake of glucose by the parasites, and depleting their glycogen stores. Medical management is commonly used as an adjunct to surgical resection. Intact removal of lesions is extremely important at nephrectomy as spillage of cyst contents results in a severe anaphylactic reaction. The use of scolicidal agents such as hydrogen-peroxide before resection is recommended [33, 36]. Puncture-aspiration-injection-reaspiration (PAIR) procedure is a minimally invasive treatment option to remove hydatid cysts. It is a US-guided percutaneous puncture of the cyst, aspiration of the fluid with instillation of the scolicidal solution for 30 minutes, and followed by reaspiration of the fluid. Percutaneous thermal ablation of the cystic germinal layer by radiofrequency ablation is a new alternative currently being explored [37].

12.4.3 Fungal Infections

Fungal infection occurs in patients who are immunocompromised and those that have been given broad-spectrum antibiotics. Scanning and urine cultures are the main route of investigation. The main course of treatment is the use of antifungals. Ureteroscopy and removal of fungal balls in the renal collecting system may also be required to facilitate clearance.

12.4.4 Brucellosis

This is a zoonotic disease from infected animals. Human infections come about from ingestion of contaminated unpasteurized and un-boiled diary produces. It is rare in
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the UK but is seen in Mediterranean countries. Although it can affect any part of the body, renal manifestations are very rare [38].

Symptoms are variable and nonspecific, but it can cause calcifying granulomatous changes within the kidney. Treatment is with prolonged courses of tetracycline antibiotics.

12.4.5 Chyluria and Filariasis

In the Far East, chyluria is by no means uncommon. The patient presents with thick urine resembling anchovy sauce but usually without any other symptoms. Rarely, it is a cause of haematuria. The only serious consequence may be the urinary loss of protein, which occasionally leads to significant protein deficiency and loss of weight.

Investigations show a communication between the renal lymphatics and its collecting system (Figure 12.15). The condition is traditionally attributed to the microscopic round worm *Wuchereria bancrofti*, but it is rarely possible to confirm this diagnosis.

*W. bancrofti* lives in the lymphatics where it sets up an inflammatory response. The tiny worms creep at night into the peripheral blood where they are sucked up by feeding mosquitoes and injected into the next victim (Figure 12.16).

12.4.5.1 Pathophysiology

Pathogenesis is dependent on the immune system and inflammatory responses of the host. After infection, the worms will mature within six to eight months; male and female worms will mate and then release the microfilariae which can be release for up to 10 years.

An asymptomatic phase usually consists of high microfilaremia infection. Usually there is no symptoms of infection due to cytokine IL-4 suppression of the immune system.

In the inflammatory (acute) phase, the antigens from the female adult worms trigger an inflammatory response. The worms in the lymph channels disrupt the flow of the lymph, causing lymphedema. Symptoms are of fever, chills, opportunistic infections, and painful lymph nodes, lasting for about five to seven days.

Obstructive (chronic) phase is marked by lymph varices, lymph scrotum, hydrocele, chyluria, and elephantiasis.
Figure 12.15  (a) Combined lymphangiogram (left) and retrograde urogram (right) in a patients with chyluria. (b) Lymphangiogram in chyluria.

Figure 12.16  The life cycle of *Wuchereria bancrofti*. 
A key feature of this phase is scar formation and thickening of the skin and elephantiasis, which develops gradually with the attack of the lymphatic system.

12.4.5.2 Investigations
The parasite might be seen on a blood smear; however, PCR can detect filarial DNA fragments. Ultrasound detection of the parasites movements and noises can confirm parasitic infection, whereas a lymphogram will demonstrate communications between the kidney and lymphatics.

12.4.5.3 Treatment
In most cases, no treatment is needed. Prevention is key, with avoidance of mosquito bites by nets or repellent.

The medical treatment is diethylcarbamazine (6 mg kg\(^{-1}\) annually or bi-annually), which eliminates the microfilariae from the blood and kills the adult worms. It acts by inhibiting the microfilarial arachidonic acid metabolism. This makes the microfilaria more susceptible to immune attack. Combination therapy with ivermectin or albendazole plus diethylcarbamazine is more effective than monotherapy.

If the patient is obviously losing protein, the kidney is surgically explored and stripped of all its surrounding fibrotic and oedematous tissue. A preliminary lymphogram using contrast stained with a blue dye may make the dissection more exact. Every lymphatic trunk that is encountered must be meticulously ligated.

12.5 Inflammatory Conditions of the Ureters

12.5.1 Retroperitoneal Fibrosis

12.5.1.1 Introduction
Retroperitoneal fibrosis (RPF) was first described by Ormond in 1948 [39], this condition is defined by fibro-inflammatory tissue encasing the abdominal aorta and iliac vessels, which can involve the ureters. Its incidence is thought to be 1.38 per 100,000 of the population in the fifth or sixth decade of life; men are twice as commonly affected as women [40]. RPF is part of a disease spectrum known as chronic periaortitis, which is a large vessel arteritis [41]. Long-term management of this disease is undertaken by rheumatologists and nephrologists, but urological input is required to assist in drainage of the upper tracts.

12.5.1.2 Aetiology and Pathophysiology
RFP can be idiopathic (IRPF) or secondary. Though coined ‘idiopathic,’ the likelihood is that it is an autoimmune process called ‘periaortitis.’ Commonly associated secondary causes are iatrogenic or traumatic (e.g. surgery, radiotherapy, or chemotherapy), tumour or malignant process (lymphoma being the most common followed by meta-static disease), infection like TB, and drugs such as beta-blockers, hydralazine, haloperidol, amphetamine, LSD, and even methyl methacrylate cement (used in joint replacement surgery). It can be associated with autoimmune disease such as Crohn disease or Riedell thyroiditis or associated with vascular disease or treatments, abdominal aortic aneurysm, angioplasty, or intravascular stenting.

The most common cause found in more than 60% of patients is periaortitis. Inflammatory response to the leakage of insoluble lipids through the arterial wall from the atheromatous plaque leads to the formation of the fibrous whitish plaque that can extend to the ureters, pelvic organs, and retroperitoneal structures. Histologically there are chronic inflammatory infiltrates made up of macrophages, eosinophils, plasma cells, and lymphocytes; the central plaque is formed of fibrous scar tissue, while the growing periphery is active chronic inflammation. There are myofibroblasts and type 1 collagen within the fibrotic component [42].

12.5.1.3 Clinical Presentation
Clinical manifestations can be variable. Patients may present earlier on with nonspecific symptoms such as back and abdominal pains, loss of appetite or weight, night sweats, and malaise. If ureteric involvement is present, then patients may have colicky type symptoms. Late presentation is of symptoms of renal failure (acute or chronic) due to ureteric obstruction. New onset hypertension might be the only symptom. Scrotal swelling, hydroceles, and varicoceles can also occur, depending on the extent of the plaque and the vascular and lymphatic segments involved [42].

12.5.1.4 Investigations
There are no set diagnostic criteria for RPF, and the diagnosis is usually made after exclusion of other diagnoses, such as malignancy, have been ruled out. Multiple imaging modality might be needed to establish diagnosis as well as plan and follow up treatment (Figures 12.17 and 12.18).

Baseline renal function and full blood counts including inflammatory markers. ESR is elevated in the majority of cases. CT and radioisotope scanning (MAG3 or DMSA) will help to determine drainage and function of the kidneys. Retrograde pyelogram can also be used to assess narrowing and obstruction of the ureters.

CT-guided biopsy of the RPF mass confirms diagnosis; however, a negative result for cancer does not exclude it.

MRI scanning can be used to track progression and remission of the disease. On T2-weighted sequences hyper-intensity can correlate with disease activity.
Other imaging modalities used are F-fluorodeoxyglucose (FDG), positron emission tomography (PET), and CP3 67gallium (Ga) scintigraphy [43].

12.5.1.5 Management

Aims of treatment are to relieve ureteric obstruction, preserve renal function, and halt or reverse disease progression.

Relief of ureteric obstruction is a priority to preserve renal function. This can either be achieved with percutaneous nephrostomy placement (with or without anterograde stenting) or retrograde double-J stents [42, 44, 45].

Treatment of the underlying causes is critical, but in the case of IRPF, medical management is now the

Figure 12.17 Intravenous urogram (IVU), computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, and renogram show retroperitoneal fibrosis (RPF). Source: Photographs courtesy of Dr. Mark Robinson Aneurin Bevan UHB Hospital.
mainstay of treatment and should be started as soon as possible. In cases refractory to these measures, ureterolysis and omental wrapping of the ureters will be required.

12.5.1.5.1 Steroids
Glucocorticoids have been used for many years in RPF. They halt disease progression and help preservation of renal function [46, 47]. High doses are typically employed (up to 1.5 mg kg\(^{-1}\)) and titrated down once the inflammatory markers normalise. A number of studies have been performed to ascertain the optimum administration, but there is no set regime [44, 48, 49]. What is characteristic of all studies is that relapse is common (25–50%) after doses are titred down, but re-remission can be attained by reinstatement of high doses [42, 44].

High-dose long-term glucocorticoid use is associated with significant morbidity and should be avoided but may be the only route in problematic patients.

12.5.1.5.2 Steroid-sparing Drugs
Tamoxifen [50, 51], azathioprine [47, 49], cyclosporine [47], mofetil mycophenolate [47, 52–54], and cyclophosphamide [47, 55] have been utilised as possible alternatives to steroid treatment. There is no evidence that combination with glucocorticoids provides any further benefit, but these drugs can be deployed in patients who have recurrent replaces on steroid treatment or who have contraindications to glucocorticoids.

A randomised controlled trial (RCT) comparing tamoxifen to prednisolone found relapse rates were lower in the steroid group (6 vs 39%); additionally, the steroid groups sustaining longer remission times [51]. Hence, recommendations are for glucocorticoid, with or without, concomitant steroid-sparing agents should be the treatment of choice [42].

Emergent therapies consist of monoclonal antibodies such as infliximab and rituximab have shown promise but require further work [42, 56].
12.5.1.5.3 Ureterolysis

This can be done by either open, laparoscopic, or robotic approaches, depending on the surgeon’s experience. The colon is reflected off the ureter first on one side and then the other (Figure 12.19). The plane of cleavage between the ureter and the surrounding sheath of fibrous tissue is dissected away, liberating the ureter (Figure 12.20).

This is sometimes very difficult because the fibrosis actually penetrates the muscular wall of the ureter, and when the lumen is breached, a nephrostomy is a

Figure 12.18 (a–c) Retroperitoneal fibrosis: the ureters are compressed and drawn medially by a gard white sheet of fibrous tissue around the aorta and inferior vena cava.
mandatory precaution if one is not already in position. If the injury is small, it can be left to heal with a stent in situ; however, if extensive ureteric segment is damaged, primary anastomosis, ureteric reimplantation, or even nephrectomy might be required. To prevent a return of the fibrosis, it is safest to wrap each ureter in omentum (Figure 12.21).

### 12.5.1.5.4 Prognosis

Whether the ureters have been placed in the peritoneal cavity or wrapped in omentum, it is necessary to follow the patient carefully. Recurrence of the fibrosis is always a possibility, and so is a new manifestation of the fibrosis in the mediastinum or porta hepatis. Fortunately, a very useful index of return of active disease is provided by the sedimentation rate. This, and the blood pressure, should be monitored indefinitely in view of the long-term risk of atherosclerotic disease. Permanent upper tract decompression may be necessary.

### 12.5.2 Ureteric Endometriosis

Although this is rare (incidence of 0.01–1%), it is a clinically important diagnosis to make as ureteral endometriosis can lead to silent loss of the kidney due to chronic obstruction [57, 58].

Lesions can be intra- or extraluminal causing stricture disease and fibrosis. Retrograde urethrography and CT urogram can be used to assess for obstructive lesions, but biopsy will confirm the diagnosis [59]. Cyclical bleeding is seldom observed, and the response to hormonal manipulation has been disappointing. Healing may be followed by obstructing fibrosis calling for reimplantation.

### 12.5.3 Amyloidosis

Amyloidosis of the ureter is extremely rare. It should be considered as a differential to a ureteral tumour causing unilateral obstruction. Only a handful of cases have been described in the literature [60, 61]. Local resection and anastomosis has been successfully accomplished where the length of ureter has been short.

### 12.5.4 Pelvic Lipomatosis

This is a rare, nonmalignant, overgrowth of firm pelvic fat which surrounds and infiltrates the bladder, colon, and ureters. It occurs in males in their thirties and is more common in those of African ancestry. It is associated with cystitis cystica and cystitis glandularis in a third of patients. Compression of the ureters causes progressive hydronephrosis and renal failure [58, 62, 63].
CT scanning is the diagnostic test of choice which will show increased adipose tissue around the bladder and dilatation of the renal collecting system. There is no definitive treatment, but surgical resection is difficult because the fat infiltrates organs and there is no clean plane of cleavage. Most patients require urinary diversion or percutaneous drainage.

**Expert Opinion**

The knowledge of inflammatory disease of the kidney and ureter is vital because they can be as detrimental to patients leading to significant reduction in quality of life or even to death if not promptly and appropriately managed.

**References**

Kidney and Ureter Inflammation


References


13

Kidney and Ureter Neoplasm

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Abstract

In the last two decades, there has been a considerable rise in the number of renal masses incidentally detected. Although the majority of these masses have distinct clinical and radiological features, a minority share similar patterns leading to diagnostic uncertainty. A clear understating of the evaluation, current management approaches, and awareness of the evolving evidence pertaining to renal masses is essential. With improvement in imaging modalities and pathological assessment techniques, a more precise diagnosis can be made. In the last few years, we have observed a significant evolution in surgical techniques with various minimally invasive approaches showing promising outcomes. The understanding of the molecular basis of many of these lesions is paramount. Translational research has led to the introduction of various novel targeted therapies in an attempt to improve oncological outcomes.

Upper urinary tract (UUT) tumours are uncommon cancers of the renal pelvis, calyces, and ureter. Upper urinary tract urothelial (transitional) cell carcinomas (UT-UCC) are notoriously aggressive cancers with a propensity for local recurrence and advancement to higher-stage disease. Additionally, they have a tendency for synchronicity and metachronicity. They bear histological resemblance to bladder urothelial cancer. Accurate diagnosis and staging is reliant on a combination of cytology, endoscopic, and UUT imaging modalities. The treatment of UT-UCC depends on the stage, grade, and volume of the disease. Radical nephroureterectomy (RNU) with ipsilateral cuff excision is the most oncological efficacious treatment option for localised UT-UCC. Other treatment options for UT-UCC include ureteroscopic and percutaneous ablation and segmental resection. The role of adjuvant treatment and systemic chemotherapy remain unclear and continue to be under the realms of future research.

Keywords renal cysts; renal cancer; kidney cancer; ureteric cancer; nephrectomy; nephroureterectomy; cryotherapy; radiofrequency ablation

Key Points

<table>
<thead>
<tr>
<th>Kidney Neoplasm</th>
<th>Upper Urinary Tract (UUT) Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Renal masses need to be carefully managed and a distinction made between benign and malignant lesions.</td>
<td>● UUT lesions are rare; however, more than 60% are invasive at diagnosis.</td>
</tr>
<tr>
<td>● Computed tomography (CT) scanning is the optimal imaging modality.</td>
<td>● Diagnosis is based on a combination of cytology, endoscopic, and imaging modalities.</td>
</tr>
<tr>
<td>● The majority of benign diseases can be conservatively managed.</td>
<td>● Radical nephroureterectomy and ipsilateral cuff excision is the gold standard for localised disease.</td>
</tr>
<tr>
<td>● Malignant lesions can be treated with either a radical or a partial nephrectomy, ablative treatment, or actively surveyed, depending on the stage of the disease.</td>
<td>● Nephron-sparing procedures can be adopted in selected patients.</td>
</tr>
<tr>
<td>● Adjuvant and systemic treatments can be adopted for more advanced diseases.</td>
<td>● The role of adjuvant and systemic treatment is unclear.</td>
</tr>
</tbody>
</table>
13.1 Kidney Neoplasms

Renal masses can be broadly classified into (Table 13.1): (i) malignant, (ii) benign, and (iii) inflammatory. This chapter will comprehensively discuss common types of malignant and benign lesions. Discussion on inflammatory masses was addressed in Chapter 12.

13.1.1 Malignant Renal Masses

13.1.1.1 Renal Cell Carcinoma

13.1.1.1.1 Incidence

Renal cell carcinoma (RCC) accounts for nearly 90% of all renal malignancies, making it the most common solid renal lesion. RCC accounts for up to 2.5% of all adult malignancies and accounts for 1–2 per 100,000 of all cancer-specific mortality worldwide [1–3]. It is most common in the sixth and seventh decades of life. RCCs have a preponderance for male gender with a male to female ratio of around 3:2 [1–3].

13.1.1.1.2 Aetiology

Modifiable Risk Factors

Smoking (especially pipe or cigar smoking), obesity, and hypertension have all been implicated in the development of RCCs. The relative risk for male and female smokers for the development of RCC was 1.54 and 1.22, respectively [2]. Smoking cessation for 10–15 years also appeared to reduce the chance of one developing RCC [2, 4–6]. Although smoking is the principal risk factor for RCC, obesity is on the rise as a direct risk factor. Interestingly, however, the prognosis of RCC in patients who are obese is better than in patients who are not obese [2, 4, 5, 7]. Again weight loss and optimisation of hypertension has been suggested to reduce chances of RCC.

Nonmodifiable Risk Factors

Patients with a family history of RCC in a first-degree relative have been reported to have more than a fourfold increased risk of RCC [8, 9]. Familial syndromes with distinct heredity forms of RCC have also been described.

13.1.1.2 Von Hippel–Lindau Disease

Von Hippel–Lindau (VHL) is an autosomal dominant disease that affects 1 in 36,000 live births and is manifested by a group of tumours including: (i) clear cell RCC, (ii) central nervous system haemangioblastoma, (iii) pheochromocytoma, (iv) retinal angiomas, (v) rarely pancreatic cysts or tumours and (vi) epididymal cystadenomas [10–12].

RCC develops in about 50% of patients with the disease, typically in their third to fifth decades of life [10–12]. The genetic characterisation of VHL disease is the loss or mutation of both alleles of the VHL tumour suppressor gene located at chromosome 3p25–26 [13, 14]. This has been confirmed as the cause for RCC development [13, 14].

Three variants exist: Type I VHL has a low risk of pheochromocytoma; type II VHL has a high risk of pheochromocytoma and is subdivided into type IIa: low risk of developing RCC, type IIb: high risk of RCC, and type IIc: risk of pheochromocytoma only; and type III VHL disease which is an autosomal recessive form. The VHL protein or VHL complex normally targets transcription factors such as the hypoxia inducible factors (HIF) 1 and 2 (which play a role in the cellular response to hypoxia and starvation). The inactivation of the VHL gene leads to disregulation of the HIF-1 and -2. HIF-1 and -2 accumulation leads to up-regulation and overexpression of vascular endothelial growth factor (VEGF) mainly; however, in addition to this change, overexpression in expression of platelet-derived growth factor and transforming growth factor-α have been reported and have also been implicated in RCC.

Table 13.1 Pathology of renal masses.

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
<td>Simple renal cysts</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Infected renal cysts</td>
<td>Oncocytoma</td>
<td>Wilms tumour</td>
</tr>
<tr>
<td>Xanthogranulomatous pyelonephritis</td>
<td>Angiomyolipoma</td>
<td>Transitional cell carcinoma</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Renal cortical adenoma</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Metanephric adenoma</td>
<td>Sarcomas</td>
</tr>
<tr>
<td></td>
<td>Cystic nephroma/mixed epithelial/stromal tumour</td>
<td>Lymphoma</td>
</tr>
<tr>
<td></td>
<td>Leiomyoma</td>
<td>Leukaemia</td>
</tr>
<tr>
<td></td>
<td>Vascular masses</td>
<td>Metastatic</td>
</tr>
</tbody>
</table>
13.1.1.3 Familial Papillary RCC or Hereditary Papillary RCC
Familial papillary RCC or hereditary papillary RCC (HPRCC) is an autosomal dominant disease characterised by trisomy for chromosomes 7 and 17 and abnormalities in chromosomes 1, 12, 16, 20, and Y [15, 16]. Activation of a proto-oncogene c-MET located on chromosome 7q31 leads to production of hepatocyte growth factor, which acts through the tyrosine kinase receptors, which leads to cellular proliferation and tumorigenic effects on organs [15–19].

13.1.1.4 Hereditary Leiomyomatosis
Hereditary leiomyomatosis and RCC syndrome is an autosomal dominant disease that is manifested by cutaneous leiomyomas, uterine fibroids, and papillary RCC [11, 20]. Normally developing in the fourth decade of life, it is characterised by loss or mutation of the fumarate hydratase tumour suppressor gene located on chromosome 1q42–44 [20]. Unlike the previous two hereditary diseases, HLRCC syndrome is more aggressive and invasive [18, 19].

13.1.1.5 Birt-Hogg-Dubé Syndrome
Birt-Hogg-Dubé (BHD) Syndrome is an autosomal dominant disease manifested by cutaneous fibrofolliculomas (i.e. hair follicle hamartomatous tumours), lung cysts, pneumothoraxes, and chromophobic RCC [11, 15, 20, 21]. The RCC develops in the fifth decade of life and is characterised by loss or mutation in the BHD gene located on chromosome 17p11.2, which encodes for folliculin a tumour suppressor gene [21, 22].

13.1.1.6 Histological Types
RCCs are adenocarcinomas originating from the epithelium of the renal tubules. Through continual understanding of tumour histology and genetics, the subtypes of RCCs have drastically changed in the last decade [16]. Generally there have been three more common subtypes of RCC: (i) clear cell (80–90%), (ii) papillary (6–18%) (Type 1 and Type 2), and (iii) chromophobe (4–6%) [16, 23]. The classification has recently been expanded from the previously adopted World Health Organisation histological classification based on the advances and development in cytogenetics and immunohistochemistry (Table 13.2) [16].

13.1.1.7 Clinical Features
More than half of RCCs are incidentally detected when imaging is undertaken for another condition and are asymptomatic on presentation [23, 24]. The classical presentation of RCC is a combination of flank pain, palpable loin mass, and visible haematuria. This triad is a reflection of advanced disease and is fortunately uncommonly seen in contemporary urological practice [24, 25]. Table 13.3 depicts the more common clinical features encountered [24–30].

RCC can be associated with paraneoplastic syndromes, which can be particularly distressing. The normal physiological function of the kidney (i.e. production of renin, erythropoietin, prostaglandins, and 1, 25-dihydroxycholecalciferol) is inappropriately increased in RCC. The increased production of these hormones and proteins give rise to an array of symptoms (Table 13.3). In addition to the normal kidney hormones produced, RCCs also have been found to produce adrenocorticotropic hormone giving rise to Cushing syndrome, prolactin leading to galactorrhea, insulin leading to hypoglycaemia, and gonadotrophins leading to gynaecomastia, decreased libido in men or hirsutism, amenorrhea, and male pattern balding in women [30].

These symptoms tend to resolve once the diseased kidney has been removed. However, persistent symptoms would indicate residual or metastatic disease, implying a poorer prognosis.

13.1.1.8 Diagnosis
13.1.1.8.1 Investigations
The majority of RCCs are initially diagnosed by an ultrasound or a computed tomography (CT) scan while investigating a different medical ailment [27]. Ultrasonography is the most common investigation for haematuria and can accurately distinguish between cystic and solid mass (Figure 13.1).

Triple-phase contrast CT scans are the gold standard renal characterisation imaging modality. Enhancement
Kidney and Ureter Neoplasm

seen on the CT scan is an important criteria to distinguish between benign and malignant complex cystic masses (Figure 13.2) [31]. A difference in Hounsfield units of 15 or more between a pre- and postcontrast CT image of the mass is considered enhancement and strongly suggestive of a malignancy. A chest and abdominal CT scan is indicated once a malignancy is suspected for staging. This can adequately assess the extent of the primary tumour, anatomical consideration such as renal artery location, and the presence of accessory arteries, venous, and lymphatic involvement, presence of metastases, as well as assess the contralateral kidney.

Investigating bone and brain metastasis is indicated only if there are symptoms; otherwise they are not required [31–34]. In addition, a renogram and renal function assessments are carried out in patients with impaired renal function to best optimise their management plan. Angiography is rarely needed; however, it can accurately delineate the arterial supply of the kidney and tumour and can be done during renal artery embolisation (Figure 13.3). CT scans are also used during follow-up post-treatment to detect recurrences (Figure 13.4).

If a CT is contraindicated because of an allergy to the contrast medium, renal impairment, equivocal venous involvement, or if the patients is pregnant, a magnetic resonance image (MRI) scan can also accurately characterise the mass (Figure 13.5). MRI is superior to CT in establishing whether or not invasion into adjacent

Table 13.3 Clinical features of renal cell carcinoma.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Clinical features</th>
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<tbody>
<tr>
<td>50%</td>
<td>Asymptomatic, incidentally detected</td>
</tr>
<tr>
<td>6–50%</td>
<td>Localised or locally advanced disease</td>
</tr>
<tr>
<td></td>
<td>• Visible haematuria</td>
</tr>
<tr>
<td></td>
<td>• Flank or loin pain</td>
</tr>
<tr>
<td></td>
<td>• Palpable abdominal mass</td>
</tr>
<tr>
<td></td>
<td>• Vena caval obstruction: bilateral leg oedema, irreducible or acute (left-sided) varicocele</td>
</tr>
<tr>
<td></td>
<td>Systemic or metastatic disease</td>
</tr>
<tr>
<td></td>
<td>• Bone pain</td>
</tr>
<tr>
<td></td>
<td>• Coughing or haemoptysis</td>
</tr>
<tr>
<td></td>
<td>• Lymph node enlargement</td>
</tr>
<tr>
<td></td>
<td>• Weight loss, cachexia, night sweats, fatigue</td>
</tr>
<tr>
<td></td>
<td>• Amyloid deposits</td>
</tr>
<tr>
<td></td>
<td>• Pyrexia of unknown origin</td>
</tr>
<tr>
<td>10–40%</td>
<td>Paraneoplastic syndrome (ectopic hormone production):</td>
</tr>
<tr>
<td></td>
<td>• Hypertension (renin secretion, or atrioventricular fistula, or renal artery compression)</td>
</tr>
<tr>
<td></td>
<td>• Polycythaemia (erythropoietin section)</td>
</tr>
<tr>
<td></td>
<td>• Anaemia (haematuria/chronic disease)</td>
</tr>
<tr>
<td></td>
<td>• Hypoglycaemia (insulin secretion)</td>
</tr>
<tr>
<td></td>
<td>• Hypocalcaemia (para-thyroid hormone-like secretion)</td>
</tr>
<tr>
<td></td>
<td>• Cushing’s syndrome (adrenocorticotropic hormone secretion)</td>
</tr>
<tr>
<td></td>
<td>• Stauffer syndrome (hepatic dysfunction) (unknown cause resolves in 60–70% after nephrectomy)</td>
</tr>
</tbody>
</table>

Figure 13.1 Ultrasounds of different-sized renal cell carcinomas (RCCs).
structures is present, in addition to a detailed delineation of the vasculature (Figures 13.5 and 13.6) [31, 32, 35–38].

**Histological Evaluation** The role of percutaneous renal core biopsy has evolved over the last few years. Concerns such as diagnostic inaccuracy and complications (such as bleeding and pneumothorax) have been largely mitigated by the improvement in image guidance techniques. Furthermore up to 20% of T1a renal tumours are benign, and hence, aggressive surgical intervention maybe needless in these patients. Some of the specific indications for image guide renal biopsy include:

1. Before ablative treatments or systematic-targeted therapy for metastatic disease.
2. Small renal mass before advocacy of active surveillance particularly in younger patients.
3. Diagnostic uncertainty on images (particularly during concerns of lymphoma, metastasis from an alternate primary).

![Figure 13.2 Computed tomography (CT) scans of different staging of renal cancer: (a and b) T1; (c and d) T2; (e) T3; (f and g) T4.](image-url)
13.1.1.9 Staging and Grading

The tumour, node, and metastasis (TNM) classification has been adopted for RCC staging based on the primary tumour, lymph node involvement, and presence of metastasis (Table 13.4) (Figure 13.7) [39]. The Fuhrman (F) nuclear grade has been used for histological grading based on the nuclear size, outline, and nucleoli [40]. The Fuhrman grading system groups RCCs into four categories:

- F1: Well differentiated
- F2: Moderately differentiated
- F3 and F4: Poorly differentiated

The classification allows for a distinction for low-grade disease (F1 and 2) and high-grade disease (F3 and 4) (Table 13.5) [41, 42].
13.1.1.10 Prognosis

Despite the advancement in our understanding of RCC and its management, 20–40% of patients with localised disease develop recurrence even with optimal surgical excision [43]. Important prognostic factors in assessing the likelihood of disease recurrence and survival rates are the TNM classification, histological grading (Fuhrman grade), pathological subtype, and the patients overall health status and comorbidity [40, 43–45]. The presence of sarcomatoid or rhomboid differentiation, tumour necrosis, and microvascular invasion features indicate a poorer prognosis [42].

Using various prognostic factors or nomograms have been developed, which can aid clinicians on management plans by predicting the likelihood of disease recurrence and survival [43, 45–47]. There is not yet consensus on one standardised nomogram; however, their importance in predicting cancer survival is evident, and therefore,
they are commonly used in clinical practice to guide treatment decision making [43, 45–48].

### 13.1.1.1 Treatment

There is a wide array of treatment options available for patients with RCCs. These include

1) Surgical intervention with radical and partial nephrectomy (employing open, laparoscopic, and robotic approaches).

2) Ablative options (radiofrequency ablation, cryotherapy).

3) Active surveillance.

4) Systemic chemotherapy and immunotherapy.

Factors influencing treatment of renal tumours are tumour stage, renal function, function of contralateral kidney, availability of local expertise, and associated comorbidities.

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**Figure 13.4** Computed tomography (CT) showing (a and b) tumour recurrence near nephrectomy bed (c and d) lymph node recurrence.
13.1 Kidney Neoplasms

13.1.1.1 Surgery

Partial Nephrectomy Contemporary evidence would suggest that partial nephrectomy shares oncological equivalence with radical nephrectomy for T1 tumours [49]. Additionally by nephron preservation, partial nephrectomy, irrespective of approach employed, confers an overall survival benefit and improved quality of life (QoL) [49, 50]. It is therefore currently recommended that, if technically feasible, partial nephrectomy should be offered to all patients with T1a and selected T1b tumours. In terms of the approach employed, laparoscopic partial nephrectomy tends to be associated with higher complications compared to the open approach. Open approaches have, therefore, tended to be the favoured option. There is some evidence to suggest that robotic partial nephrectomy may have favourable early

Figure 13.5 Magnetic resonance image (MRI) showing (a) right renal simple cyst (b) left kidney renal cell carcinoma (RCC) (c and d) left renal vein RCC.
outcomes. The eventual approach employed is usually dependent on available local expertise and is discussed on an individual patient basis.

**Radical Nephrectomy** Organ-confined tumours larger than 7 cm (T2) and smaller tumours not suitable for partial nephrectomy should ideally be managed with a laparoscopic radical nephrectomy. Minimal invasive approaches (laparoscopy and robotic) have better immediate outcomes than their open counterpart [50]. Laparoscopic and robotic procedures have similar operative and postoperative outcomes [50, 51], although robotic surgery is potentially less cost effective. Therefore, laparoscopic radical nephrectomy should be the first choice and considered the gold standard if appropriate expertise exists.

In expert hands, selected locally advanced cases (T3 or higher) can be managed with a laparoscopic approach, although the majority are managed with open approaches, particularly if there is venous involvement. In some of

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**Figure 13.6** Tumour invading the inferior vena cava: (a–c) computed tomography (CT) scan (d) magnetic resonance image (MRI).
cases RCC, tumour thrombus grows into the renal vein and can extend into the inferior vena cava and even into the right atrium of the heart. The resulting venous tumour thrombus occurs in up to 10% of cases with cardiac involvement occurring in at least 1% of cases. This can give rise to clinical features of venous occlusion such as lower limb oedema, nonreducing varicocele, or isolated left-sided varicocele, dilated superficial vessels (dilated to accommodate the increased venous drainage required), or the thrombus might embolise and lead to signs of a pulmonary tumour embolus [52–54]. The management of such advanced disease requires thorough preoperative planning of the surgery and collaborative involvement of cardiovascular and hepatic surgeons. The need for vascular bypass depends on the level of tumour thrombus. The described levels of venous involvement are:

Level I: Tumour adjacent to the ostium of the renal vein.
Level II: Tumour extends up to the lower aspect of the liver.
Level III: Tumour involves the intrahepatic portion however below the diaphragm.
Level IV: Tumour above the diaphragm [52–54].

Despite the higher stage of the disease (Table 13.4), five-year survival rates have been reported to be between 30 and 75% of patients that undergo a radical nephrectomy and tumour thrombectomy [52, 53]. However, the procedure comes with significant morbidity (8–39%) and mortality (2–13%).

Adrenalectomy improves oncological outcomes only if there is radiological or intra-operative evidence of local invasion or metastasis, and hence, is only indicated only in these situations [49].

The role of template lymphadenectomy remains debatable, and it is currently not routinely recommended and should only be carried out if there are palpable or enlarged nodes. Routine preoperative embolisation does not improve outcomes; however, in patients who are surgically unfit with a nonresectable cancer and significant symptoms, palliative embolisation can be considered [55–57].

### Procedures
The anterior approach of a radical nephrectomy includes an incision through a midline or transverse; the colon and duodenum are reflected medially. The renal artery is tied in continuity before ligating and dividing the renal vein (Figure 13.8).

On the right side when there is a very large tumour, the renal artery can be dissected on the left side of the vena cava where it lies between the aorta and vena cava (Figure 13.9). On the left side, the left renal artery may be located behind the duodenal region. If necessary, access may be improved by dividing the inferior mesenteric vein (Figure 13.10).

In approaching the renal veins, watch out for large lumbar veins which can enter the renal vein just where it joins the vena cava, whereas on the left side, a double vein encircling the aorta is a common anatomical variant (Figure 13.11).
For large tumours of the upper pole of either kidney, a 10th rib thoracoabdominal incision may give good access (Figure 13.12). However, many surgeons have adopted a ‘rooftop’ subcostal incision (supra 12th or 11th rib) which gives better access with a smaller incision. Be wary of the pleura posteriorly.

Once the vessels have been secured, the kidney and all its surrounding tissues within the envelope of Gerota fascia are removed.

For a partial nephrectomy, expose the kidney through an adequate incision. Tape the renal artery and occlude it with a vascular clamp (Figure 13.13). Remove the tumour with a good margin of healthy tissue. Before the renal artery is unclamped, vessels in the cut surface of the kidney are secured by meticulous suturing to achieve haemostasis. Remove the clamp and identify and control any remaining vessels.

For tumours in the middle third of the kidney, a similar procedure can be carried out, taking a wedge of parenchyma. When a prolonged dissection is anticipated, cooling of the kidney with sterile ice slush protects function.

Management of tumour in the renal vein depends on how far it has grown into the inferior vena cava. Often only a small finger of tumour thrombus protrudes into the vena cava from a cancer in the right kidney. On the right side, having ligated the right renal artery in continuity, the back of the vena cava is exposed by dividing the lumbar veins. The vena cava above and below the right renal vein and the left renal vein are all secured with a tourniquets (Figure 13.14). Only then is the cava opened, the tumour thrombus extracted and the vein sutured (Figure 13.15).

If the thrombus is growing into the edge of the cava, it is necessary to remove a cuff of cava along with the renal vein. If the whole thickness of the vena cava is invaded by
When tumour thrombus is discovered in the left renal vein, it is essential to make a wide anterior approach to gain safe access to the vena cava and the large veins that drain into it (Figure 13.17).

If the CT or MRI scans have shown tumour thrombus extending above the liver, the cardiothoracic team should be involved in planning the operation. In principle, a long midline incision is made, first into the abdomen to confirm the preoperative findings and then it is carried up into the chest by splitting the sternum. The inferior vena cava is occluded where it enters the right atrium, unless tumour thrombus has extended into the right atrium. The superior vena cava and ascending aorta are cannulated, and the patient is put on a cardiopulmonary bypass.

Figure 13.8 (a) On the right side the colon and (b) duodenum are mobilised medially to reveal (c) the inferior vena cava and the right renal vessels. (d) The right renal artery is ligated in continuity.

Figure 13.9 The right renal artery may be ligated in continuity where it lies between the inferior vena cava and the aorta.
13.1.1.11.2 Ablative Approaches

Thermal ablation includes renal cryotherapy and radiofrequency ablation. Both of which can be performed either percutaneously or laparoscopically [58]. Though this modality option is readily available to all localised RCC disease, it is best suited for a select group of patients. These patients include patients who are elderly or with significant comorbidities who are at a high-risk surgery, but want active treatment, patients with local recurrence after a partial nephrectomy, or patients with multifocal lesions in a single kidney as part of a hereditary renal cancer [59]. The long-term oncological outcomes for these approaches remain undetermined.

Cryotherapy The principle of cryotherapy is rapid freezing of the tissue leads to ice formation of the extracellular space while the intracellular space is initially more resilient to icing. This leads to an increase in the osmolarity in the extracellular space which in turn causes a hypertonic environment, which causes a change in the pH, intracellular solute composition, and protein denaturation [60]. The eventual icing of the intracellular space leads to cellular structural changes and death follows. Following rapid freezing is a gradual thawing then repetition of the cycle, this causes delayed microcirculatory failure which further leads to cellular death through anoxic environment [58, 60, 61]. The freezing temperature required is $<-20^\circ C$ with a distance of 3.1 mm beyond the edge of the target lesion [60]. Cryotherapy can be done by either CT guidance or during laparoscopy [62].

Radiofrequency Ablation Radiofrequency ablation uses high-frequency, alternating current within the target lesion by generating frictional heat, which denatures intracellular proteins resulting in cellular destruction [58, 59, 61, 63]. Temperatures between 45 and 55°C lead to irreversible cellular damage whereas 55–60°C result in cellular death.

Both these modalities have been reported to have high success rates in ablating the tumour completely with report of 80–100% [61, 63, 64].

13.1.1.11.3 Active Surveillance

Active surveillance is commonly reserved for patients who are elderly, who are unfit, or who have small renal masses (<T1a) thought to be benign [65]. Regular active surveillance with serial imaging (ultrasound, CT, or MRI scans) is done to detect any change in size of tumour, which might indicate a progression in the disease and trigger treatment. In a pooled analysis of patients under active surveillance, Smaldone et al. have shown that small renal masses potentially grow at a relatively slow rate; the mean linear growth rate was $0.31 \pm 0.38$ cm per year with a mean follow up of 33.5 – 22.6 months, with a mean initial greatest tumour diameter of 2.3 – 1.3 cm, [66]. However, about 23% of patients displayed no growth at all and only a small proportion (2%) of the masses...
Figure 13.12 Tenth rib thoracoabdominal approach to the kidney. (a) The anterior part of the incision is made first, to make sure the tumour is operable; and (b) the incision is carried back along the 12th rib. If the periosteum is stripped off the upper border of the rib there is no need to resect it.

Figure 13.13 Partial nephrectomy. (a) After clamping the renal artery, a clean guillotine amputation is made well clear of the tumour. (b and c) Haemostasis is obtained by suture ligature of every cut artery and vein.
progressed, while almost 0.02% progressed to metastatic disease [66]. Therefore, it is safe to say that surveillance can be considered as an alternative treatment modality in a select group of patients who are elderly and might have significant comorbidity leading to a limited life expectancy, understanding that intervention might be required if the tumour progresses, and therefore, the risks of comorbidity, risks of intervention, and risks of cancer progression need to be weighed. Furthermore, nephrectomy has shown to have a 9.4% increased survival benefit at five years compared to surveillance, and therefore, surveillance should not be considered in patients who are healthy with small renal masses who can undergo intervention as risk of progression increases with increasing age >75 years of age, in patients with large tumours >4 cm, or tumours increasing in size >0.8 cm per year [66, 67].

13.1.1.11.4 **Systemic Therapies**

Metastatic disease has a poor prognosis, estimated survival of 7–16.7 months with a 10–20% survival at five years [68]. However, treatment modalities exist that have been shown to improve survival outcomes such as

**Figure 13.14** When there is a tumour in the right renal vein and vena cava, after ligating the right renal artery, the cava and left renal vein are secured with tapes.

**Figure 13.15** (a) The vena cava is opened, (b) the tumour is extracted, and the cava is closed. (c) If the tumour thrombus is limited to the renal vein a Satinsky clamp may be applied to the inferior vena cava after (d) making sure the Rummel tapes are in readiness.
immunotherapy or surgical resection. Based on the presence of certain risk factors, patients can be stratified into three groups to aide prediction of survival (Table 13.6) [69].

**Immunotherapy** The body’s immunity has been believed to play a vital role in cancer control. This can be witnessed when a primary cancer has been resected and metastatic lesions then reduce in size. Furthermore, the

---

Figure 13.16 (a) When tumour has blocked the inferior vena cava (IVC), there will be an adequate collateral circulation, and the entire segment of vena cava (b) may be removed.

Figure 13.17 When the vena cava is invaded by tumour from the left renal vein a wide anterior approach is used (a) the vena cava is (b) taped and opened, the tumour extracted and the cava closed (c and d).
presence of T cytotoxic T cells in resected specimens seems to justify the immunological strategies for treating RCC. This gives the rise to the use of cytokines such as interferons and interleukins in the management of metastatic RCC, specifically clear cell subtype.

**Interferon-α** Interferon-α has been shown to have a modest survival benefit in that it can reduce the risk of death at one year by 46% and at two years by 36%; however, it has a low chance of shrinking cancers with a partial remission seen only in 12.5% of patients [70]. Nonetheless, based on certain risk factors, prognostic stratification for survival can be predicted that allows management to be tailored (Table 13.7) [29]. Trials comparing anti-angiogenic drugs have shown superiority to interferon-α, and therefore, its use has been limited to a select group of patients (those with good performance status, clear cell RCC, and lung metastases only) [71–74].

Interleukin-2 has been used for metastatic RCC since the 1980s, and although it does have modest survival benefits, it is associated with significant toxicity. Furthermore, no added survival benefit was found from administering a high-dose interleukin-2 compared to a low-dose interleukin-2 plus interferon-α [70]. Its use is limited to a select group of patients with good performance status and clear cell RCC only [74].

**Table 13.6 Prognostic stratification for survival of patients with metastatic renal cell carcinoma (RCC).**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cut-off point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky performance status</td>
<td>&lt;80%</td>
</tr>
<tr>
<td>Prior nephrectomy</td>
<td>Absence of prior nephrectomy</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&lt;lower limit of laboratory reference range</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>&gt;1.5× the upper limit of laboratory reference range</td>
</tr>
<tr>
<td>Corrected serum calcium</td>
<td>&gt;2.4 mmol⁻¹</td>
</tr>
</tbody>
</table>

**Survival prediction**  
Number of risk factors | Median survival (months) | 1-year survival (%) | 3-year survival (%) |
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Favourable)</td>
<td>20</td>
<td>71</td>
<td>31</td>
</tr>
<tr>
<td>1 or 2 (Intermediate)</td>
<td>10</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>3, 4, or 5 (Poor)</td>
<td>4</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 13.7 Prognostic stratification for survival of patients with metastatic renal cell carcinoma treated with interferon-α.**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cut-off point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky performance status</td>
<td>&lt;80%</td>
</tr>
<tr>
<td>Time from diagnosis to</td>
<td>&lt;12 months</td>
</tr>
<tr>
<td>treatment with interferon-α</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&lt;lower limit of laboratory reference range</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>&gt;1.5× the upper limit of laboratory reference range</td>
</tr>
<tr>
<td>Corrected serum calcium</td>
<td>&gt;2.4 mmol⁻¹</td>
</tr>
</tbody>
</table>

**Survival prediction**  
Number of risk factors | 1-year survival (%) | 3-year survival (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Favourable)</td>
<td>83</td>
<td>45</td>
</tr>
<tr>
<td>1 or 2 (Intermediate)</td>
<td>58</td>
<td>17</td>
</tr>
<tr>
<td>3, 4, or 5 (Poor)</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

**Progression-free survival**  
Number of risk factors | 6 months (%) | 12 months (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Favourable)</td>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td>1 or 2 (Intermediate)</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>3, 4, or 5 (Poor)</td>
<td>19</td>
<td>10</td>
</tr>
</tbody>
</table>

**Vascular Endothelial Growth Factors (VEGF)** Through the mapping of the VHL gene, its role in normal physiology has come to be understood, whereby it encodes for a protein that targets a protein transcription factor, the HIF for proteolysis and degradation [75]. This is important because in hypoxic conditions coupled with VHL gene inactivation, the HIF accumulation leads to subsequent overexpression of genes that cause tumour angiogenesis [75]. With understanding the physiological function of VEGF, specific drugs have been designed for anti-angiogenic effect, such as tyrosine kinase inhibitors and monoclonal antibodies, against circulating VEGF [75].

**Tyrosine Kinase Inhibitors** Tyrosine kinase inhibitors (TKI) include sorafenib, sunitinib, pazopanib, axitinib, and tivozanib all of which have shown to increase the overall response rate (by 8, 25–40, 27, 44, and 28%, respectively), the progression-free survival (by 3–4, 6, and five months for sorafenib, sunitinib, and pazopanib),
and overall survival rates [76–86]. Sunitinib is recommended as first-line therapy in favourable and patients with an intermediate risk, whereas sorafenib is recommended as second-line therapy after cytokine failure, pazopanib as first-line or after cytokine failure in favourable and patients with an intermediate risk, and axitinib as second-line treatment after failure of cytokines or other TKIs [74].

**Monoclonal antibody against VEGF** Bevacizumab alone and in combination with interferon-α was found to a higher response rate as well as increased progression-free survival when compared to an interferon alone or a placebo [71, 87, 88]. Therefore, advocated for use as first-line therapy in favourable and patients with an intermediate risk [74].

**Mammalian Target of Rapamycin Inhibitors (MTOR)** Mammalian target of rapamycin inhibitors (MTOR) include temsirolimus and everolimus, which were both, found to improve overall response rates, survival rates, and progression-free survival [73, 89, 90]. Temsirolimus is advocated as first-line treatment in patients in the poor risk group, and everolimus is recommended as second-line treatment after failure of cytokines or TKIs [74].

13.1.1.11.5 **Surgery for Metastatic Disease** Resection of lung metastases increased the five-year cancer-specific survival rate from 19 to 74% in patients with lung-only metastases, whereas complete resection of non-lung metastases improved five-year survival from 12 to 33% [91].

13.1.1.11.6 **Chemotherapy and Radiotherapy** Chemotherapy or radiotherapy for metastatic disease do not offer improvement in survival, and their use has not been advocated; however, radiotherapy can be offered for palliative treatment for symptom control [92–94].

13.1.1.11.7 **Surveillance after Curative Treatment** Recurrences after radical or partial nephrectomy are dependent on the stage and grade of the cancer [95–99]. Local recurrences in the tumour bed are about 1–4% for tumours <4 cm and up to 10% recurrence for tumours >4 cm [59, 63, 95–100]. Contralateral kidney recurrences, about 1–6%, are associated with positive surgical margins and multifocality for clear cell RCC and the nuclear grade for papillary RCC [95–97, 101]. The recurrence after primary radiofrequency ablation has been reported to be about 6.5–18%, whereas post-cryoablation recurrence is about 3–7% [59, 63, 102–104].

Early detection with in the first three months to a year is vital because subsequent management can be offered in some cases, such as repeated ablation or surgical resection which can still lead to a cure [48, 95–97, 103, 104]. Although, repeated excision of an isolated local recurrence increases overall survival (30–40%), it comes with an increased risk of surgical complications (13–33%), and therefore, the benefits and risks need to be weighed [95].

All patients who undergo intervention for RCC have to be therefore kept under surveillance with regular blood profiling, clinical evaluation, and imaging. The objective for postintervention surveillance is for evaluation of complications, renal function, detection of loco-regional recurrence, and metastatic disease. The frequency and period of surveillance is variable and has not been standardised. However, recent validated nomograms have been designed, based on patient risk factors, to classify them into various risk groups. These normograms are a useful guide for clinicians to formulate their follow up protocols (Table 13.8) [74, 105, 106].

### Table 13.8 Based on European Association of Urology recommendation for renal cell carcinoma follow up after treatment.

<table>
<thead>
<tr>
<th>Risk Profile</th>
<th>Treatment</th>
<th>6 months</th>
<th>1 year</th>
<th>2 year</th>
<th>3 year</th>
<th>4 year</th>
<th>5 year</th>
<th>&gt;5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Radical/partial nephrectomy Ultrasound</td>
<td>CT</td>
<td>CT</td>
<td>Ultrasound CT</td>
<td>CT</td>
<td>Ultrasound CT</td>
<td>CT</td>
<td>CT</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Radical/partial nephrectomy Cryo therapy/radio frequency ablation</td>
<td>CT</td>
<td>Ultrasound CT</td>
<td>CT</td>
<td>Ultrasound CT</td>
<td>CT</td>
<td>CT</td>
<td>CT once every 2</td>
</tr>
<tr>
<td>High</td>
<td>Radical/partial nephrectomy Cryo therapy/radio frequency ablation</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>CT once every 2</td>
</tr>
</tbody>
</table>

CT, computed tomography.

### 13.1.1.12 Other Types of Malignant Renal Masses

13.1.1.12.1 **A Wilms Tumour (Nephroblastoma)** This is the most common paediatric malignancy and accounts for 3% of adult cases [107]. Wilms tumour contains metanephric blastema (primitive renal tubular epithelium) and connective tissue. Pathological staging is similar for both adults and children; therefore, management protocols follow similar patterns [107]. Clinically and radiologically, these tumours are similar to RCC and can only be differentiated pathologically by having three cell type appearances a distinctive blastemal stromal, and
epithelial cells, [107, 108]. As there is lack of sufficient data on the adult population, the following discussion will be based on paediatric Wilms tumour.

**Aetiology** Nearly 1% of Wilms tumour is familial; 10% of patients have associated congenital malformations such as Wilms, aniridia, genitourinary malformation, and mental retardation (WAGR) syndrome, Denys–Drash syndrome (male pseudohermaphroditism and renal failure secondary to progressive, diffuse glomerular nephropathy), and Beckwith-Wiedemann syndrome (i.e. macroglossia, macrosomia, hypoglycaemia, visceromegaly, and omphalocoele, in addition to a predisposition to several tumours) [108–110].

Loss of chromosome 11p13 (WT1) tumour suppressor gene was identified as the genetic cause behind the development of the cancer [108, 111]. However, only 5–10% of tumours have been demonstrated to have the WT1 mutation [112]. Other mutations include 11p15.5 (WT2), X chromosome (WTX), and CTNNB1. Tumour-specific loss-of-heterozygosity (LOH) for chromosomes 1p and 16q (WT3) identifies a subset of Wilms tumour who have worse prognosis.

**Clinical Features, Investigation, and Staging** The majority are asymptomatic and are incidental findings on general routine check-ups whereby an abdominal mass is felt [108]. However, they may present with classical features such as fever, haematuria, loin pain, or hypertension.

Investigations are similar to those for RCC, whereby ultrasound, urography, CT, and MRI scans are the main stay, and the diagnosis of nephroblastoma is made after surgical resection. Intravenous involvement occurs in 11% of cases with inferior vena caval extension occurring in 6% [108].

Staging is vital as with all other cancers to determine the most appropriate management plan (Table 13.9) (Figure 13.18) [107, 108].

**Treatment** Surgery Similar to RCC treatment, radical nephrectomy is considered the gold standard [108]. However, partial nephrectomy is only possible in 8–33% of cases, whereas minimally invasive surgery is still in development in the paediatric cancer field [108]. These tumours can be big and can extend to the contralateral side; therefore, careful resection should be done (Figure 13.19).

**Chemotherapy and Radiotherapy** Wilms tumours are chemo- and radiosensitive and recommendations for treatment are shown in Table 13.10 [107].

**Prognosis and Metastatic Disease** Prognosis is good with a 10-year survival between 78 and 96% for those with favourable histology (Table 13.11) [108, 109]. Poor prognostic indicators are the presence of features of anaplastic tumours (extreme nuclear and cytological atypia), clear cell sarcoma, or rhabdoid tumours. Recurrence will occur in about 15% of those with favourable histology and 50% of anaplastic tumours; metastases most commonly occur in the lung (60%) or abdomen (30%) [108].

Nearly 12% of patients will have metastatic disease at diagnosis, 80% of which are in the lung [108]. However, a
good prognosis can still be achieved with metastasectomy followed by chemotherapy.

13.1.1.12.2 Sarcoma
Sarcoma represents <2% of malignant renal tumours, with a peak incidence in the fifth decade of life [113, 114]. Clinical presentation, investigation, and treatments are similar to RCC, and only pathological examination can provide the diagnosis [113, 114]. Various subtypes exists, with leiomyosarcoma comprising 50% of sarcomas; the remaining subtypes include fibrosarcoma, liposarcoma, haemangiosarcoma, osteogenic sarcoma, malignant schwannoma, and Ewing sarcoma. Renal sarcoma has a poor prognosis with nearly 15% of cases having metastatic disease at presentation and a recurrence-free survival at one year being around 75–100% dropping to 42–48% at three years and 25% at five years, in addition to a metastasis-free survival at one year around 74% dropping to 29% at three years [113].

13.1.1.12.3 Renal Haematological Malignancy
Renal involvement with lymphoma or leukaemia is common (47%) in patients suffering with these disease and represent <1% of all renal tumours [115]. Clinical presentation is usually rare (15%) and is similar to RCC clinical features [115]. Treatment is usually along the line of medical therapy with chemotherapy with or without radiotherapy, and therefore, enlisting the consultation of the haematologists and oncologists are the mainstay of treatment [116].

13.1.1.12.4 Metastatic Tumours
Metastatic foci to the kidney from other organs occur in 7–20% of patients who died of cancer [116]. Clinically the majority of patients are asymptomatic (95%); however, it can present with haematuria (3%) or flank pain (2%) [116]. Scanning typically finds multiple small nodularities that slightly enhance. Biopsy of the lesion can give an indication to the primary [116]. Treatment is usually of the primary cancer, with systemic therapy for more likely palliative care with nephrectomy rarely needed.

Other types of malignant renal cancers such as carcinoid and small cell carcinoma are exceedingly rare and are limited to case reports.
Renal cysts are the most common renal lesions and make up about 70% of all asymptomatic renal masses. Risk factors for developing renal cysts include being a male, increasing age, having hypertension, renal impairment, or end-stage renal failure [117, 118].

Renal cysts range from being simple cysts to indeterminate and complex. The Bosniak classification is the most widely accepted method for classifying renal cysts based on the cystic wall, presence of septa, calcification, solid components, and enhancing nature of the cyst (Table 13.12) [35].

Though the vast majority of these lesions are detected incidentally on routine imaging of other organs, patients can present with symptoms specific to the cysts. Clinical features usually arise if the cyst gets infected, bleeds, ruptures, or expands. In which case, the patient can present with loin pain, discomfort, haematuria, or signs and symptoms of an infection.

Initial renal ultrasound can easily detect the cysts and provide an initial assessment of whether the cysts are simple or complex. If the cysts are irregular, septated, calcified, or seem to have a solid component, then a CT scan is indicated to further characterise the lesion according to the Bosniak classification. In instances where CT was unhelpful, or there is a contraindication to obtaining a CT scan, an MRI can also aid classification of the cysts [35].

This aids the management in that Bosniak I and II lesions are more likely benign, while a classification of IIIF will require regular follow up and assessment. However, classes III or IV might require surgical interventions. This
is based on the incidence of malignant conversion, whereby class I has an incidence of 1.7%, class II: 18.5%, class III: 33%, and class IV: 92.5% [119].

Though it is recommended that classes III and IV cysts are surgically excised, cysts that cause recurrent or severely distressing symptoms as a result of pressure associated with size or hypertension will also require surgical or radiological intervention [120, 121]. Interventions available are radiological aspiration, sclerotherapy injection, surgical resection, or decortication. However the risk of recurrence and further intervention needs to be discussed with the patients to be weighed against the symptoms.

13.2.2 Oncocytoma

Oncocytoma is one of the most common benign masses composed of epithelial cells with granular eosinophilic cytoplasm. Oncocytomas account for 3–7% of all renal masses [122]. They have a male predominance and are usually solitary and unilateral. Several genes have been associated with oncocytomas. These include loss of chromosome 1, Y, or 14q rearrangement of 11q13, or translocations in the short arm of chromosome 11 [123, 124].

The majority present as an incidental finding of a renal mass; however, they can also present with loin pain or haematuria.

Oncocytomas are a diagnostic challenge. They share similar radiological appearances with RCC and core renal biopsies cannot conclusively differentiate between these two entities [125, 126]. More often than not, the diagnosis is made after surgical excision of a tumour thought to be RCC. Oncocytomas have an angiographic ‘spoke wheel’ appearance due to the arterioles around the mass and the capsule gives a ‘lucent rim sign’; however, even these features typical of an oncocytoma are seen in some RCCs [127, 128].

In view of their benign nature, oncocytomas do not require any treatment. However, in real life practise, because of the diagnostic uncertainty, they are often treated aggressively similar to a RCC [129, 130]. A nephron-sparing approach is recommended to avoid needless loss of nephrons [129, 130]. Their prognosis is good [131].

13.2.3 Angiomyolipomas

Angiomyolipomas (AMLs) are benign tumours that account for less than 10% of renal masses and have an incidence of about 13 per 100 000 adults [132]. As the name suggests, AMLs are characterised by containing mature fat cells, with smooth muscles and blood vessels. AMLs are found in patients with tuberous sclerosis (TS), which is an inherited autosomal dominant disorder comprising of adenoma sebaceum, mental retardation, and epilepsy. However, these signs may not necessarily all be present. Almost 60% of TS will develop renal manifestations, AMLs being the most occurring, followed by renal cysts and a small proportion will develop RCCs (4%) [133]. TS2 mutations (chromosome 16p13.3) are associated with AMLs and cysts more than TS1 mutations (chromosome 9q34) [133–135].

As with most benign renal masses, AML is more commonly incidentally detected and asymptomatic [132, 136]. However, nearly 25% of AMLs commonly present with spontaneous rupture and perirenal haemorrhage which can be massive and life threatening (Wunderlich syndrome) [136, 137]. Otherwise, symptoms can be related to an increase in the size of the tumour and present with pain, palpable mass, or bleeding and haematuria [136].

AMLs can be confidently diagnosed on radiological imaging. High-intensity echogenicity are seen on ultrasound which are typical for AMLs, whereas on a CT scan they are typically non-enhancing with –20 to –80 Hounsfield units [138, 139]. Angiography can show increased neovascularization and 50% of AMLs are found to have aneurysms of the vessels [139]. If CT scans are contraindicated, then an MRI scan is indicated. In addition, if the AML is not confidently diagnosed on a CT scan, due to low lipid content of the AML making it appear similar to an RCC, then an MRI can aid the distinction [139–141]. Liposarcomas or an RCC with high lipid content can also be mistaken for AMLs. In which case, a biopsy of the mass may have a role to determine more definitive management.

The management of an AML is based on an individual basis depending on the symptomology, tumour size, and the patient’s comorbidity. Increasing tumour size correlates with worsening symptoms as well as a higher risk of haemorrhages [136, 142–144].

If the patient is asymptomatic and the lesion is <4 cm, then conservative management with regular surveillance by either CT or ultrasound is recommended. However, if the mass is >4 cm, present with significant symptoms, then the patient should undergo nephron-sparing surgery or arterial embolisation [136, 143–145]. Special care is warranted in pregnant women with an AML, whereby there is an increased risk of growth and bleeding and consideration for early interventions [145]. If there is severe haemorrhage, then selective embolisation can be considered before or as an alternative to surgical exploration because invariably exploration will lead to loss of the kidney [146]. Furthermore, in patients with TS with bilateral AMLs, the mainstay should be conservative management where possible. MTOR inhibitors have been used in this group of patients.
13.2.4 Renal Cortical Adenoma

The incidence of renal cortical adenoma (RCA) is between 7 and 23% [128, 147]. Although RCA has been traditionally classified as a benign renal mass, recent studies have suggested RCAs are premalignant precursors to papillary RCC [147]. Nonetheless, RCA are mainly asymptomatic and their treatment is still debated.

13.2.5 Metanephric Adenoma

The majority of these adenomas are asymptomatic; however when present, they can mimic the clinical features of RCC. These tumours are rare and difficult to distinguish from RCC; however, if a high level of suspicion exists, then percutaneous biopsy and fine-needle aspiration of the mass and histological staining can aid the distinction [148–152]. These adenomas express the Wilms tumour marker, WT1; poorly express the α-Methylacyl-CoA racemase (highly expressed in papillary RCC); and highly express S-100 protein (poorly expressed in Wilms tumour and absent in papillary RCC) [148–150].

13.2.6 Cystic Nephroma and Mixed Epithelial or Stromal Tumour

This is a rare benign tumour that is difficult to distinguish from cystic RCC and Wilms tumour in adults or children, respectively. Therefore, the mainstay of treatment is surgical excision with either radical or partial nephrectomy where possible.

13.2.7 Leiomyoma

Leiomyomas are rare benign lesions (<1.5% of all benign masses) that arise from the renal capsule. Though they may have variable enhancements on CT scan, differentiation from RCC is difficult and have been treated as such.

13.2.8 Columns of Bertin

A variant of normal anatomy, when a duplex collecting system or an extrarenal system is present, then an extra-large normal kidney tissue is apposed in between the junction of the two moieties of the collecting system; these are called columns of Bertin (Figure 13.20). These are easily distinguishable from a pathological renal mass in that they have the same density as the rest of the renal parenchyma. If doubt exists, however, a biopsy will show normal renal tissue.

Renal artery aneurysms and arteriovenous malformations will be discussed in another chapter.

13.2.9 Expert Opinion

Over the last few decade, there has been significant development in the understanding and management of RCCs. Despite these commendable efforts, several important aspects of RCC remain unclear and are yet to be elucidated. Understandably several trials are underway in RCC addressing various the various day-to-day dilemmas encountered in contemporary practice. Sporadic RCC is considered to have heterogeneous genetic basis, and decoding the genetic biology of RCC has been a subject of significant interest in recent years, leading to the development of various targeted therapies. Trials such as the GPKC study are specifically evaluating the genetic basis of papillary RCC. Several trials are currently addressing various permutations of targeted-therapy regimes. In the current era of targeted therapy, the role of cytoreductive nephrectomy requires clear establishment. The CARMENÁ trail is comparing outcomes between sunitinib and sunitinib after cytoreductive nephrectomy. The SURTIME Trial is assessing outcomes based on the timing of sunitinib and cytoreductive nephrectomy. Surgical evolution with larger, advanced tumours being managed with minimally invasive and nephron-sparing approaches has been a common theme in recent years. Furthermore, there continues to work on novel treatment option such as microwave thermotherapy, high-intensity focused ultrasound (HIFU) and photodynamic therapy (PDT). Unfortunately though, a significant number of these surgical developments have not been scrutinised by high-quality evidence, highlighting issues with research in surgery in general. In conclusion, the future of RCC remains exciting, although enigmatic.

Figure 13.20 A large column of Bertin may mimic a renal cell cancer.
13.3 Ureter and Renal Pelvis Neoplasms

13.3.1 Incidence

Upper urinary tract urothelial cell carcinomas (UT-UCC) are aggressive and uncommon cancers. They represent about 5–10% of all urothelial cancers [153, 154]. More than half of UT-UCCs are invasive at presentation. Concurrent bladder cancer occurs in 8–17% of cases [154–157]. Bilateral UT-UCCs are observed in 2.5–6% of patients [154–157].

13.3.2 Aetiology

13.3.2.1 Modifiable Risk Factors

A number of environmental risk factors have been shown to increase the incidence of developing upper urinary tract cancer (UUTC), and these are depicted in Table 13.13 [154, 158].

13.3.2.2 Nonmodifiable Risk Factors

A hereditary form of UUTC has been seen in patients with hereditary nonpolyposis colorectal carcinoma (HNPCC) or Lynch syndrome, an autosomal dominant multi-organ cancer syndrome caused by germline mutations of mismatch repair genes [159]. Patients with HNPCC have a 6% risk (22x higher than general population) of developing UUTC and should be closely monitored [159]. Patients are at risk of hereditary status if they are diagnosed with HNPCC at <60 years of age, personal history of HNPCC-associated cancer, have a first-degree relative <50 years of age with a HNPCC-associated cancer, or two first-degree relatives with a HNPCC-associated cancer [159].

Genetic polymorphism have been linked to an increased risk of developing UUTC as well as faster disease progression. Two such polymorphisms include a variant allele, SULT1A1*2, which reduces sulfotransferase activity, and polymorphism located at the T allele on chromosome 8q24, which has been linked to aggressive UUTC.
Research into the genetics of UUTC is ongoing, especially differentiating it from bladder carcinoma as two distinct entities with two separate pathophysiological processes [160].

### 13.3.3 Histology Types

#### 13.3.3.1 Benign

Nephrogenic adenomas, urothelial papillomas, and inverted papillomas (IP) are benign lesions. IP recur in about 1–7% of patients and up to 23% of IP have been reported to be associated with UUTCs and therefore require regular surveillance [162].

Other benign upper tract lesions include fibroepithelial polyps, villous adenomas, squamous papillomas, leiomyomas, neurofibromas, fibrous histiocytomas, haemangiomas, periureteric lipomas, and hibernomas [163].

#### 13.3.3.2 Malignant

Urothelial (transitional cell) carcinomas (TCC) represent 90–95% of UUTC and are structurally similar to that of bladder TCC [163, 164]. However, due to the naturally thinner muscular layer of the UUT, muscle invasion is seen earlier than in the bladder. Morphological variants of urothelial carcinomas have been reported and are exceedingly rare, limited to case reports or series. Nonetheless, they are associated with higher-grade disease and a worse prognosis; these include micropapillary, clear cell, neuroendocrine, sarcomatoid, and lymphoepithelial [164–166].

Squamous cell carcinoma (SCC) and adenocarcinomas represent <10% and <1% of UUTCs, respectively, and are associated with chronic inflammation such as stones or recurrent or chronic infections, as well as chronic obstruction [164, 165, 167, 168]. Sarcomas of the UUT have also been reported.

---

**Table 13.13 Risk factors for developing upper urinary tract cancer.**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Relative risk</th>
<th>Odds ratio</th>
<th>Incidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>2.5–7</td>
<td>4–11</td>
<td>—</td>
<td>Multiple inhaled toxic substances (aromatic amine with arylamine, benzopyrene, dimethylbenzanthracene) are metabolised and are carcinogenic</td>
</tr>
<tr>
<td>Aromatic amines</td>
<td>—</td>
<td>8.3</td>
<td>—</td>
<td>Exposure of an average 7 with a nonexposure latency of 20 years</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>—</td>
<td>1.3–1.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chlorinated solvents</td>
<td>—</td>
<td>1.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phenacetine</td>
<td>1.4–5.4</td>
<td>5.3–6.5</td>
<td>—</td>
<td>An analgesic no longer in production</td>
</tr>
<tr>
<td>Aristolochia acid–containing plants</td>
<td>—</td>
<td>—</td>
<td>29.2/100000 in endemic areas in 1998</td>
<td>Plants such as <em>Aristolochia fangchi</em> and <em>Aristolochia clematis</em>, endemic in the Balkans. The acid mutates the p53 gene on codon 139 and is very rarely seen in the nonexposed population</td>
</tr>
<tr>
<td>Coffee</td>
<td>1.3</td>
<td>—</td>
<td>—</td>
<td>Consumption of more than 7 cups a day.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.5</td>
<td>—</td>
<td>—</td>
<td>If drinks two or more of either 12 oz (oz) of beer, 4 oz of wine, or 1 oz of liquor</td>
</tr>
<tr>
<td>Chinese herbs nephropathy</td>
<td>—</td>
<td>—</td>
<td>40–46% of exposed patients in Europe</td>
<td>—</td>
</tr>
<tr>
<td>Blackfoot disease (arsenic poisoning–induced vasculitis)</td>
<td>—</td>
<td>—</td>
<td>20–26% of upper urothelial cancer in endemic areas</td>
<td>—</td>
</tr>
<tr>
<td>Urinary tract calculi</td>
<td>1.5–2.5</td>
<td>—</td>
<td>—</td>
<td>Chronic inflammation of the urothelium by the calculi or obstructive uropathy may promote cancer proliferation.</td>
</tr>
<tr>
<td>Long-term habitual laxative use</td>
<td>9.62</td>
<td>—</td>
<td>—</td>
<td>Particularly anthranoids (e.g. Senna) and chemical laxatives</td>
</tr>
<tr>
<td>Chronic urinary tract infections</td>
<td>—</td>
<td>1.5–2</td>
<td>—</td>
<td>Weakening of the urothelium predisposes to carcinogenesis.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>3.2</td>
<td>—</td>
<td>—</td>
<td>Carcinogenic via its metabolite, acrolein.</td>
</tr>
<tr>
<td>External beam radiotherapy</td>
<td>1.9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>—</td>
<td>1.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yerba mate</td>
<td>—</td>
<td>2.2</td>
<td>—</td>
<td>Its consumption lead to accumulation of high levels of polycyclic aromatic hydrocarbons.</td>
</tr>
</tbody>
</table>
13.3.4 Clinical Features
UUTCs can present with visible or non-visible haematuria (70–80%), flank or renal pain (20–40%), and the presence of an abdominal mass (10–20%) [163, 164]. Alarming systemic symptoms such as anorexia, weight loss, malaise, fatigue, night sweats, or coughs or palpable lymphadenopathy or hepatomegaly are suggestive of metastatic disease [164].

13.3.5 Diagnosis
The diagnosis of UUTCs is reliant on a combination of urinary biomarkers, imaging, and endoscopic evaluation.

13.3.5.1 Urine Cytology
Urine cytology has a sensitivity rate of 20–77% and a high specificity rates of 90–100% in detecting urothelial cancers [169]. Abnormal urine cytology in the presence of a normal bladder cystoscopy is highly suggestive of an UUTC and should be carefully investigated. However, its use in routine practice has been questioned due to the variable sensitivity (due to interobserver discrepancy in analysis and sampling of the specimen) and additional costs [169, 170].

13.3.5.2 Radiological Investigations
Intravenous urography and ultrasonography (Figure 13.24) have been replaced by CT urography (CTU) with excretory imaging as the first line investigation for UUTC (Figures 13.25 and 13.26) [153]. CTU has a variable sensitivity ranging from 36 to 96% and a high specificity of 96–99% [153, 171]. CTU can accurately detect any thickening of the UUT, filling defects, non-visualisation of the collecting system, or obstruction. However, it can miss flat lesions such as CIS and dysplasia; hence, why there is variability in the sensitivity for all UUTC [153]. MR urography (MRU) can be used if CTU is contraindicated [171].

13.3.6 Staging and Grading
The morphological classifications of UUTCs are similar to that of the bladder classification [164, 173]. The previous classification according to differentiating grade (G1: well differentiated, G2: moderately differentiated, and G3: poorly differentiated) has been replaced by

Figure 13.23 Computed tomography (CT) scan showing (a) large filling defect in the ureter (b) with a tortuous dilated ureter proximal to the tumour.
a more descriptive histological classification system: dysplasia (preneoplastic falling short of CIS), CIS (flat lesions, whose surface epithelium contains cells that are cytologically malignant), and noninvasive papillary tumours (papillary urothelial tumours of low malignant potential, low-grade papillary urothelial carcinoma, high-grade papillary urothelial carcinoma, and invasive papillary carcinoma) (Figure 13.25) [163, 164].

The TNM classification of UUTC is depicted in Table 13.14 [163, 164].
13.3.7 Prognostic Factors

The stage and grade are the most important prognostic factor [174]. The five-year cancer survival is <50% for pT2/3 disease and <10% for pT4 [164]. Other prognostic factors implicated in UT-UCC include [164, 175–178]:

- Advanced age at the time of radical surgical treatment.
- Obesity (body mass index >30).
- Smoking.
- Ureteral tumours.
- Lymphovascular invasion.
- Positive surgical margins.
- Tumour necrosis.
- Sessile tumour architecture (as opposed to papillary).
- Concomitant CIS.
- Previous history of bladder CIS.

13.3.8 Treatment

- Radical nephroureterectomy (RNU) with ipsilateral cuff excision
- Nephron-sparing approaches
- Ureteroscopic ablation
- Percutaneous ablation
- Segmental resection

13.3.8.1 Surgery

13.3.8.1.1 Radical Nephroureterectomy

Radical nephroureterectomy (RNU) with ipsilateral bladder cuff excision is the gold standard of UUTC [164, 178, 179]. Surgical intervention should not be delayed beyond 45–90 days because there is risk of disease progression with delay beyond this period [164]. Both open and laparoscopic approaches have similar oncological outcomes, although laparoscopic approach has better early surgical outcomes [179]. Ipsilateral ureteric cuff excision is imperative because recurrences in the ipsilateral ureteral stump or orifice range between 30 and 64% [178]. After initial RNU, the bladder cuff can be excised through a transvesical, extravesical, or endoscopic approach [178]. Robotic RNU and bladder cuff excision has emerged to replace laparoscopic approaches [180].

Procedure A RNU can be performed employing open, laparoscopic, or robotic approaches. Both extraperitoneal
Kidney and Ureter Neoplasm

and transperitoneal approaches have equivalent oncological and early surgical outcomes.

It has a similar technique as that of a radical nephrectomy with a midline incision; the kidney is mobilised and its pedicle divided. If performed using a laparoscopic approach, the specimen can be removed through an extension of a lower port incision.

Various techniques have been described for ipsilateral bladder cuff excision.

In a transvesical approach, the bladder is opened (Figure 13.26) and the whole nephroureterectomy specimen is delivered through the wound.

In an extravesical technique, the entire ureter is dissected till the bladder, and then ureter is clamped with a portion of the bladder. The distal segment is then transected and the bladder is closed.

The Semple manoeuvre (endoscopic technique) is the least invasive for tumours arising in the upper part of the ureter [181]. With the patient in the cystoscopy position, the bladder is kept semi-distended to prevent excessive extravasations. A hook electrode incises a circumferential area of bladder cuff mucosa around the ureteral orifice, followed by endoscopic dissection to the perivesical fat, which leads to detachment of the intramural ureter (Figure 13.27). After the nephrectomy part, the distal ureter, including the bladder cuff, is gently retracted and removed (Figure 13.28). The ureter is checked for complete removal by identifying the coagulated edge of the bladder cuff at the distal ureteral end. A Semple manoeuvre is not appropriate for a tumour in the lower third of the ureter, and it should not be used for ureters that are surrounded by fibrosis because that can cause injury to the common iliac artery.

<table>
<thead>
<tr>
<th>T (Primary Tumour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>Ta</td>
</tr>
<tr>
<td>Tis</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td>N (Regional lymph nodes)</td>
</tr>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
<tr>
<td>M (Distant metastasis)</td>
</tr>
<tr>
<td>Mx</td>
</tr>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

TNM Staging

Stage 0
- 0a: Ta N0 M0
- 0is: Tis N0 M0

Stage I
- T1 N0 M0

Stage II
- T2 N0 M0

Stage III
- T3 N0 M0

Stage IV
- T4 N0 M0
- Any T N1,2,3 M0
- Any T Any N M1

TNM, T, N, and M are the tumour, node, and metastasis.

Nephron-Sparing Approaches In recent years with the evolution of endoscopic and laser technology nephron-sparing approaches have gained popularity. Nephron-sparing surgery is commonly considered for patients with a single functioning kidney or a patient with renal insufficiency. In patients with normal contralateral kidney, nephron-sparing surgery can be considered in carefully selected patients with low-grade and stage disease, which are less than 1 cm in size [164].

Ureteroscopy and Percutaneous Approaches Endoscopic management of selected low-grade disease has similar oncological outcomes and survival rates as RNU [177, 179]. However, 20% of patients will proceed to a RNU [177]. For tumours in the renal pelvis or collecting system, the percutaneous approach can be implemented. Recent evidence has suggested that the application of photodynamic diagnosis assistance has the potential to improve the detection rates of superficial flat lesions [153, 172].

Segmental Resection Distal ureterectomy and ureteral reimplantation can be considered for distal ureteric tumours. Ureteral resection of diseased section with ureteroureterostomy can be performed for mid-upper ureteral tumours.

Although nephron-sparing surgery shares oncological equivalences with RNU for low-grade, stage, and volume
disease, the overall oncological efficacy of the nephron-sparing trend is significantly inferior to RNU. Furthermore, current investigative modalities are unable to accurately stage and grade UT-UCC. Hence, it is imperative that patients being treated with nephron-sparing surgery are kept under strict and stringent surveillance.

### 13.3.8.2 Adjuvant Treatment

Instillation of the ureter with bacillus Calmette-Guerin (BCG) or Mitomycin C in the UUT can be done after conservative treatment of UUTC or for treatment of CIS [182, 183], although no long-term results are available to verify outcomes. However, a single postoperative dose of intravesical Mitomycin C following RNU reduces the risk of bladder tumours within the first postoperative year; (absolute reduction in risk is 11%, the relative reduction in risk is 40%, and the number needed to treat to prevent one bladder tumour is nine) [184].

### 13.3.8.3 Treatment of Advanced Disease

Surgery is considered in metastatic disease only as a palliative option.

Although evidence to date is scanty, platinum-based chemotherapy has been suggested to achieve recurrence-free rate of up to 50% [164, 185].

### 13.3.8.4 Follow-Up

Meticulously close follow-up regimes for patients treated both surgically and conservatively are vital to detect recurrences either locally, distantly, or in the bladder (Table 13.15). Although local recurrence after radical surgery is rare, bladder recurrence ranges between 14 and 54% [179]. The local and bladder recurrence rate for patients managed ureteroscopically is 52% and 37% for patients managed with percutaneous endoscopy is 34% and 24%, respectively [177].

| Table 13.15 European Association of Urology recommended guidelines for upper urinary tract cancer follow-up regimes. |
|-----------------|---------------------------------------------------------------|
| **After RNU, over at least 5** | **After conservative management, over at least 5** |
| Noninvasive tumour: Cystoscopy and urinary cytology at 3 and then yearly; CT every year | Urinary cytology and CT urography at 3 and 6, and then yearly |
| Invasive tumour: Cystoscopy and urinary cytology at 3 and then yearly; CT urography every 6 over 2 and then yearly | Cystoscopy, ureteroscopy and cytology in situ at 3 and 6, and then every 6 over 2, and then yearly |

CT, computed tomography.


References


References


152 Bosco, M., Galliano, D., La Saponara, F. et al. (2007). Cytologic features of metanephrine adenoma of the


14

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4 Urological Research Center, Department of Urology, Fredericia Hospital, Institute of Regional Health Services Research, University of Southern Denmark, Fredericia, Denmark
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Abstract

Urinary stones are an ailment that can leave the patients asymptomatic or lead to significant morbidity or even mortality. Understanding the basic concepts of stone formation is vital in its prevention, which is key not only as a preventative measure but also to ensure patients do not form further stones. In this chapter, we discuss the pathophysiology of stone formation as well as the diagnostic and management modalities.

Keywords urinary stones; urinary calculi; renal stones; renal calculi; renal colic; noncontrast computed tomography lithotripsy; ureteroscopy (URS); percutaneous nephrolithotomy (PCNL); urinary diversion; stone-free rate (SFR); residual fragments (RF)

Key Points

- Key to stone treatment is prevention.
- Majority of stones can be treated conservatively.
- Investigations should be tailored to the patients depending on whether they are first-time or recurrent stone formers.
- Noncontrast computed tomography (CT) scan is the best imaging modality to assess stones for stone diagnosis.

14.1 Epidemiology

Renal stone disease is common, with a worldwide prevalence of between 2 and 20%. Epidemiological studies in the United States show a lifetime risk for men of 12% and for women 5%. Stone recurrence is also common; it is estimated that almost 10% with a stone will form another stone within a year and nearly 50% of stone formers will have a recurrence within 10 years [1]. Recurrent stone formers also have lower estimated glomerular filtration rates (eGFR) when compared to non-stone formers matched for age, sex, race, and body mass index (BMI) [2].

14.2 Pathophysiology

Stones in the urinary tract are usually predominantly crystalline. Crystallisation is a physicochemical process involving a change of phase in which dissolved salts condense into solids – all phase changes are driven by
supersaturation. At supersaturation values less than one crystals of a substance will dissolve, whereas values greater than one crystals form and grow. Urine with supersaturation values greater than one is referred to as metastable because the excess dissolved material, being present at a concentration above its solubility, must eventually precipitate. The upper limit of metastability (also called the 'formation product') is lower amongst patients with stones, indicating that mechanisms protect against solid-phase development are less effective in patients with stones [3].

There are three important processes for crystallisation: crystal nucleation, crystal growth, and crystal aggregation. All three of these processes are dependent on the degree of supersaturation.

It is not enough that crystals should precipitate in the urine because loose grains would be flushed out the next time the patient passed urine. Another factor is always present, the protein matrix, which glues particles together into a coherent mass. Matrix forms from 2.5 to 60% of the dry weight of stones, even those in which supersaturation is the most obvious underlying factor (e.g. uric acid and cystine calculi).

Urine contains molecules that retard the formation of solid phases (i.e. reaching formation product). Urinary citrate binds calcium to form a soluble complex and inhibits nucleation and growth of calcium crystals. Osteopontin (uropontin), calgranulin, Tamm Horsfall glycoprotein, and glycosaminoglycans can all bind with surface calcium atoms and prevent crystal growth [3]. Urine pH is also a modulator of stone formation because some crystals such as calcium phosphate are more soluble in acid urine, whereas uric acid and cystine are more soluble in alkaline urine (Figure 14.1).

14.3 Formation of Calculi in the Kidney

14.3.1 Concretions

Most stones that form in a papilla begin as multiple minute calcium oxalate stones (Figure 14.2). Later, an accumulation of these minute concretions forms a layer under the tip of the papilla – Randall’s plaque. This subsequently separates into the lumen of the calyx.
14.3.2 Papillary Necrosis

A second mechanism for stone formation in the renal papilla is ischaemic necrosis seen with many of the conditions that cause interstitial nephritis. The dead papilla acts as a nucleus for secondary accumulation of calcium oxalate or struvite.

14.3.3 Medullary Sponge Kidney

In medullary sponge kidney (MSK), the renal collecting tubules become grossly dilated. Stones may form as a result of stasis, but there may also be an element of renal tubular acidosis. The condition may appear in one calyx and gradually spread through the kidney. Its cause is unknown, but it is associated with unilateral hemi-hypertrophy and other congenital conditions.

14.3.4 Hydronephrosis and Hydrocalyx

A fourth type of stone is seen in a chronically diluted renal pelvis or calyx; these stones are usually multiple and rounded and may be so numerous that they are called 'milk of calcium stones'.

14.3.5 Recumbency Stones

In spinal injury and major trauma, stone formation was once a common complication. There were several contributing factors: hypercalciuria from loss of calcium from the skeleton resulting from inactivity, urinary infection, and dehydration. Frequent turning, early mobilisation, and active treatment of infection can largely prevent this condition.

14.4 Common Types of Urinary Stones

Against this background, it is appropriate to consider some of the different types of stone (Table 14.1).

### Table 14.1 Types of stones.

<table>
<thead>
<tr>
<th>Main composition of stone</th>
<th>Percentage of all stones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate</td>
<td>60–85%</td>
</tr>
<tr>
<td>Struvite (infection or triple phosphate stones)</td>
<td>1–20%</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>1–10%</td>
</tr>
<tr>
<td>Uric acid</td>
<td>5–10%</td>
</tr>
<tr>
<td>Cystine</td>
<td>1%</td>
</tr>
</tbody>
</table>

14.4.1 Calcium Stones

The most common type of stone is made of calcium oxalate occurring in approximately 60–80% of patients, with calcium phosphate stones making up 10% [4]. The majority of calcium oxalate stones form on the surfaces of renal papillae over collections of suburothelial calcium phosphate particles known as Randall's plaques. The origin of the plaques is the basement membrane of the deep thin loops of Henle [5].

Common biochemical risk factors for calcium oxalate stones include hypercalciuria, hypercalcaemia, and hyperoxaluria. Along with urine volume, urine calcium and oxalate concentrations are the main determinants of calcium oxalate supersaturation.

Idiopathic hypercalciuria is the most common metabolic abnormality in calcium oxalate stone formers. Diagnosis of idiopathic hypercalciuria requires exclusion of conditions such as hypercalcaemia, sarcoidosis, and rare monogenic disorders such as Dent disease. High dietary sodium also increases urinary calcium excretion as does excessive protein intake [6].

Urinary oxalate is a critical factor in calcium oxalate stone formation because its concentration is much less than that of urinary calcium, and so a small decrease will have a greater impact on reduction in stone risk than a reduction in urinary calcium.

Oxalate is a metabolic end product of no known use. Its origins are either exogenous (i.e. dietary) or endogenous (i.e. metabolic). Foods high in oxalate content include, tea, coffee, dark chocolate, rhubarb, berries, and spinach [7]. Hyperoxaluria causing renal stones is seen in three main forms:

1) Dietary causes of hyperoxaluria include excessive intake of foods high in oxalate content, a low calcium intake because of reduced calcium oxalate crystallisation in the gastrointestinal lumen, and a high animal protein intake.

2) Enteric hyperoxaluria occurs in conditions that are associated with fat or bile acid malabsorption, such as inflammatory bowel disease, pancreatic insufficiency, or bowel syndromes, such bowel resection, jejunooileal bypass, and Roux-en-Y gastric bypass. Hyperoxaluria complicating Roux-en-Y gastric bypass is under-recognised [8]. In the normal state, calcium and oxalate within the lumen of the intestine combine to form insoluble calcium oxalate complexes that are excreted in faeces. In fat malabsorption and enteric hyperoxaluria, excessive intraluminal free fatty acids bind to and saponify calcium within the intestine, thereby inhibiting the formation of calcium oxalate. As a result, greater quantities of soluble-free oxalate are absorbed by the colonic mucosa (Figure 14.3). In addition, free fatty acids and bile salts enhance the colonic mucosa's permeability to oxalate.
3) Genetic: The primary hyperoxalurias are a rare group of autosomal recessive disorders. There are three forms of primary hyperoxaluria in which the underlying defects have been identified. Each is caused by an enzyme deficiency, and each affects a different intracellular organelle. Primary hyperoxaluria can occur at almost any age from birth to the sixth decade of life. The clinical presentation varies from infantile nephrocalcinosis to occasional stone formation in adulthood. However, 20–50% of patients have advanced chronic kidney disease at the time of diagnosis. Progressive systemic involvement can occur with major sites of crystal deposition being the kidneys, blood vessel walls, and bones [9].

Hyperoxaluria also occurs with ethylene glycol poisoning and overdose of ascorbic acid.

When calcium phosphate becomes the main constituent of a stone, it is classified as a calcium phosphate stone. However, pure calcium phosphate is rare. The most important calcium phosphates involved in urinary stone disease are apatite and brushite (i.e. calcium hydrogen phosphate dihydrate) stones. Although both minerals contain calcium and phosphate, they form as a consequence of very different mechanisms. Apatite is often found in association with struvite as a consequence of infection (see below). Pure brushite stones typically form in distal (type 1) renal tubular acidosis where there is a defect in renal acid excretion and an inability to reduce urine pH below 5.5 [10]. In the complete form, there is a systemic acidosis frequently accompanied by hypokalaemia, hypercalciuria, and hypocitraturia. The incomplete form is more common and under-recognised and is not associated with metabolic acidosis.

14.4.2 Struvite Stones or Infections Stones

Struvite calculi are typically referred to as infection stones because of their association with urinary tract infections with urease-producing bacteria. The most important urease producers include *Proteus*, *Pseudomonas*, *Klebsiella*, and *Staphylococcus* spp. [11]. Bacteria-produced urease breaks down urinary urea into ammonia and carbon dioxide, which then hydrolyses to ammonium ions and bicarbonate. Binding to available cations then produces carbonate apatite and magnesium ammonium phosphate hexahydrate (struvite). Carbonate apatite crystals start to form when the urine pH is greater than 6.8, but formation of struvite crystals require an alkaline urine (pH > 7.2) and ammonia in the urine. However, formation of a biofilm is also important contributing to the stone matrix within which bacteria adhere.

Infection stones are characterised by their large size and exceptionally rapid growth. As little as four to six weeks may be sufficient for an infection stone to form and to develop into a staghorn stone that involves the entire renal pelvis or calyces.

14.4.3 Uric Acid Stones

Uric acid stones account for approximately 5–10% of kidney stones. Uric acid is filtered in the glomeruli, reabsorbed in the proximal tubule, and secreted again in the distal tubule. Uric acid is the end result of purine metabolism and is relatively insoluble. Furthermore, urine pH is a key regulator of uric acid solubility in urine with an unduly acid urine (pH < 5.5) an invariable feature in uric acid stone formers.

Contrary to expectation, unless massive, hyperuricosuria does not appear to be a significant risk factor for
uric acid stones [12]. The explanation of the acidification defect in idiopathic uric acid stone formation is uncertain. Epidemiological and clinical data have demonstrated an association between uric acid stone formation and diabetes, glucose intolerance, metabolic syndrome, and obesity. The evidence from clinical studies suggests this association may in part be related to insulin resistance [13].

14.4.4 Cystine Stones
Cystinuria is the purest example of the simple supersaturation stone. They are the hardest type of stones due to their disulphide bonds. Cystinuria is responsible for 1% of adult and 6–8% of paediatric stone disease. It is an inherited autosomal recessive disorder of a heterodimic amino acid transporter resulting in decreased absorption of cystine from the intestine and the proximal tubule of the kidney. Mutations in SLC3A1 (chromosome 2) and SLC7A9 (chromosome 19) are known to cause cystinuria resulting in impairment of reabsorption of the dibasic amino acids cystine, ornithine, lysine, and arginine [14]. Although all of these amino acids reach high concentrations in the urine, only cystine is insoluble enough to form stones. Type A cystinuria refers to patients with mutations in SLC3A1 and type B where there are mutations in SLC7A9.

In heterozygote patients’ urine excretion of cystine depends on type; in type A, cystine excretion is normal, whereas in type B, cystine excretion is increased and patients may form stones. The incidence of stone formation increases when urinary cystine concentration exceeds 170 mg l⁻¹. Cystine is also poorly soluble at physiological urine pH.

14.4.5 Drug-Induced Stones
These are rare and occur in less than 1% of all stones analysed. Stones are either made of the drug, or drug metabolite, or form as a consequence of the metabolic effect of the drug. Contemporary drugs that can be found in stones include protease inhibitors and sulphonamides such as sulfadiazine. Carbonic anhydrase inhibitors, topiramate, and antacid preparations containing calcium carbonate or calcium phosphate are examples of drugs that cause stones through their metabolic effects.

14.5 Clinical Features
Stones present in a number of ways:

- Asymptomatically
- Visible or nonvisible haematuria
- Renal or loin pain
- Ureteric colic pain
- Recurrent infections
- Obstruction with or without an acute kidney injury or sepsis

14.5.1 Kidney
Pain in the kidney is experienced in the distribution of the dermatomes T9–T11, in the loin radiating down to the testicle and groin. When there is acute dilatation, the pain is colicky; in other circumstances, the stone may be entirely silent or cause a vague backache.

Sometimes it is difficult to believe that a small caliceal calculus, without any dilatation, could possibly give rise to pain. Nevertheless, experience shows that removing such a stone may relieve the pain permanently.

Some of the least obtrusive of all stones are the giant staghorn calculi, which are nearly always made of struvite. These stones may be silent, but they are not safe, and the risks of pyonephrosis and sepsis far outweigh the risks even of open surgery, let alone those of combinations of percutaneous nephrolithotomy (PCNL) and shockwave lithotripsy (SWL).

14.5.2 Ureter
Acute ureteric colic strikes without warning. The pain comes in waves. Dysfunction of the overlying intestine – probably caused by extravasation of urine into the retroperitoneal tissues – leads to vomiting and dilatation of the bowel, which may mimic intestinal obstruction and has led to many a mistaken laparotomy.

There is often a trace of blood in the urine passed at the time of the attack.

If there is infection in the urine, there may be septicaemia with all its sequelae.

14.5.3 Bladder
Stones in the bladder give pain referred typically to the tip of the penis. It is relieved by lying down and made worse by standing up and moving about. There is frequency and pain on voiding, and the last drops of urine are often bloodstained. Most patients with a bladder calculus also have long-standing prostatic outflow obstruction, whose symptoms predominate, and the stone being found only by chance in the course of investigation.

14.6 Complications of Stones
14.6.1 Renal Stones
The most important complication of a stone is obstruction, giving rise to acute or chronic hydronephrosis.
When this is further complicated by infection, there may be septicaemia, cortical abscesses, perirenal abscess, erosion into the bowel, and xanthogranuloma. Very rarely metaplasia in the urothelium adjacent to a chronic stone leads to squamous cell carcinoma or adenocarcinoma.

### 14.6.2 Stones in the Ureter

With a complete obstruction, there is a risk of septicaemia if the urine is infected because of the backflow of urine into renal veins and lymphatics. There is also a remote but well-documented risk of reflex renal shutdown from spasm of the contralateral calices and ureter. In the course of time, oedema of the wall of the ureter can develop around the stone, however small, which may mimic a urothelial cancer of the ureter.

Stones which get stuck in the ureter for many months may form little pockets past which urine flows without impediment. Sometimes these become infected and erode into adjacent viscera such as the appendix or fallopian tube.

### 14.6.3 Stones in the Bladder

Most stones which are small enough to pass out of the ureter into the bladder will be voided via the urethra. Stones that start off in the ureter linger in the bladder, act as a nucleus for the deposition of successive shells of calcium oxalate or struvite and grow so large that it is impossible for them to pass through the urethra.

Bladder stones can be seen in men when there is existing outflow obstruction. In women, there is usually a foreign body at the centre of a stone (e.g. a fragment of a Foley catheter or a nonabsorbable suture).

Just as the trauma of a stone gives rise to metaplasia of the urothelium in the kidney, so also in the bladder, longstanding calculi may lead to squamous metaplasia and cancer.

### 14.6.4 Stones in the Prostate

These arise in dilated prostatic ducts, usually on a nucleus of corpora amylacea and are often secondarily infected.

### 14.6.5 Stones in the Urethra

Urethral stones are still common in the tropics. The stone travels through the ureter, grows a little in the bladder, and then gets stuck at the external urinary meatus. Stones are also seen in urethral diverticula, as in any other undrained pocket of urine.

### 14.7 Investigations

Investigation of a patient with symptoms suggesting a stone in any part of the urinary tract has three objectives:

1) to make sure that the shadow is indeed a stone;
2) to find out what trouble the stone is causing, so that it can be corrected; and
3) to stop it from happening again.

#### 14.7.1 Is the Shadow Really a Stone?

In the kidney, it is easy to mistake a calcified renal artery aneurysm or calcification in the lymph nodes for a stone. Calcification in the wall of the bladder or ureter in schistosomiasis can resemble a stone as can that caused by another extraordinary fluke (*Paragonimus westermani*).

Phleboliths in the pelvis exactly mimic a calculus, although a computed tomography (CT) view with contrast medium or oblique X-rays with a catheter in the ureter will show the shadow well away from the ureter. A calcified fibroid, teeth in an ovarian dermoid, or a large stone in the ureter or prostate may all resemble stones in the bladder.

#### 14.7.2 What Trouble Is the Stone Causing?

Urography is still the key to the diagnosis of any stone in the urinary tract because most stones are radio-opaque, and most obstruction is revealed by dilatation in the urogram.

The catch is the radiolucent stone. For practical purposes, these are uric acid stones, although it is better to be aware of xanthine stones in patients who have received protracted treatment for gout, and the excessively rare, silicate stones in patients given long courses of magnesium trisilicate for indigestion. The difficulty is quickly solved by ultrasound, supplemented where necessary by CT.

If the stone is more than 5 mm in diameter, its chance of leaving the renal pelvis or completing its journey down the ureter is so small that it ought to be removed. A small stone in an outlying calix, in the absence of infection, can be safely monitored.

#### 14.7.3 Renal Function

An error may arise if a contrasted scan is performed soon after the onset of ureteric colic when it may show no ‘function’ in the kidney. The cause of the silent urogram in acute colic is not certain; there may be spasm of the calices and ureter or obstruction to the flow of urine.
Investigations

along the nephron, but the phenomenon is temporary and completely reversible.

Imaging plays a key role in diagnosis, treatment planning, and follow-up of patients with urolithiasis. Noncontrast computed tomography (NCCT) is the best investigation for diagnosing stones. It has largely replaced plain abdominal radiography of the kidney, ureter, and bladder (KUB) and intravenous pyelography (IVP) (Table 14.2). Unlike IVP, NCCT identifies stones of any composition, with the exception of stones formed by protease inhibitors, such as indinavir [15]. KUB X-rays show stones that are largely calcium containing (i.e. radiodense or radio-opaque). Stones that are radiolight or radiolucent do not show up on X-rays, such as uric acid stones. Some stones are in between, or relatively radiolucent, and can just be identified, such as infection stones (without calcium deposits) and cystine stones.

NCCT correctly measures stone transverse diameter but tends to overestimate cranio-caudal length [16]. Nonetheless, it is sometimes essential to measure the whole volume. Volume = Surface area × 0.6; Surface area = length × width × 0.785 (which is: \( \pi \times 0.25 \)).

Although NCCT is not a dynamic study, it does present indirect signs of obstruction, which in the majority of cases are sufficient for safe clinical management (Figure 14.4). A reliable qualitative assessment of presence of obstruction may be achieved by adding a contrast-enhanced phase (excretory CT) or by an IVP if needed (Figure 14.5). Beyond identifying the stone, NCCT provides significant alternate diagnoses in 10–25% of patients presenting with acute flank pain, such as acute appendicitis, ovarian cysts, or aortal aneurisms.

Isotope functional studies yield the most certain measure of obstruction [17]. Furthermore, they can assess functionality of the kidney to better determine management (Figure 14.6). In the acute management of urolithiasis ultrasound has been shown to be inferior to NCCT with regard to both sensitivity and specificity (Table 14.1). However, as an initial bedside investigation, ultrasound may be useful for diagnosis of obstruction and planning of subsequent diagnostic and therapeutic actions (e.g. drainage) [18]. Although magnetic resonance imaging (MRI) has the ability to detect the secondary effects of obstructive urolithiasis, MRI is unreliable with regard to identifying both renal and ureteral calculi, and at present, MRI has no role in stone evaluation. In case of younger patients, patients who are pregnant, and patients that have undergone multiple prior CT exams in which you want to avoid ionised radiation, ultrasound is the better alternative.

### Treatment Planning

Apart from diagnosis of stones, NCCT is useful for treatment planning. It gives you information on CT attenuation values (Hounsfield Units [HU]), inner-stone structure, and skin-to-stone distance (SSD), all of which have been shown to be independent predictors of stone fragility during shock wave lithotripsy (SWL).

Stones >900–1000 HU seem to predict a poorer outcome of SWL, as does a high SSD (>10 cm) [19]. Additionally, it has been shown that inhomogeneous (NCCT bone window) calcium oxalate monohydrate (COM) and cystine stones, which traditionally are considered SWL resistant, fragment much easier than homogeneous stones with equivalent crystalline composition [20, 21]. These predictors of stone fragility on NCCT may be used in the clinical setting for selecting...
patients for primary SWL or endourological treatment, and thereby increase efficacy of both treatment approaches (Figure 14.7) [22].

Although there are overlaps in HU values between different stone types, CT densitometry gives you a rough estimation of stone composition, which may be useful in the further clinical management of the patients (Table 14.3) [23].

Although controversy exists whether a contrast study is needed prior to stone treatment, it might be useful if stone removal is planned and the anatomy of the renal collecting system needs to be assessed [15, 17, 24–26]. For this purpose, both excretory CT (ECT) and IVP may be used. ECT provides the possibility of performing multiplanar reconstruction and

Figure 14.4 (a) Noncontrast computed tomography (NCCT) showing dilatation of the renal pelvis in the left kidney (blue arrow) and kidney enlargement (green arrow) suggestive of obstruction resulting in intrarenal backflow. The space around the kidney (yellow arrow) is completely dark (clean) indicating that the obstruction is not causing pyelolymphatic backflow, which is an indirect sign that the obstruction probably is not severe. (b): NCCT showing dilatation of the renal pelvis and calyces of the left kidney (blue arrow) and perirenal stranding (space around the kidney dusty) suggestive of an obstruction causing pyelolymphatic backflow. The right kidney contains a complex renal cyst with a calcified septum (red arrow).
Figure 14.5 (a) Left: Intravenous pyelography (IVP) showing an enlarged ‘white kidney’ (blue arrow), dilatation of the renal pelvis (yellow arrow), and a dilated ureter down to the level of spina ischiadica (red arrow). The stone is not clearly seen. (b) Excretory computed tomography (CT) of the same patient showing an enlarged contrast-dense right kidney (blue line) and perirenal fluid collection indicative of fornix rupture (green arrow). In the minor pelvis the small stone is clearly seen. (The small stone passed spontaneously, and these imaging signs do not demand drainage unless the patient show signs of infection).
three-dimensional reformatting (i.e. 3D CT), which may be highly valuable in cases with complex anatomy or stone burden in which surgical difficulty is anticipated (Figure 14.8) [22].

14.7.4.1 Follow-Up and Radiation Safety

It is unquestionable that the applied imaging modality has a significant impact on detection rate of residual stones and the estimated size of the residuals, which
unequivocally affects clinical decision making (see Section 14.35.5). There is no currently agreed-upon strategy for evaluation of residual stones after stone treatment. All imaging involving ionised radiation must be conducted according the as low as reasonably achievable (ALARA) principle.

Ionised radiation risk should be thoroughly considered, when planning follow-up regimes for patients with kidney stone. Nearly a fifth of these patients receive potentially harmful radiation doses in acute and short-term management of urolithiasis in the follow-up setting [27]. This does not suggest that clinicians should avoid CT technology with its entire well-documented benefits in stone disease. On the other hand, be well aware of the benefits and risks of all diagnostic procedures.

In the case of evaluating residual stones, the risks of ionised radiation should outweigh the risks of having a residual stone. This calls for selective evaluation, in which the high sensitive conventional NCCT evaluation should be restricted to those patients who have a high risk of residuals and in whom the residual stones mandate aggressive treatment, for instance patients with infection stones.

Recently, the concept of low-dose NCCT has been introduced. A low-dose NCCT may be defined as a CT-examination applying less than 3 mSv for the entire examination [15, 28]. Low-dose NCCT performs with equivalent sensitivities to conventional NCCT for diagnosis of ureteric and renal stones [29, 30], except for diagnosis of ureteric calculi in patients with a BMI > 30 kg m⁻², in which sensitivity and specificity drops to 50 and 89%, respectively, compared to 95 and 97% in patients who are not obese [28].

Ultra-low-dose CT protocols with radiation doses close to KUB also have been developed, which opens up for using NCCT for diagnosis of urolithiasis, even in children (Figure 14.9) and patients who are pregnant [30, 31].

### Table 14.3 Approximate computed tomography-attenuation values (Hounsfield Units) for different stone compositions at noncontrast computed tomography.

<table>
<thead>
<tr>
<th>Crystalline composition</th>
<th>Hounsfield units (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>400–600</td>
</tr>
<tr>
<td>Struvite</td>
<td>550–700</td>
</tr>
<tr>
<td>Cystine</td>
<td>650–800</td>
</tr>
<tr>
<td>Capapatite</td>
<td>850–1050</td>
</tr>
<tr>
<td>Calcium oxalate dihydrate (COD)</td>
<td>1100–1200</td>
</tr>
<tr>
<td>Calcium oxalate monohydrate</td>
<td>1200–1400</td>
</tr>
<tr>
<td>Brushite</td>
<td>1500–1800</td>
</tr>
</tbody>
</table>

**Figure 14.7** Noncontrast computed tomography (NCCT) (left) and kidneys, ureter, bladder (KUB) (mid) showing a partial staghorn stone in the upper pole of the right kidney (blue arrow). The size of the stone would according to guidelines be most suitable for percutaneous nephrolithotomy (PCNL). However, due to its inner inhomogeneous structure with void regions (white arrow), shock wave lithotripsy (SWL) was performed. The KUB on the right shows an excellent result after just one SWL session with only minor residual stones left (red arrow).
There are few pains to compare with that of ureteric colic, and patients are anxious to be spared a second episode. Whether to investigate patients after a single episode depends on the presence or absence of risk factors.

Any of the follow is considered high-risk category:

- Young age (<25 years).
- Recurrent kidney stones within a year apart.
- Bilateral or multiple stones.
- First-degree family history of stones.
- History of gout or gastrointestinal disease.
- History of non-calcium oxalate stones.
- Stones associated with diabetes mellitus.
- Single functioning kidney or renal impairment (eGFR <60 ml min⁻¹) with stones.

14.8.1 The First Episode or a Patient with Low-Risk Symptoms

Tests should include serum calcium, phosphate, parathyroid hormone (PTH), as well as serum creatinine and blood for HbA1c or a fasting plasma glucose level.
The stone must be analysed wherever possible. Current technology such as Fourier-transform infrared spectroscopy makes it possible to make an accurate identification of the composition of the stone even from tiny fragments such as those obtained by sieving the urine after extracorporeal SWL.

14.8.2 The Recurrent Stone Former or a Patient with High-Risk Symptoms

Intervention in the form of lifestyle advice and medical therapy can reduce the rate of stone recurrence, and metabolic investigation and medical treatment are important components in the clinical management of renal stone disease. This type of patient is often investigated in a dedicated metabolic stone clinic [32]. Investigations, in addition to those already noted for patients with low-risk symptoms, should include urine for pH measurement and exclusion of cystinuria and an accurate 24-hour collection of urine on which calcium, oxalate, urate, citrate, magnesium, and sodium excretion can be calculated.

If renal tubular acidosis is suspected, investigations for an acidification defect include the ammonium chloride (unpleasant for the patient because of nausea, vomiting, and gastric irritation) test or furosemide-fludrocortisone test [33]. If the urine in either test acidifies (pH <5.3), distal renal tubular acidosis is excluded.

14.9 Medical Management of Stones

Fluid intake is an important intervention in all stone formers. Increasing the urine volume to at least 2 l/day can reduce recurrence rates by 40–50%. If idiopathic hypercalciuria is diagnosed, then a thiazide diuretic is prescribed. A low calcium diet is now no longer recommended and is associated with an increase in stone formation episodes. Thiazide diuretics are cheap and safe and have been shown to reduce stone recurrence rate. Calcium supplementation can be used in enteric hyperoxaluria.

Hypokalaemia should be avoided because this can cause hypocitraturia. Potassium citrate can be used in calcium oxalate stone formers with hypocitraturia. Potassium citrate is also the treatment of choice in patients with uric acid stones and renal tubular acidosis and as an adjunct in patients with cystinuria.

Pyridoxine reduces oxalate excretion in some patients with primary hyperoxaluria type I. In approximately 30% of patients with cystinuria treatment with D-penicillamine or alpha-mercaptopropionylglycine is required. Both of these agents are thiol derivatives, which cleave a single cystine molecule into two cysteine molecules to make a highly soluble disulphide compound. Allopurinol is prescribed for patients who have calcium oxalate stones and hyperuricosuria unresponsive to lifestyle intervention [18].

14.9.1 Management

Management of stones depends on various factors; however, it is largely dependent on site (i.e. kidney, ureter, or bladder), number and size of the stone(s), and whether it is asymptomatic or symptomatic (acute or chronic). In all settings, the patient must be assessed for pain, infection, or obstruction, which will also determine treatment needed for it.

14.9.1.1 Acute Management

In the acute setting, whether renal or ureteric stones, the main focus is to control the pain and manage the obstruction with and without infection (Figure 14.10).

14.9.1.1.1 Pain Control

Acute renal colic is an extremely painful condition requiring immediate and efficient pain management. Pain is often accompanied by nausea, vomiting, sweating, and changes in heart rate and blood pressure. This is caused by the anatomical localization of the autonomic nervous system, which is in close proximity of the visceral nerves, allowing interaction between nerves [34]. The pain sensation in renal colic is due to the obstruction of urinary flow leading to increasing wall tension in the urinary tract [34]. This stimulates the release of prostaglandins, which further increases the wall tension and intraluminal pressure. This can be seen with both renal and ureteric stones.

- Nonsteroidal anti-inflammatory drugs (NSAIDs)

  NSAIDs are first-choice analgesia in patients with acute renal colic [35]. NSAIDs act directly on prostaglandin release and thereby decrease the renal pressure resulting in pain relief. NSAIDs are particularly potent when administered intravenously [36]. Patients with renal colic treated with NSAIDs have significant fewer colic episodes compared to patients not treated with NSAIDs [37].

  Gastrointestinal bleeding and renal failure in patients with pre-existing renal disease are well-known side effects to prolonged use of NSAIDs, but myocardial infarction (MI) is also a recognised potential side effect, and cardiovascular disease is considered a relative contraindication to the use of NSAIDs. Patients with prior MI are at increased risk of death and recurrent MI, even during short-term (<1 week) treatment with most NSAIDs [38]. The use of NSAIDs, therefore, should be limited to an absolute minimum in patients with cardiovascular disease. Healthy individuals with no cardiovascular history also have a dose-dependent increase in cardiovascular events for COX-2-inhibitors and diclofenac [39].
• Opioids
  NSAIDs have been shown to be more effective than opioids in treating renal colic [35]. Patients receiving NSAID are less likely to need further analgesia and achieve greater reductions in pain score. Opioids, particularly pethidine, are associated with a higher rate of vomiting and other adverse effects, compared to NSAIDs. In case of NSAID intolerance or contraindications for the use of NSAID, hydromorphone, pentazocine, or tramadol are second-choice options. Combination therapy with ketorolac and morphine may be even more effective than NSAIDs or opiates alone [40].

• Alpha-blockers
  To reduce recurrent renal colic attacks, daily α-blockers could be given in combination with analgesics [41]. Alpha-blockers are generally well tolerated and reduce the frequency of renal colics in patients with ureteral stones.

14.9.1.1.2 Acute Urinary Drainage
Urinary obstruction and accompanying infection due to calculi is an emergency condition requiring immediate decompression of the collecting system. Stones can not only obstruct the ureteric drainage, but also block intrarenal calyces or a calyceal diverticulum.

Patient stabilisation with conservative measures should not be delayed: fluids; analgesics; antibiotics; basic investigations: routine blood tests, clotting, and cultures; and followed by immediate CT to confirm diagnosis. If obstruction is confirmed, decompression relief is the only way to improve the patient.

Placement of a percutaneous nephrostomy (PCN) tube with or without a retrograde insertion of a JJ-stent are both well-established drainage procedures, but the optimal method of decompression is controversial. Appropriate antibiotic treatment should always be initialized immediately, and the definitive stone treatment should be delayed until infection has been successfully treated.

PCN avoids general anaesthesia and allows placement of a large calibre drainage tube to secure optimal decompression; however, its potential disadvantages are leakage, dislodgement of the tube, and bleeding complications, particularly in patients who are coagulopathic [42].

Insertion of a JJ-stent demands general anaesthesia in most cases, which may have disadvantages in certain patients with severe comorbidity. Very large ureteral calculi may hamper placement of a stent, and furthermore, the presence of a JJ-stent has been shown to reduce quality of life (QoL) in up to 80% of patients because of pain, haematuria, incontinence, sexual dysfunction, and general discomfort [43]. Anticholinergics and α-blockers may relieve the discomfort of JJ-stenting [44].

From a patient’s perspective, there is no difference in clinical efficacy, availability, or preference between PCN and JJ-stenting for drainage of the obstructed infected urinary system [45]. PCN is less costly but requires longer procedural and fluoroscopy times. PCN is also safer in patients with sepsis and with less risk of complications [42].

Complication rate of PCN is about 4%, and all major complications are related to haemorrhage [46]. Complications related to stent insertion are poorly reported; however, they are related to worsening sepsis.
Nonetheless, there is little evidence to suggest the superiority of PCN over retrograde stenting as primary treatment of infected hydronephrosis.

The best modality of decompression is still a matter of debate, depending on several factors including stone size and location, operators’ experience, patient preference and comorbidity, available equipment and manpower, and related costs. However, in an acute setting with a patient who is moribund, most will proceed to PCN to reduce risk of worsening septic and anaesthetic complications due to the infection.

14.10 Surgery for Stones

Treatment modalities can vary and can depend on patient, stone, and experience factors. Figures 14.11 and 14.12 depict the general consensus for stone management [25, 26].
1) Observational and conservative management
2) Shock wave lithotripsy (SWL)
3) Ureteroscopy (URS; rigid/flexible)
4) Percutaneous nephrolithotomy (PCNL)
5) Laparoscopy or open stone surgery

14.10.1 Observational and Conservative Management

When treating stones, the patient needs to be treated as a whole. In other words, patients who are elderly or those with significant comorbidities with asymptomatic stones do not necessarily need treatment for their renal stones. On the other hand, obstructing ureteric stones need treatment in the acute setting, even if there is no pain. Chronically obstructing stones that have atrophied the kidney can be left alone, if there are no symptoms. In summary, treatment of stones needs to take into consideration every aspect of the patient, not just the pathology of the stone.

Taking that into consideration, there is an overall risk of stones causing complications when patients were initially asymptomatic. However, only about 10–40% of patients will require surgical intervention within three years of renal stones, if deemed suitable for conservative management (Table 14.4) [47–49]. Stones in the lower pole are more likely to increase in size, cause symptoms, and lead to an intervention [49].

Conversely, staghorn stones, especially infective struvite stones, need intervention unless the risk of management is high. Staghorn stones will cause damage and atrophy to the kidney and have a high risk of sepsis-related illnesses, renal deterioration, and death [50, 51]. Renal deterioration is seen in nearly a third of patients treated conservatively [51]. With associated death ranging between 27 and 67%, patients will die as a consequence of a staghorn calculi if left untreated [50, 51]. As opposed to 3–7% mortality associated with intervention, reducing to 0% if complete clearance was achieved [50, 51].

In ureteric calculi, the majority will pass spontaneously if left untreated within three to six weeks; those <5 mm have 70–90% chance of passing spontaneously and those >5 mm have a 50–60% chance of passing with no intervention [52, 53]. If a stone did not pass after six to eight weeks, then it will be highly unlikely it will pass, and intervention is most likely required to remove it.

14.10.2 Medical Expulsive Therapy (MET)

The rate of spontaneous passage of symptomatic ureteral calculi depends on the time, location, and size of the stone. Drugs capable of relaxing the ureteral smooth muscle cells might increase the frequency of, and reduce the time to, spontaneous stone passage. MET is typically acting through α-1 receptor blockade or inhibition of the calcium channel pumps. Treatment with α-blockers or calcium-channel-blockers increases the overall chance of spontaneous stone passage by 65% [53–55]. However, MET should be used only when there is no obvious advantage from immediate active stone relief (i.e. persistent renal colic, impaired kidney function or urinary tract infection due to urinary obstruction), and MET should never delay appropriate treatment and acute urinary drainage.

14.10.2.1 Choice of Drug

Alpha-blockers and calcium-antagonists equally augment stone expulsion rates, reduce time to stone expulsion, and lower the analgesia requirements for ureteral stones <10 mm [54, 56]. However, treatment with calcium-antagonists gives the highest frequency of side effects (e.g. hypotension, palpitations and headache) [57]. MET with α-blockers was found to be beneficial, while with calcium-antagonists was found not to be as beneficial [53]. Nonetheless, MET is recommended for ureteric stones <10 mm [52, 53].

Recently, potential new MET pharmacotherapeutics have been investigated. The selective 1A-adrenoeceptor (AR) antagonist silodosin is found to be superior to the 1A/1D-AR antagonist tamsulosin in terms of stone expulsion rate and time to expulsion [58]. Tamsulosin is found to be significantly more effective than the calcium channel blocker, nifedipine, in relieving renal colic and facilitating stone expulsion (e.g. distal ureteral calculi); side effects were more frequently reported in the nifedipine group [59].

In conclusion, MET with α-blockers should be considered a beneficial additive to pain treatment modalities and a potential facilitator of spontaneous stone passage for ureteral stones <10 mm. Moreover, benefits of MET with α-blockers are best seen with stones >5 mm and stones (any size) in the distal ureter, with a nearly 7% risk of side effects from the medication [53]. However, patients elected for MET should have well-controlled pain, no clinical evidence of sepsis, and adequate renal function. Moreover, close follow-up is mandatory to monitor stone position, renal function, and hydronephrosis.

Table 14.4 Risk of stone to require intervention, or cause pain, or increase in size.

<table>
<thead>
<tr>
<th>Stones</th>
<th>&lt;5 mm</th>
<th>5–10 mm</th>
<th>11–15 mm</th>
<th>&gt;15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causing pain (%)</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Increase in size (%)</td>
<td>50</td>
<td>55</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Requiring intervention (%)</td>
<td>20</td>
<td>25</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>
14.10.3 SWL

SWL is a noninvasive procedure reserved for the treatment of renal and ureteral stones (usually no larger than 2 and 1 cm, respectively). It consists of stones fragmentation through shock waves generated by a lithotripter (Figures 14.13–14.15), which allows the stone to break up with minimal collateral damage by using externally applied, focused, high-intensity acoustic pulse.

It may take several sessions for an optimal stone fragmentation according to the characteristics of the patient and the stone because the goal is to obtain small residual fragments susceptible for spontaneous expulsion with the urine. More than 90% of stones in adults might be suitable for SWL treatment [25, 26].

14.10.3.1 Lithotripter

Over the last two decades a lot of lithotripters of second and third generation have been developed. The first machines included a bath tub in which the patient was plunged during the treatment and usually required general anaesthesia because the crossing of shock wave through the flank was painful.

Although the progress in technology has made the new machines user-friendly and the procedure is well tolerated, the efficacy of lithotripsy has not increased.

Lithotripters differ in the tracking system and shockwave–generation process.

Figure 14.13 Lithotripter used at Tenon Hospital, Paris (LITHOSKOP®, Siemens).

Figure 14.14 The principle of the first Dornier extracorporeal shock wave lithotripsy (ESWL): the shockwaves generated by an electrical spark at the first focus of an ellipsoidal mirror were reflected onto the second focus where the stones were targeted using X-ray control.
### 14.10.3.2 Imaging System
Stone location can be obtained with ultrasonography, fluoroscopy, or a combination of both techniques. Indeed, lithotripter of new generation can offer both systems, but their simultaneous use is not possible.

Ultrasonography imaging system can monitor continuously during the procedure, and it is safer than fluoroscopy because it does not expose patient and staff to ionising radiation. However, it requires a highly trained operator and allows identification of stones located in the kidney and in the proximal or distal part of ureter; on the other hand, fluoroscopy is user-friendly and allows identification of stones along the whole upper urinary with a better evaluation of stone fragmentation. However, fluoroscopy is not recommended when stones can be easily followed with ultrasonography or in children, and it is unable to visualise radiolucent calculi. In these cases or in presence of small fragments, the injection of radiographic contrast agent can aid in stone localization.

### 14.10.3.3 Shock Wave Generator
There are various types of shock-wave-generation systems able to produce high-pressure acoustic waves, discharging their energy when it gets in touch with high-acoustic impedance index tissue (i.e. stones, bones, air). They fragment stones through complex phenomena of compression, torsion, squeezing, and cavitation.

#### 14.10.3.3.1 Electrohydraulic Generator
In the electrohydraulic shockwave lithotripter, a high-voltage (15–20 kV) spark discharge is applied to two opposing electrodes placed underwater at one focus (called F1) of an ellipsoid. To be correctly targeted by the spherically expanding shockwave generated on the electrode tip, the stones shall be placed at the other focus (called F2) of the ellipsoid. Generally, 500–2000 shock-wave impacts at 15–20 kV are enough for disrupting 1-cm stones, with a great variability according to the stone composition. To improve the stability and the convergence of the shockwaves, an electro-conductive generator has been developed, using a bulb which maintains the electrode fixed and generates a more stable and convergent shockwave front.

#### 14.10.3.3.2 Electromagnetic Generator
Electromagnetic waves are produced through a rapid displacement of two metal cylindrical plates contained into a water-filled shock tube and separated by a thin insulating sheet. When an electrical discharge crosses one or both the conductors, a strong magnetic field moves the plate against the water and generates a pressure wave. An acoustic lens allows the shockwaves to converge towards a focal point, where the stone is supposed to be placed. Shockwave impacts can go from 3000 to 4000 at 13–17.5 kV per session and cross the patient’s body over a large skin area, causing less pain.

#### 14.10.3.3.3 Piezoelectric Generator
The piezoelectric waves are generated through the excitement a mosaic of small, polarised, polycrystalline, ceramic elements (barium titanate) obtained with the application of a high-voltage pulse. The rapid expansion of the piezoelectric elements, placed on the surface of a hemispherical cup, generates the shockwaves. The focus of the system is placed at the geometric centre of the spherical dish, where the stone should be placed. It is recommended not to exceed 3000 shockwave impacts per session.

#### 14.10.3.3.4 Mechanism of Action
When shockwaves encounter the stones, they generate air bubbles organised in clusters through a cavitation phenomenon on the gas contained within the tissues,
which exercise distortion forces and circumferential pressures (squeezing) on the surface of the stones, causing the disruption of the crystalline structure and the generation of fragments of 2 mm in size. Recent studies have demonstrated that to obtain a good fragmentation, the shockwaves should focus on an area larger than the stone size to take into account the stones movements caused by respiration, and the shockwave frequency should be maintained at 1–1.5 Hz [60, 61].

To improve outcomes of SWL, some introduced the extracorporeal lithotripsy endoscopically controlled by simultaneous flexible ureterorenoscopy (LECURS) [62, 63] which allows visual evaluation of the stone fragmentation. Therefore, an inadequate targeting of the stone can be immediately assessed and the focal zone can be readjusted quickly for maximal efficacy.

14.10.3.3.6 Outcome Predictive Factors
Before addressing patient with urolithiasis to SWL, it is crucial to assess the rate of treatment success, which is strictly correlated not only to the number, size, and location of the stone, but also to its hardness and its chemical composition.

Size and Number of Stones SWL as well as endoluminal surgery can be done for the treatment of all renal stones <20 mm except for the lower pole renal calculi. Moreover, SWL is the recommended treatment option for proximal ureter stone <10 mm. It has been demonstrated that in patients with renal stones >20 mm, SWL is feasible, but the stone-free rate at three months is significantly affected by several factors (i.e. the number of stones, a surface area >400 mm², and the presence of anatomical abnormalities or multiplicity of stones) [68]. Concomitant renal failure is also associated with incomplete results and increases the risk of complications [69]. Although a stone size of 20–30 mm represents the most accepted cut-off value for considering a patient eligible for SWL, it has been proposed a maximum of 7 mm for the treatment of distal ureteral stones [70].

Lower Pole Stones For the lower pole stones, SWL is not recommended if any of unfavourable factors for success are present – namely, shockwave-resistant stones (calcium oxalate monohydrate, brushite, or cystine), steep infundibular-pelvic angle, long lower pole calyx (>10 mm), and narrow infundibulum (<5 mm). However, the impact of the anatomy of the collecting system in patients with lower pole stones has not been unequivocally demonstrated, as shown by a study which found that neither the infundibulum length and width nor the infundibular-pelvic angle significantly affected the stone-free rate in patients with lower calyx stones [71].

Stone Density at CT Scan Stone density at CT scan represents a major predictor of SWL success. Initially the maximum density correlated with acceptable stone fragmentation rate was comprised between 750 and 1000 HU [72]. Subsequently, a cut-off value of 1000 HU has been suggested for admitting patients to SWL [73, 74]. Indeed, stone-free rate reported at three months in patients with 5–20 mm stones treated with SWL were 46% and 17% in patients with stones <1000 and >1000 HU, respectively [75]. Moreover, HU >1000 resulted the only independent predictive factor of the presence of residual fragments after SWL [76].

Physico-Chemical Stone Characteristics In vitro studies showed that the efficacy of SWL depends on stone composition and its crystalline structure. The softest stones are represented by those composed of uric acid, followed by magnesium ammonium phosphates...
Kidney and Ureter Calculi

(struvite structure), calcium oxalate di-hydrate (wheddelite structure), and carbonate apatite phosphate (dahllite structure). On the other hand, stones made of calcium hydrogen phosphate (brushite structure), calcium oxalate mono-hydrate (whewellite structure), and cystine are the most difficult to break.

Therefore, several studies tried to predict the stone composition relying on the stone attenuation coefficient at CT scan measured as HU [77–80]. Recently, the introduction of dual-energy CT scan has allowed defining the composition of the stone with good accuracy [81, 82]. However, the correlation between CT scan characteristics and SWL failure rate is not linear because the cystine stones have lower X-ray attenuation coefficient than calcium oxalate di-hydrate stones, but its resistance to SWL is greater compared to wheddelite. Moreover, despite identical chemical composition, wheddelite and whewellite stones respond very differently to shockwaves. These data suggest that not only the chemical composition but also the crystalline organisation of the stone has a relevant impact on SWL efficacy [83].

**14.10.3.7 SWL Complication**

The introduction of new lithotripters and the optimization of SWL parameters allowed reduction of side effects, which include direct tissue effects on renal parenchyma and nearby organs and obstructive problems due to residual fragments and systemic complications.

**Renal and Nearby Organ Injury**  The passage of shockwave front through the body has plenty of interactions with tissues and can cause different side effects in terms of severity and involved organs.

- Blood test or urinalysis alterations are often found but generally regress spontaneously without any relevant clinical impact (a transitory increase of bilirubin, lactic dehydrogenase, transaminases reveal liver injury; alterations of myoglobin and creatinine phosphokinase reveal muscle contusion; and proteinuria indicate renal parenchymal injury).
- Pain during the procedure can affect outcomes; however, simple analgesics, NSAIDS, and opioids can control pain adequately [84].
- Haematuria is the most common event after SWL but usually ends in few days and does not require any further treatment.
- Perirenal hematomas (subcapsular or intraparenchymal) are detected at ultrasound or CT scan in 15–30% of patients who undergo SWL, but it can rarely become symptomatic and require treatment (i.e. arterial embolisation or surgical evacuation) in less than 1% of the cases [85, 86].
- Microvascular injury associated with shockwave has been also suggested to have a role on long-term effects, manifested as a vasoconstriction which could cause a decrease in glomerular filtration rate (GFR) [87, 88], diabetes mellitus – secondary to pancreatic lesions and hypertension [89, 90]; however, these hypotheses remain controversial [91].

**Residual Fragments**  Residual fragments after SWL are often expelled spontaneously. However, if they remain inside the renal cavities, they increase the risk of new stone formation and persistent urinary tract infection.

It has been demonstrated that size is the most important predictor of stone progression and further intervention [92–94]. Therefore, if a patient remains asymptomatic and does not have associated metabolic alterations, stone fragments <4–5 mm can be followed-up regularly to monitor disease course and avoid complications.

According to stone analysis, patient risk group, and metabolic evaluation, medical therapy should be considered to improve fragment clearance [95, 96]. Tamsulosin has been demonstrated to increase stone-free rate and painful episodes recurrence [97], especially in patients with >10 mm stones treated with SWL [98].

According to the size, the number, the location, and the anatomy of the excretory axis, residual fragments can dislocate and cause an obstruction of the upper urinary tract and painful episodes (renal colic). A column of stone fragments accumulated in the ureter (steinstrasse) has been observed after SWL in 24% of patients with renal stone ≥2 cm and 9.5% of patients with ureteral stone ≥1 cm [99]. The hardness of the stone, which affects the efficacy of SWL and the size of residual fragments, was found to be the strongest predictor of steinstrasse [100]. In such cases, a drainage of renal cavities is often necessary, obtained through either the placement of JJ stent or PCN. Residual fragments need to be subsequently treated with a second SWL treatment or endourological or percutaneous procedure.

**Systemic Complications**

- Bacterial superinfection after SWL is uncommon but can occur especially in case of infection stones (struvite or carbonate apatite phosphate stones) because shockwave release a considerable amount of germs when they impact the stone, or in the presence of residual fragments, which can cause obstruction and acute pyelonephritis. It requires patient hospitalisation and proper measures, consisting of wide spectrum antibiotics and drainage of the excretory axis [101, 102]. To prevent this condition, urine culture is mandatory before any treatment option, and antibiotics must be administered in case of bacterial colonisation or infection stone for three to five days before SWL.
- Acute renal failure occurs only in case of bilateral SWL if residual fragments dislocate into both ureters, causing bilateral obstruction or for the establishment of acute tubulopathy, which usually regress without sequelae.

14.10.3.3.8 Factors Affecting SWL Results

To obtain satisfactory results, the expertise of the operator is essential [103], together with the effectiveness of the lithotripter, which needs to supply a wide focal width, which takes account the spontaneous respiratory movement for a good real time imaging system, and shock-wave parameters (i.e. frequency, potency, pulse number) [104] adjustable according to patient characteristics. In particular low frequency (1 Hz) [105] and progressive increase of voltage provides better outcomes [106].

14.10.3.3.9 Follow-Up

It is mandatory to evaluate the results of stone fragmentation and eventually the presence of residual fragments at KUB or ultrasound within one week after SWL. The patient should be advised to filter the urine to monitor spontaneous expulsion fragments. If residual stone persist, radiological imaging is recommended every three to six months during the first year and then annually.

14.10.3.4 URS (Rigid/Flexible)

Over the last two decades, the use of URS has been continuously rising thanks to the miniaturisation of technology, the development of flexible tools, enhanced optical quality, and the amelioration of stone intracorporeal fragmentation. The technique consists of accessing to upper urinary tract crossing the urethra and the bladder with an endoscopic instrument (ureterorenoscope) which allows localisation, extraction, or fragmentation the stone and removal of residual fragments.

The optimal outcome of URS is the relief of ureteral or renal collecting system obstruction and stone extraction or disruption with complete removal of residual fragments. When these conditions are satisfied, the patient is considered stone free.

URS and stone fragmentation or retrieval can be performed using a rigid or semi-rigid or flexible ureterorenoscope, according to the location of the stone (Figure 14.16).

Usually, when the stone is located along the ureter, especially under iliac vessels, a rigid or semi-rigid ureterorenoscope is preferred because it straightens the ureter and allows it to easily ascend the ureter as well as help maintain to fix the stone in front of the instrument during lithotripsy.

However, the stiffness of a rigid or semi-rigid instrument becomes a disadvantage when the stone is located in the kidney and an exploration of all the renal cavities is required. For this reason, the flexible ureterorenoscope has been developed over the last two decades, allowing an endoscopic retrograde treatment in almost all the cases [107, 108].

14.10.3.4.1 Preoperative Work-Up

- An image depicting the size, number, and location of stone (ultrasound or KUB), but also the anatomy of the upper urinary tract (uro-CT scan, magnetic resonance urography (uro-RM), anterograde or retrograde) is mandatory before surgery to evaluate the feasibility and safety of a retrograde stone manipulation.
- Urine culture has to be negative before URS, and antibiotics prophylaxis should be administered. The presence of obstructive pyonephrosis forces the procedure to be postponed and requires the drainage of the obstructed excretory axis through the placement of JJ stent or PCN [42, 46].

14.10.3.4.2 Anaesthesia

General or loco-regional anaesthesia can be used according to surgeon and anaesthetist preference, although for stones located in the kidney or the proximal part of the ureter, a general anaesthesia with curarisation of the patient may help the progression of the ureterorenoscope along the ureter releasing ureteral smooth muscle fibres [109]. Moreover, with general anaesthesia, a
limited period of apnoea is feasible and prevents kidney movement due to respiratory acts which may make the stone fragmentation more difficult.

### 14.10.3.4.3 Positioning of the Patient

The lithotomy position is used to offer the greatest mobility to the operator. In the past years the leg ipsilateral to the stone was maintained horizontal to enhance the release of psoas muscle and the passage of the ureterorenoscope, although the decrease of the size (7–9 Ch) and the increase of the flexibility of endoscopic tools has actually made this procedure inessential.

### 14.10.3.4.4 Materials Used and Technical Procedure

- **Cystoscope:** 22–25 Ch calibre (1 Charrière = 0.33 mm), with optics 12–30° for exploring the bladder and identifying ureteral orifice.
- **Ureteral dilation system:** olivary dilator, expansion plugs, and probes balloon (maximum 8 atm) are used to dilate the ureter, although this procedure is rarely required due to small diameter of the last generation tools. Moreover, to force the passage of the instruments into the ureter is not recommended because these may cause ureteral lesion and development of ureteral stricture. If ureteral access is not possible, a valid alternative is represented by the insertion of a JJ stent followed by URS after 7–14 days.
- **Guidewire:** 0.035 or 0.038 in. diameter 150 cm-long is used for cannulating ureteral orifice, having access to renal collecting system and allowing passage of stents, catheters, and ureterorenoscopes. One ‘safety’ and one ‘working’ wire should be used.
- **Ureteral catheter:** 5–7 Ch open tip, for retrograde pyelography, for guide-wire positioning or for obtaining urine sample for culture at the beginning of the procedure.
- **Irrigation system:** saline is used to clean the renal cavities during the whole procedure. An adequate flow allows a good view, which is essential for achieving an optimal outcome. The flow depends mainly on the size of the ureterorenoscope and the presence of an instrument into the working channel. Indeed, when a 2.4 Ch instrument is placed into the working channel, the flow provided by a bag of saline placed at 60 cm height decreases from 40 to 10 ml min⁻¹ [110]. For this reason, irrigation pump system has been developed to provide an adequate flow during all the phases of the surgery [111].
- **Video Camera:** it allows operative assistance and active training. Since 2006, the introduction of a miniaturised digital system (CMOS and CCD sensors), incorporated within the distal part of the instrument, has improved the quality of view. It has been recently demonstrated that digital ureterorenoscope significantly reduced operative time compared to fibre optics ureterorenoscope by 20–25% [112]
- **Rigid or semi-rigid ureterorenoscope:** 7.5–12 Ch, the size usually decreases progressively moving towards the tip. The optical system adopted makes the difference between rigid and semi-rigid instrument. Indeed, the use of fibre optic (semi-rigid) rather than lens (rigid) gives a certain flexibility to the ureterorenoscope. It is generally used for the treatment of ureteral stones.
- **Flexible ureterorenoscope:** 7.4–9 Ch, as well as the rigid instrument, the tip is thinner than the proximal part. Moreover, the tip has an active deflection of 180° either ventral or dorsal. Since 2001, the deflection degree has been increased at 270°, generally towards the ventral side, to gain access to small calices with a steep infundibulopelvic angle. As well as the rigid instrument, it has a working channel which allows the placement of operative tools (i.e. laser or basket), but it causes a reduction of the inflow. The quality and the number of fibre optics contained in the instrument for transmitting the light source and especially for acquiring the images determine the quality of view (Figures 14.17 and 14.18).
- **Stone fragmentation tools:** Holmium-YAG laser has become the standard for intracorporeal lithotripsy during ureterorenoscopy, although other methods still exist (i.e. pneumatic or ultrasonic system). Its wavelength (2140 nm) allows a strong absorption of the water and a tissue penetration of only 0.4 mm. It acts on the energy of light beam is delivered in a pulsatile manner, and it is transformed in a thermomechanical action able to fragment any type of stones [113]. Each pulse is defined by a specific energy (Joule) and frequency (Hz). The power, expressed in Watt, is the product of energy multiplied by frequency. It is possible to modulate the laser effect changing the values of these parameters. Usually laser fibres adopted for lithotripsy allow a maximum power of 10 W. The diameter of laser fibres goes to 150–365 um, and they have to be managed carefully because they are very fragile and may break inside the ureterorenoscope, especially when the tip is strongly deflected, causing a damage of the instrument.

Though largely replaced by the advancement in laser technology: some centres still use:

- **Ultrasonic probe:** A toothed cylinder is made to oscillate at ultrasonic frequency (Figure 14.19). It grinds the surface of the stone into fine powder, which is sucked away in a current of irrigant.
14.10 Surgery for Stones

- **Electrohydraulic lithotriptor.** A pair of parallel or concentric electrodes connected to a condenser emits a spark in contact with the stone (Figure 14.20).
- **Jackhammer.** A miniature road-drill is powered by compressed air. Of all the gadgets, this appears to be the most effective and versatile. It is also one of the least costly of these expensive implements (Figure 14.21).
- **Extraction tools.** Graspers or baskets of different size (1.2–3.0 Ch) and shape are placed through the ureterorenoscope working channel and used for residual fragments extraction. The most common used baskets are made of nitinol 1.9 Ch because they guarantee resistance and does not lose flexibility [114]. Tipped baskets are routinely used in the ureter; however, they have a risk of causing ureteric damage. Tipless baskets are used in the renal pelvis and calyces.

**Figure 14.17** Different ureteroscopy available on the market: digital (URF-V, URF-V2 – Olympus – and Flex-XC – Storz) and fibre optic (URF-P5 – Olympus –, Flex-X2 – Storz – and URF-P6 – Olympus).

**Figure 14.18** The ‘semi-flexible’ URF-V2 and URF-P6 (Olympus) versus the flexible URF-V and URF-P5 (Olympus).

- Hollow cylinder oscillating at ultrasonic frequency
  - Fragments of calculus aspirated

**Figure 14.19** Ultrasonic lithotripsy: a toothed cylinder is made to oscillate at ultrasonic frequency to grind the stone to a powder which is aspirated in a current of irrigant.
Kidney and Ureter Calculi

Figure 14.21 The Swiss lithoclast: on the principle of the jackhammer probes of varying flexibility may be passed up the ureter or into the renal pelvis to break up a stone.

- **Imaging system.** Fluoroscopy is essential during any procedure because it allows to follow the progression of endoscopic tools inside the ureter and to evaluate the anatomy of the excretory axis with medium contrast injection before the beginning of the procedure and the presence of stones or residual fragments.

- **Ureteral access sheath.** 9.5–11.5 Ch, 10–12 Ch, 11–13 Ch and 12–14 Ch, it is placed in the ureter with the aid of fluoroscopy over the guidewire till the ureteropelvic junction, but it can reach the renal cavities or be stopped along the ureter according to the urologist’s preference. It protects the ureterorenoscope and facilitates its positioning into the upper urinary tract, especially when the surgeon has to go back into the renal cavities repeatedly to remove residual stone fragments after laser lithotripsy. Finally, it guarantees a constant backflow during all the procedure and avoids elevated pressure in the kidney, reducing the risk of intraparenchymal reflux and thereby decreasing infectious complications. However, it should be placed gently because it can cause ureteral lesion (Figure 14.22) [63].

- **Ureteral drainage.** Ureteral catheter or JJ stent (of different size, shape and materials) (Figure 14.23) may be placed at the end of the endoscopic procedure to guarantee the drainage of renal cavities and avoid postoperative complications, especially after a long procedure, in presence of residual fragments or ureteral lesion, and when URS is used [115]. It should be removed within 1–2 weeks. In case of uncomplicated URS with no residual fragments, stenting should be avoided because it is found to be associated with higher postoperative morbidity [116–118]. As well as for SWL, routine stenting is not recommended before URS, although it can facilitate ureteroscopic management of stones and potentially improve the stone-free rate [119].

**14.10.3.4.5 URS Outcome**

Major technological progress achieved for new generation flexible ureterorenoscopes allows to offer higher treatment success than their predecessors [120]. The stone-free rate following URS for the treatment of ureteral stones varies from 80 to 97% depending on the location and size of the stone [52, 121–123]. URS is the best treatment option for all ureteral stones, except for the proximal ureter stones <10 mm, where SWL shows higher stone-free rate (89 vs. 84%, respectively).
Flexible URS is equally recommended along with SWL for the treatment of all renal stones <20 mm because stone-free rate are comparable [124, 125] and can achieve up to 90% [126]. However, for 10–20 mm lower pole stone ureterorenoscopy becomes the first treatment option [127, 128], especially when there are unfavourable factors for SWL success. It is recommended to relocate the lower pole stone into the superior calyx or into the renal pelvis for laser lithotripsy [129], to make the stone fragmentation easier to perform, and to reduce the risk that the laser fibre can fail under a tight bending and damage the ureterorenoscope.

Moreover, flexible URS for the treatment of renal stones >2 cm is feasible and has a high stone-free rates and low complication rates [130].

14.10.3.4.6 URS Complication

The overall complication rate after URS is up to 10% [52, 131]. The miniaturisation of endoscopic tools and improvement of technology has decreased the incidence of complications related to ureterorenoscopy. Because the major cause of complications is the trauma caused by the surgery, they occur more often after rigid or semi-rigid URS than after flexible URS.

Early Complications They may happen during the procedure or immediately after.

They include:

- Ureteral false passage and mucosal injury: no need for specific manoeuvres, the ureterorenoscopy can be continued and a JJ stent should be placed afterwards.
- Ureteral perforation: suspected in presence of trauma or bleeding and diagnosed by retrograde pyelography, which shows medium contrast extravasation; it requires the interruption of the procedure to avoid the development of a urinoma and the placement of a JJ stent for three to four weeks to promote the healing process.
- Ureteral avulsion: it represents the most feared complication. It occurs in 0.2% of the cases usually at the pelviureteric junction or at the pre-vesical tract, which are the most fragile point of the ureter. It requires a reconstructive surgical intervention (i.e. ureteral
reimplantation or ureter-ileum interposition according to the location of the avulsion). The surgeons must prevent it by avoiding removal of large stone fragments from the renal cavities and stopping the extraction of the stone fragments when an excessive resistance is perceived.

- Renal colic and fever: back pain and fever usually regress spontaneously within 24–48 hours or with the use of analgesic and antibiotics, respectively. If the urine was sterile and an antibiotic prophylaxis was given before the surgery, serious infectious complications are uncommon.

Late Complications The incidence of late complications is 0.5%. They include:

- Ureteral stricture: caused by ureteral trauma, it can be avoided placing a JJ stent after the surgery. A CT scan with delayed images, during follow-up is recommended not only to evaluate the presence of residual fragments but also to exclude this condition. It can require ureteral balloon dilation, endoscopic ureterotomy or laparoscopic or open surgery.
- Vesicoureteral reflux: when occurs, it usually involves the distal part of the ureter only and it can be managed conservatively.

14.10.3.5 Percutaneous Nephrolithotomy

The first description of PCN tube to obtain kidney drainage was described by Goodwin and associates in 1955. Then in 1976, Fernstrom and Johannson were the first to report the placement of percutaneous access with the planning of kidney stone removal. Today, the rates of percutaneous nephrolithotomy (PCNL) performed for kidney stone treatment is between 3 and 5%, and this procedure is mainly reserved for large stone burden.

Having inserted a nephrostomy tube over a guidewire, the track is dilated until a 28 Ch sheath can be passed (Figure 14.24). This is large enough to admit telescopes, forceps, and lithotriptors.

14.10.3.5.1 Indications

With the technology emergence of flexible ureteroscopy (FURS) in the last decades, which can be effective even for stone larger than 2 cm and staghorn calculi, PCNL is likely to decrease and remain principally in the specialised centres.

There are still indications to perform a PCNL including the following: stone larger than 2 cm; inferior polar stone larger than 1.5 cm; failed FURS for the treatment of calyceal diverticula calculi; partial or complete staghorn calculi; and some cases of ureteral calculi [25, 26].

14.10.3.5.2 Contraindications

During the initial evaluation, the urologist should be prepared to identify the PCNL contraindications, such as uncorrected coagulopathy, active and untreated urinary tract infection or bacteriuria, nontreated high blood pressure, intrarenal vascular malformations, and a complex staghorn which requires more than two percutaneous tracts (relative contraindication). Severe obesity and severe skeletal malformations are not contraindications; nevertheless the technique and equipment should be adapted [25, 26, 132, 133].

14.10.3.5.3 PCNL Surgery

Patient Anaesthesia and Antimicrobials PCNL is usually performed under general anaesthesia. Perioperative antimicrobial prophylaxis for all cases of PCNL is recommended. Local protocol should dictate the type of antibiotic. Duration of treatment should be less than 24 hours, and a short course of antimicrobials at the time of tube removal can also be considered. When there is a preoperative positive culture, appropriately directed antimicrobials should be administered for 7–10 days, particularly, when struvite infected stones are suspected [25, 26].

Patient Positioning The first approach to PCNL initially described in 1955 was the prone position. When prone position is performed, the initial step
is retrograde placement of a ureteral catheter with fluoroscopic guidance. A ureteral occlusion balloon catheter can be used to prevent stone migration into the ureter during the surgery. It allows more cavities distention during the pyelography before the puncture, but there is also more chance of calyceal rupture and contrast extravasation with deterioration of vision for getting the access. Furthermore, there is a risk of ureteral rupture if the balloon is not carefully inflated in the renal pelvis. Depending on the surgeon’s preference, the catheter can be placed directly in the prone position with a flexible cystoscope or in lithotomy position with subsequent prone repositioning.

Completely supine position PCNL has also been reported in 1987, as an alternative to the prone position. Many have added variations of this position, including supine with the ipsilateral side elevated and supine with ipsilateral side elevated combined to asymmetric lithotomy position. The advantage of combined approach is the opportunity to operate simultaneously for URS and percutaneous surgery (Figure 14.25). This could be especially helpful in complex renal calculi or large proximal ureteral stones. It could prevent the need to do a second puncture with all the associated risk and reduce the operative time. Furthermore, this approach is recommended for patients with spinal deformities, pulmonary pathologies, ASA 3, and who are morbidly obese.

A less commonly applied method is the lateral decubitus position, which could be valuable in patients who are obese or have spinal deformities. Moreover, providing access to the anterior and posterior calyces.

**Renal Calculi Tracking** The principal two methods used for stone localization into the collecting system are ultrasound and fluoroscopy. The use of CT scan or MRI is uncommon and only reserved for some complex cases.

Ultrasound guidance (3.5 or 5-MHz transducer) has the advantages of having no radiation, evaluation of the renal parenchyma aspect and thickness, and greater assurance that there is no essential organ on the future percutaneous access. Retrograde indigo-carmine instillation can be used to confirm the accurate site of the needle into the collecting system.

Fluoroscopic guidance is usually used for gaining access to the collecting system. Retrograde contrast filling is used to provide upper tract urinary system anatomy and stones location within the pelvis and calyces. Air into the cavities could also assist in locating the posterior calyces while the patient is in a prone position.

Furthermore, combining these techniques is also an excellent and safety approach.

**Access into the Collecting System** Once the urologist has chosen the appropriate calyx, the needle (18 G) is advanced under guidance into the urinary cavities. During the puncture, the surgeon’s forearm should be stabilised on the patient’s back to obtain a better movement control and security. The needle should be inserted back to the posterior axillary line and the shorter cortico-papillary distance feasible to reduce the cortical haemorrhage risk (Figure 14.26). Afterwards, a 0.038-in. guidewire is placed within the pelvis and ordinarily down the ureter. Subsequently, an extra-stiff guidewire may be inserted, and the dilation of the tract is made.

There are some techniques to provide a good tract dilation. Alken’s rigid dilators are a series of enlarging coaxial metal steel rods passing over a guide rod and are remarkably effective principally, although there is perirenal scarring. Nevertheless, their rigidity can also cause
incommensurable damage. Amplatz semi-rigid plastic dilators are supposed to be less traumatic and are passed one after the other, not coaxially like Alken’s dilators. Another dilator is the balloon catheter dilator. This is currently the most used dilator. These benefits are being able to simplify the introduction in urinary cavities with only one entry and be more effective in case of a hyper-mobile kidney. Although, it could be less efficient than rigid or plastic dilators while there is perirenal fibrosis. Once the dilation is created, the working sheath is positioned with fluoroscopic guidance (Figure 14.15).

**Intracorporeal Lithotripsy**  Once the nephroscope is introduced into the cavities, there are different ways to extract the stones. The stones smaller than 1 cm are usually removed immediately in one piece with a basket or grasper. Calculi larger than 1 cm require fragmentation first. Many types of lithotripters are used during a PCNL. The ballistic lithotripsy uses energy generated by the movement of a projectile that transfers energy to an object. Ultrasonic lithotripsy applies electrical energy to excite a piezoceramic plate. The plate resonates at a particular frequency and generates ultrasonic waves with transmitted energy. Including with this lithotripter is a suction mechanism that can remove continuously small particles during the fragmentation. The combined ballistic and ultrasonic devices are significantly better for the stone clearance. It may be activated separately or simultaneously, and the surgeon has the benefits of each instrument. After a maximal stone removal with the rigid nephroscope, exploring the renal cavities and the proximal ureter with a flexible nephroscope to ensure there is no residual stone fragment is advised. Otherwise, these fragments can be repositioned or fragmented with Holmium: YAG laser.

In large stones, combination PCNL and FURS can be done (Figures 14.25 and 14.27).

**Nephrostomy Drainage after the Procedure**  At the end of the surgery, a nephrostomy tube is inserted (12–24fr), and the adequate placement is confirmed with fluoroscopy and pyelography. Day one postoperatively, a CT scan or abdominal X-ray is performed to rule out any residual significant fragments. When there are significant fragments, a second look is recommended 48–72 hours after the PCNL. However, where imagery confirms there are no stones and urine are clear, the nephrostomy may be removed 24–72 hours later with a clamp test just before. The possibly externalised tubes are Malecot catheter, Malecot re-entry, the balloon catheter (Foley and Council), Cope catheter, and circle nephrostomy tube.

Some authors report tubeless percutaneous procedure with a ureteral stent. It seems to have an advantage of reducing narcotic use and decrease the length of hospitalisation, and the complications appear similar. The nephrostomy, on the other hand, provides more security and rapid access if the patient requires a second look. The selected patients for tubeless have to be operated with care in a high volume centre. Totally tubeless has also been reported, but there appears to be significant concern with the theoretical risk of haemorrhage from the tract following PCNL.

**Hospitalisation and Recovery**  Hospitalisation may vary from one to five days. Patient’s occupation should allow two weeks following the surgery unless this is a hard
physical work. Sport activities could be reintroduced after four weeks.

Complications The overall complication rate for a PCNL varies from 10 to 25%. The urologist aspiring to practice this procedure has to be aware of the potential complications and be conscious of how controlled the situation to avoid significant morbidity.

Patient Positioning A meticulous verification of every pressure point has to be accomplished by the anaesthesiologist and urologist because nerve compression, stretch injury, ocular or facial pressure wound, and rhabdomyolysis have been described in the prone position [134, 135].

Haemorrhage Acute Acute haemorrhage is the most prevalent complication. Transfusion rate varies from 6 to 24% and depend on several considerations. Intraoperative haemorrhage necessitates ending of the procedure and placement of a nephrostomy tube to allow the formation of a clot into the renal cavities. A balloon catheter could reinforce the local pressure and permit more haemostasis with a small traction. A venous bleeding could be controlled most of the time with this method. If the bleeding originates from the tract of the working sheath after its removal and is refractory to the techniques described previously, a Kaye nephrostomy tamponade balloon can be used. If the haemorrhage cannot be controlled, a supra-selective angio-embolisation must be required. Nephrectomy is rarely needed [132, 136].

Delayed Less than 1% of PCNL are complicated with a delayed haemorrhage and are usually secondary to a pseudo-aneurysm or arteriovenous fistulas. Delayed haemorrhage occurs mostly between two and seven days after the surgery. The diagnosis is made with angiography, and the treatment is selective angio-embolisation with high success rate (>90%) [137].

Irrigation Absorption Major fluid absorption is rare (<1%). A procedure more than two hours, venous laceration, and more than 301 of irrigation are the risk factors. While complex and prolonged case is planned, the surgeon should recommend the in and out irrigation monitoring [132].

Renal Urinary Collecting System Laceration Renal pelvic perforations are usually identified intraoperatively (3–6%). It is recommended to abort the surgery and insert a ureteral stent catheter and a nephrostomy tube. A nephrostogram could be done after two to seven days, depending on the severity, and maintaining the ureteral stent for some weeks is more suitable. Antimicrobial prophylaxis depends on the surgeon’s preference, the risk of urinary extravasation, or urinoma formation [138].

Visceral Injury Pleural Pleural injuries are usually associated with punctures above the 11th and 12th ribs and remain rare complications (<0.5%). Hydrothorax or pneumothorax can be treated most of the time with a small-calibre tube depending on the clinical indication. Rarely a large-bore thoracostomy is needed. Urinotherax (nephropleural fistula) is a persistent communication between renal cavities and thoracic cavity. Drainage of each cavity is recommended with antimicrobial prophylaxis [139].

Colon Colon injury occurs less than 1% of PCNL in the prone position. Left lower pole punctures are the principal zone associated with colon injury. Intraoperative detection is easier to manage; the nephrostomy tube should be pulled into the colon, and a retrograde ureteral stent catheter or a new nephrostomy should be inserted. In addition, broad-spectrum antibiotics and no oral intake for a couple of days are recommended. The principle of care is a separate drainage of the urinary system and digestive system. Open surgery is rarely required unless intraperitoneal injury with sepsis is diagnosed. Colonic injury can be avoided when the puncture is performed with ultrasound guidance [140].

Others Duodenal, jejunal, gallbladder, splenic, and hepatic injuries have all been reported in few cases, and the clinical presentation and seriousness of the injury would decide the future management.

Postoperative Fever and Sepsis Fever following PCNL can develop in 15–20% of patients. However, sepsis occurred in less than 1% of patients. All infected stones should receive preoperative antibiotic treatment for seven days. This patient should also have an intraoperative pelvis urine culture and a stone culture because frequently the bacteria identified in the preoperative urinary culture is different from the pelvis and stone cultures. Absolutely no patient should be operated with a preoperative positive culture [141, 142].

Parenchyma Injury Significance All the studies to evaluate parenchymal injuries after PCNL have demonstrated that the loss of renal parenchyma is less than 1%. Moreover, no significant difference for kidney injuries has been associated between the miniperc (11 Fr) or standard PCNL (30 Fr) [143, 144].

MINIPERC The mini-PCNL or miniperc was initially developed for the treatment of children with complex stones, and there are great efficiency and less morbidity. The advantage is the working sheath of 13 Fr–20 Fr.
Indications expansion have been attempted for adult community with mainly stones less than 2 cm, but with all the advancement in the retrograde intrarenal surgery with flexible URS, the field for miniperc is still limited [145–148].

14.10.3.6 Laparoscopy, Robotic, and Open Stone Surgery
Historically, open surgery was the treatment of choice for symptomatic upper urinary tract calculi. However, the technology advancement in minimally invasive endourology procedures (i.e. PCNL and FURS) have considerably reduced the place for open and laparoscopic stone surgery, which is now used in less than 1% of cases.

The FURS, PCNL, or combined surgery have advantages in comparison to laparoscopic or open surgery with lower morbidity and similar overall stone-free rate. Invasive procedures continue to be an option for some specific conditions, including treatment failure with endoscopic procedures, intrarenal anatomical abnormalities (i.e. infundibular stenosis, calyceal diverticula), pyeloplasty with pyelolithotomy, and stones in a non-functioning polar or nonfunctioning kidney.

Currently, for rare cases requiring more invasive surgery, laparoscopic, or robotic approaches should be recommended first, and it may be advisable to refer the patients at an experienced center. Chosen methods may change depending on the location and size of the stone.

14.10.3.6.1 Kidney Calculi
The possible operative procedures for complex kidney calculi include the following: anatomic or radial nephrolithotomy, simple or extended pyelolithotomy with or without concomitant pyeloplasty, and partial or simple nephrectomy.

The nephrolithotomy is principally reserved for cases that have failed with endoscopic procedures. The most common is a complex diverticulum or a long narrow infundibulum. Throughout the laparoscopic intervention, the stone is localised, and a nephrotomy is performed to completed the stone extraction. Intraoperative ultrasound has been described to find stone location and identified the avascular area in the renal parenchyma. A careful cavities closure and haemostasis is mandatory. Upper tract urinary drainage is dependent on the surgeon’s preference, and a perinephric drain should be placed for a few days.

Pyelolithotomy is used most of the time through concomitant laparoscopic pyeloplasty surgery. Concurrently, a flexible cystoscope is entered in the pyelocalyceal cavities, and a basket removal of the stone is completed. Some urologists prefer first to do a minor pyelotomy sufficient to enter the flexible cystoscope and to get irri-gation in the cavities. Following the stone removal, they complete the dismembered pyeloplasty.

Partial, polar, or simple nephrectomy are reserved for complex cases with partial and total nonfunctioning kidney or recurrent infection or abscess, as in xanthogranulomatous pyelonephritis. These patients need a definitive treatment for their pathology [25, 26, 132].

14.10.3.6.2 Ureteral Calculi
Open and laparoscopic surgery for ureteral stone remain a seldom procedure. Invasive surgeries are reserved in situations such as failed previous endourology procedures or SWL, complex stone burden, and extended stenosis that need to be corrected through the same procedure. Laparoscopic ureterolithotomy has been used successfully with lower than 2% conversion rate to open surgery.

A longitudinal ureterotomy is performed at the ureteral stone level, and the stone is removed. Then, a ureteral stent is inserted in the course of laparoscopic surgery while achievable. The authors advise to insert a ureteral stent because there is frequently inflammation at the level of the stone, and the mucosa is crumbly during the closure. A ureteral stent may contribute to decrease the formation of ureteral stenosis. Furthermore, to monitor any urinary leak, a retroperitoneal drainage deprived of suction could be left in place in postoperative period, depending on the surgeon’s preference. A follow-up imaging with ultrasound or technetium-99m mercaptoaetlytriglycine (MAG3) diuretic scan is preferable to exclude a ureteral stenosis formation during follow-up [149, 150].

In summary, with all technology and equipment advancement, there are only seldom indications regarding laparoscopy and open surgery as first-line treatment for kidney and ureteral calculi. Surgeons should never hesitate to refer patients in a specialised endourology center if FURS and PCNL are not feasible, which are now the first-line modalities before further invasive procedures.

14.10.3.6.3 Chemolytic Dissolution for Stones
No effective and safe dissolution therapies (chemolysis) exist for calcium-containing stones [151, 152]. Stones that can be dissolved include uric acid, cysteine, and struvite calculi. Chemolysis may be achieved by agents given orally or intravenously or by instillation of chemolysic into the collecting system. Dissolution of stones may be divided into primary and secondary chemolysis, referring to whether chemolytic agents are used as initial therapy to dissolve stones, or secondarily in patients with residual fragments after some other primary therapy.

Oral Chemolysis Although oral chemolysis anecdotally have been described for cystine [153] and struvite calculi [154], uric acid stones are the only stones that effectively
can be dissolved by oral chemolysis. Treatment consists of systemic alkalinisation in the form of sodium bicarbonate (650–1000 mg 3–4 times a day) or potassium citrate (15–30 mEq 3–4 times a day) [155, 156]. Complete dissolution rates of 62.5% have been achieved; however, such a high success rate demands prolonged therapy (three to six months), and thus is only an acceptable option in nonobstructing calculi [157, 158]. Success is related to stone size as well as patient compliance. An important part of compliance is patient self-monitoring to verify that the urinary pH increases [159]. Goals of therapy is to achieve a urine pH between 6.0 and 7.0. Below pH of 6.0 will form uric acid stones, while pH above 7.0 will form calcium phosphate stones. Intravenous alkalinisation is more effective than oral, but it requires hospitalisation. Larger stones demands longer therapy, and in these, cases SWL may increase treatment efficacy by increasing stone surface area [160].

**Instillation of Chemolytic Agents**  Instillation of chemolytic agents may be done a retrograde, percutaneous antegrade, or in a combined approach. Antibiotics (i.e. prophylactic or culture-specific) should be maintained throughout the instillation period. Intrapelvic pressure should be monitored (<25–30 mm H2O) to avoid pyelovenous and pyelolymphatic backflow that may result in septic or agent-specific toxic complications and alterations in serum chemistries [151, 161]. Preferably, inflow and outflow is achieved through separate catheters or channels. The safest way of controlling inflow and outflow is through two nephrostomy tubes. Perirenal extravasation should be excluded by contrast studies. The major disadvantage of the retrograde approach is outflow limitation, resulting in high intrarenal pressures with potential harmful effects. Techniques to overcome this have been described [162–164]. However, in case of large stone burden that demands prolonged chemolysis, the antegrade approach seems most ideal and also most comfortable for the patient.

Dissolution of uric acid stones can be achieved by irrigation of alkaline solutions (Table 14.5) [25]. Usually prolonged irrigation is not needed.

<table>
<thead>
<tr>
<th>Stone composition</th>
<th>Irrigation solution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>Tham – 0.3 mol l−1 – pH 8.5</td>
<td>Unless a nephrostomy is present, oral chemolysis should be tried first.</td>
</tr>
<tr>
<td></td>
<td>Tham – 0.6 mol l−1 – pH 9.0</td>
<td></td>
</tr>
<tr>
<td>Struvite</td>
<td>Hemiacidrin 10% – pH 3.5–4</td>
<td>Usually used as secondary chemolysis.</td>
</tr>
<tr>
<td>Carbonate apatite</td>
<td>Suby’s G</td>
<td>Hypermagnesaemia may occur.</td>
</tr>
<tr>
<td>Cystine</td>
<td>Tham – 0.3 mol l−1 – pH 8.5</td>
<td>Prolonged irrigation is needed.</td>
</tr>
<tr>
<td></td>
<td>Tham – 0.6 mol l−1 – pH 9.0</td>
<td>Usually used as secondary chemolysis.</td>
</tr>
<tr>
<td></td>
<td>N-acetylcysteine (200 mg l−1)</td>
<td>Tham and N-acetylcysteine can be used in combination.</td>
</tr>
</tbody>
</table>

**Chemolytic dissolution of cystine stones** may be done with highly alkaline solutions (THAM or THAM-E), the chelating solution N-acetylcysteine, or preferably, the two types of solutions in combination creating a synergistic effect [159, 165] (Table 14.5).

The solubility of struvite is markedly increased at a pH < 5.5, which may be achieved by irrigation of Suby’s solution or Hemiacidrin (Renacidin) (Table 14.5). Fatal infectious complications have been reported using Renacidin [166, 167], and absorption of magnesium may result in hypermagnesaemia with potential cardiovascular hazards. The safety aspects of instillation therapy consisting of antibiotics and monitoring of pressure and serum chemistries including serum magnesium, therefore, should be strictly observed.

Instillation therapy for cystine and struvite stones are normally performed as secondary chemolysis for residual fragments after SWL, PCNL, or URS because chemolysis monotherapy of most of these stones will require unacceptable prolonged irrigation [151, 162, 165, 168].

**14.10.3.6.4 Stones in the Bladder**

The introduction of the lithotrite 150 years ago may be said to have started modern instrumental urology. The best instruments are still the oldest ones, not forged, but cut from a solid block of steel. The skill of using this historic instrument has now been bypassed by the modern lithotritors which can be passed down a resectoscope sheath to fragment a calculus in the bladder and the fragments evacuated with an Ellik evacuator. The Mauermayer punch is a most useful device for breaking up residual small fragments.

In boys and in patients with very large stones (Figure 14.28a–c), it is safer to remove them through a formal open cystotomy because the passage of urethral instruments is apt to lead to stricture.

**Calyceal Diverticular Stones** A calyceal diverticulum (CD) is presumed to be congenital. The have been defined as a nonsecretory transitional urothelium-lined cavity within the renal parenchyma. Usually communicating with the collecting system (i.e. calyx and rarely renal pelvis) through...
a narrow diverticular isthmus or 'neck' (Figure 14.29). The theory is that small divisions of the ureteral bud fail to degenerate, resulting in a CD. Alternatively, some propose that CD are an acquired condition, secondary to sequelae of vesicoureteric reflux, rupture of a simple cyst, or fibrosing infundibular stenosis.

A rare disease with an unknown incidence; however, it is reported in about 3% of IVP investigations, occurring bilaterally in nearly 3% of patients (REF). Patients usually present with either haematuria, pain, or sepsis and form stones in up to 50% of cases.

Stones are thought to be due to either urinary stasis, whereby urine fills the cavity, and with a narrow neck, stagnates, precipitating calculi crystals. However, an underlying metabolic abnormality for stone formation is seen in over 50%.

There has been no consensus on either classifying CD or on how best to manage them. Various treatment modalities have been proposed from conservative treatment, SWL, PCNL, URS, and partial or total nephrectomy. However, management tends to be an upward trend from the less invasive to the more invasive.

**Stone Management in Urinary Diversions**

Patients with urinary diversions are at increased risk of upper urinary tract stones as well as calculi within the diversion segment [169]. Both medical and surgical management of stone disease related to urinary diversions are often challenging.

**Risk Factors for Stone Formation**

Frequency of stone formation in different types of urinary diversions ranges from 2 to 27% depending on the type of diversion, with...
highest frequency reported in the Kock pouch [142]. The stone disease may be classified as either infectious or metabolic.

**Infectious Causes** Rate of colonisation with bacteria ranges from 14 to 96% in different series depending on type of conduit or reservoir [170, 171]. Stone formation in the diversion segment is usually related to colonisation with urease-producing organisms (e.g. *Proteus* and *Providencia* spp.), resulting in struvite and carbonate apatite crystallisation. Presence of foreign bodies (e.g. staples and nonabsorbable sutures) may act as a nidus for stone formation, which usually recurs unless the nidus is removed at time of stone removal [172]. Reflux of urine and mucus may colonise the upper tract, resulting in formation of infection stones in the upper urinary tract as well. Stomal stenosis and stenosis of the uretero-intestinal anastomosis result in stasis of urine, which predisposes to infection and subsequent stone formation.

**Metabolic Causes** Metabolic risk factors for stone formation may be more or less prominent depending on which segment of the intestine that is used for the conduit or reservoir. Usage of long segments of ileum may lead to intestinal fat-malabsorption and subsequently enteric hyperoxaluria, increasing risk of calcium oxalate (CaOx) kidney stone formation [173]. Patients with continent reservoirs are at increased risk of chronic diarrhoea depending on the length of ileum resected [169]. Chronic diarrhoea leads to gastrointestinal losses of bicarbonate, resulting in acid urine with increased risk of uric acid stone formation. Furthermore, exclusion of ileal and colonic bowel segments may result in hyperchloremic metabolic acidosis: When colonic or ileal segments are exposed to urine, ionised ammonium and chloride (Cl\(^-\)) are reabsorbed by the mucosa [174–176]. Mediated by a sodium–hydrogen antiport, ammonium absorption occurs in exchange of sodium. The exchange of ammonium for H\(^+\) in turn is coupled with the exchange of bicarbonate for Cl\(^-\). Furthermore; ionised ammonium may be also absorbed into the blood through potassium channels, resulting in potential bicarbonate and potassium losses [176]. The resulting systemic acid load leads to hypocitraturia and hypercalciuria, which is known to increase risk of calcium stone formation [177]. Metabolic acidosis has been reported in up to 10% of ileal conduit diversions [178], whereas in continent urinary diversions it may be as high as 50%, due to longer periods of contact between urine and intestinal mucosa [179].

**Medical Management** Increased fluid intake, correction of metabolic abnormalities, and prophylaxis against recurrent infections are crucial in avoiding recurrent stone formation. Prevention of uric acid and calcium stone formation as a result of acidosis may be achieved by alkali supplementation (e.g. potassium citrate). CaOx stone formation as a result of enteric hyperoxaluria may be treated by measures to control fat-malabsorption and by increasing calcium intake at meals, thereby reducing intestinal hyperabsorption of oxalate.

**Surgical Management** In principle, stones in patients with urinary diversions can be managed similarly to other stone patients.

**Renal and Ureteric Stones** SWL may be used for smaller renal and ureteric stones in cases without strictures distally to the stone. Retrograde ureteric access is often challenging due to difficulty in locating the neo-ureteric orifices. In general, ureteric access is more easily achieved in ileal conduits than in reservoirs owing to the lack of an afferent limb [169].

In case of anastomosis-stricture, an antegrade or a combined antegrade-retrograde approach is usually the best choice. Percutaneous access is best obtained ultrasonographically because retrograde opacification...
of the collecting system with contrast medium is often impossible. For access to ureteric stones, flexible scopes are usually necessary, and the use of a ureteric access sheath may ease the procedure dramatically.

**Stones in Neobladders and Reservoirs** Stones in orthotopic diversions may be approached transurethrally. For small stones in reservoirs a trans-stomal approach using small-calibre rigid or flexible endoscopes may be an option. For larger stones, a trans-stomal access is usually not advisable because these will require significant manipulation and usage of larger scopes, which may disturb the continence mechanism. In such cases, a percutaneous access guided by ultrasound or cystoscopic guidance usually is preferred [169].

**Stone-Free Rate and Residual Stones** The main goal of stone treatment is to render the patient stone free, and stone-free rate (SFR) is the key parameter for success outcome. Results expressed as SFR in the literature varies a great deal, partly due to variability in follow-up imaging and in definitions.

The term ‘stone free’ ideally is defined as 100% free of any stone material, but there is no consensus or standardised definition. In published series the definition of stone free varies or is often not accounted for [180], and SFR often include cases with minor residual fragments (RF).

The term ‘clinically insignificant residual fragments’ (CIRF) was introduced in 1986 with SWL and is most often defined as small asymptomatic nonobstructive, noninfectious residual fragments. The defined maximum size of fragments however varies from ≤3 to ≤5 mm [181–183].

CIRF may also be present after PCNL and retrograde intra renal lithotripsy.

Methods to increase fragment clearance immediately following stone treatment include medical expulsive therapy (MET) and inversion therapy [25, 26].

Imaging in the follow-up after stone treatment may include ultrasound plain X-ray (KUB), tomography or NCCT. The detection of RF depends on the imaging modality applied. The sensitivity of NCCT is close to 100% [184]. The sensitivity of plain X-ray, tomography, and ultrasound is 62.9, 74.3, and 48.6%, respectively, in radio-opaque stones. For weak radio-opaque or radiolucent stones the sensitivity was 11.1, 22.1, and 22.2%, respectively [184]. Comparing ultrasound with NCCT in detecting renal calculi, a sensitivity of 26% was found for stones 3–7 mm, and 71% for stones >7 mm [185].

The measured size of residuals is also dependent on imaging modality. CT accurately estimates transverse size but overestimates the craniocaudal size; KUB overestimates size; tomography underestimates size; and ultrasound tends to overestimate size [185–189].

Several studies have investigated the fate of RF, and it has become evident that the term CIRF is a misnomer because RF often become significant with time. RF may dislodge resulting in pain or ureteral obstruction or may serve as a nidus for new stone formation or persistent infection [93, 94, 190, 191]. Ranging from 20 to 60% of patients with RF required treatment within five-years [92–94, 190, 191]. The risk is much higher in infection stones [192].

Adequate preventive measures depending on stone analysis and metabolic evaluation should be made to decrease the risk of regrowth [95, 96, 193, 194]. Long-term follow-up of patients with RF must be personalised depending on individual risk factors. It is recommended that patients with RF should be followed up regularly [25, 26].

**Pregnancy** The presence of urolithiasis during pregnancy is rare with an incidence ranging from 1 in 1500 to 1 in 2000 [195]. Compared to the lifetime risk of developing urolithiasis in the non-pregnant population (1–10%), the risks during pregnancy are much lower, ranging between 0.03 and 0.53% [195]. The diagnosis of urolithiasis in pregnancy is usually made after the first trimester when the disease becomes symptomatic.

Urolithiasis is the second most common cause of abdominal pain in the pregnant patient after UTIs, but it is the most common cause of nonobstetric reason for hospital admission [195].

During pregnancy, the body undergoes a series of anatomical and physiological changes that may be associated with an increased likelihood of stone formation. The ureters dilate as early as the first trimester and remain dilated throughout pregnancy. This allows the migration of any renal stones down into the ureters, leading to obstruction or pain. As well as migration, the dilated ureters can lead to urinary stasis, thereby facilitating the aggregation of urinary crystals.

There is also an increase in GFR during pregnancy by 30–50%. This increased GFR results in more sodium, calcium, and uric acid filtered by the kidneys. This, with the anatomical changes further increases the likelihood or urinary crystal formation. However, this increase in GFR does also increase the urinary excretion of citrate, glycoproteins, and magnesium, which have been documented to inhibit stone formation both in vivo and in vitro.

The physiological hydronephrosis caused by the enlarged uterus during pregnancy causes diagnosis of intramural obstruction of the ureter difficult. With distal ureteric stones, where the obstruction may be below the pelvic brim and knowing that pregnancy-related hydronephrosis does not tend to go this low, the diagnosis is easier than with proximal or mi-ureteric stones.
The presence of stones that reside in the urinary tract can lead to renal colic, infection, and obstruction, which pose significant risks to both mother and child.

Diagnostic modalities remain a dilemma due to the fear of exposing the foetus to ionising radiation that can cause foetal malformations, gene damage-causing mutations, or even cancer in later life. The foetus is most at risk during the early development of organs (organogenesis) during the first trimester. However, radiation exposure <50 mGy is not associated with an increased risk to the foetus and considered negligible [196, 197]. Nonetheless, most urologists and radiologists will obtain an ultrasound. In rare instances, plain film, NCCT, or magnetic resonance urogram can help with the diagnosis.

When managing a pregnant patient with urolithiasis, conservative management is favoured where possible. This is because 70–80% of stones have been shown to pass spontaneously [195]. The mainstay of conservative management is for rehydration, anti-emetics, analgesia, and antibiotics if an infection is suspected.

In the remaining 20–30%, surgical intervention is required. The indications for surgical intervention are for those that do not improve with conservative measures, such as infected hydronephrosis with declining renal function or uro-epis [195].

Temporisation methods:
- Ureteric stent insertion
- Percutaneous nephrostomy

Either under local anaesthetic, sedation, or a short general anaesthetic. However, this will need to be changed regularly, at least every six to eight weeks, due to the high risk of encrustation. However, both options are poorly tolerated.

Definitive treatment:
- URS

With the advancements in technology and endourological techniques, URS has become safer with ever-improving results with stone-free rates as high as 86% [195]. However, the risk might still be considered high with a 8–16% developing procedure related complications, as well as obstetric complications, including premature uterine contractions or even premature delivery [195].

PCNL is best avoided, and SWL is a contraindication.

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15

Kidney and Ureter Vascular Disorders

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Abstract

Variations of the renal vessels are not uncommon. These vascular abnormalities are usually diagnosed using computed tomography (CT) or angiography. Knowledge of the normal anatomy of the renal vessels and the various abnormalities is important for every surgeon who operates on the kidneys to avoid inadvertent injury.

Keywords renal artery; renal vein; stenosis; aneurysm; haemangioma

15.1 Congenital Anomalies of the Renal Vessels

The pattern of the arterial supply of the kidney was established by Graves in 1971 [1]. There are five main renal segments arranged like the fingers of the hand (Figure 15.1). There are many variations: two or three of the main branches may spring from a common trunk or arise separately from the aorta (multiple renal arteries) [1]. Aberrant arteries usually originate from vessels other than the aorta and the main renal artery. They could arise from the lumbar, gonadal, common, and external iliac arteries [2]. The term ‘accessory artery’ is used when two arteries supply the same renal segment. These variations are more common in pelvic kidney or renal ectopia. It is common for the upper segmental vessel to cause an indentation on the neck of the upper calix, an appearance which can be mistaken for a tumour (Figure 15.2). Very rarely this artery can cause actual obstruction [3]. The relationship between the artery and the vein could vary (i.e. artery dorsal to the vein, artery ventral to the vein, or artery cranial and caudal to the vein).

Aberrant, accessory, or multiple vessels may constrict the pelviureteric junction causing symptoms like haematuria, pain, urinary tract infections, and calculi. The anatomy could be confirmed using arteriography or contrast computed tomography (CT).

15.1.1 Haemangioma

It is unclear whether these should be considered to be benign hamartomas or congenital anomalies of the renal arteries. They occur in all sizes, from minute capillary naevi on a papilla to large arteriovenous malformations. The main symptom is repeated or persistent haematuria, sometimes accompanied by clot colic. Only with large malformations are there any physical signs; then, there may be hypertension and a bruist heard over the loin.

The routine investigations for haematuria, cystoscopy and retrograde urogram reveal blood issuing from one ureter. CT or an angiogram will confirm the diagnosis, but in small angiomas, there is no mass and nothing
shows up on the CT scan. Even an angiogram may fail to detect the source of the bleeding in some cases. Ureteropyeloscopy may show blood issuing out of one of the calices and allow it to be coagulated using laser (Figure 15.3). Otherwise a partial nephrectomy may be possible [4].

15.1.2 Renal Segmental Hypoplasia (Ask–Upmark Kidney)

This is a rare deformity of the kidney seen in younger patients with hypertension [5]. Histologically, it is characterised by absence of glomeruli and the thickening of arterial wall which appears stenosed [6]. The kidney is grossly scarred and has similar appearances to reflux nephropathy without the inflammatory changes [7].

Most patients present with hypertension at a young age. Recurrent urinary tract infections (UTIs) are a rare manifestation.

The renal function could be normal as the condition could be unilateral. Renal ultrasound or CT will reveal an atrophic scarred kidney. Mercaptotriglycerine ($^{99}$Tc-Mag3) or dimercaptosuccinic acid (DMSA) renogram can confirm the reduced renal function; arteriography will show a small renal artery.

15.2 Renal Artery Disorders

15.2.1 Traumatic Lesions of the Renal Artery

Blunt renal injuries are rare (i.e. overall incidence 0.05% of all blunt injuries) [8]. It is associated with deceleration injuries (e.g. road traffic accidents and falls from heights) [8]. Injuries to the ribs or other abdominal organs such the spleen, liver, or bowels are usually present. The injury can vary between a small leak, thrombosis, or complete avulsion and is best diagnosed with CT or angiogram. Conservative management is the most common treatment; however, surgical exploration with revascularisation or nephrectomy could be performed in patients who are unstable. Revascularisation is difficult and associated with reduced renal function [9]. This is usually reserved for patients with traumatic thrombosis who have a single kidney or bilateral injuries [9, 10].
Penetrating injuries of the renal artery are a common cause of arteriovenous fistula in incidents involving knives. Elsewhere, the most common cause is iatrogenic during renal biopsy or partial nephrectomy. There is more than the usual retroperitoneal haematoma, and within a few weeks, the patient develops a thrill and bruit over the loin, sometimes with haematuria [11]. The diagnosis is confirmed with CT or arteriography (Figure 15.4). Small lesions may be embolised through an angiographic catheter [11]. Larger ones may require partial nephrectomy. Very large arteriovenous fistulae with a large shunt and loss of renal parenchyma require nephrectomy.

15.2.2 Renal Artery Stenosis

Atherosclerosis is the most common cause of renal artery lesions [12]. Plaques of atheroma may affect the main renal artery at the junction with the aorta or along its major branches (Figure 15.5). A different pathological process affects medium-sized vessels such as the arcuate arteries where the internal elastic lamina is doubled and redoubled – intimal fibroelastic hyperplasia (Figure 15.6). A third change – arteriolosclerosis – where hyaline material accumulates just under the intima, is seen in the small afferent arterioles of the glomeruli (Figure 15.5).

These pathological processes, which may occur singly or together, restrict the flow of blood to the renal parenchyma, and ultimately block it completely. When a segmental artery is blocked, there is an infarct of the segment it supplies, and a characteristic atrophy of the full thickness of the cortex and medulla. When smaller branches are occluded, there is a more diffuse loss of parenchyma and an overall shrinkage of the kidney.

The disease progresses over time, and if serial pyelograms have been obtained, one can see the kidneys shrink over the decades (Figure 15.7). This results in a deterioration of renal function and could end with end-stage renal failure.

15.2.3 Renal Artery Dysplasia

Renal artery dysplasia affects the intima or the media to different degrees. It could be a part of fibromuscular
Figure 15.5 Atheroma and arteriosclerosis.

Figure 15.6 Fibromuscular dysplasia and hyperplasia.

Figure 15.7 Tracing of X-rays taken 15 years apart at the age of 66 (left) and 81 (right) in a physician, showing the shrinkage of the kidneys which is seen in old age. (He complained of nocturia but lived to be 92).
dysplasia that mainly affects the renal and carotid arteries but could also affect different arteries in the body. The intima is affected by patches where it is thickened, alternating with patches where it is unusually thin. This sometimes results in an aneurysmal ballooning of the intima through the wall of the artery. Fibrous tissue is seen just under the adventitia or scattered randomly throughout the entire wall of the artery. The result is to convert the artery from a smooth strong cylinder into an irregular perished pipe, giving an angiographic appearance of a string of beads.

15.2.4 Renal Artery Aneurysm

Renal artery aneurysms are usually diagnosed as an incidental finding during the investigations for other conditions like hypertension or haematuria. Occasionally they could rupture, causing major bleeding particularly during pregnancy [13, 14]. A plain radiograph sometimes shows a characteristic ‘ring’ due to calcification in the wall of the aneurysm (Figure 15.8). The diagnosis is made by colour Doppler sonography, CT angiogram (Figure 15.9), or magnetic resonance imaging (MRI). The kidney on the side of the aneurysm is often smaller than that on the other.

Indications for treatment include diameter more than 2.5 cm [15, 16], interval increase in size, hypertension, haematuria, pain and women of child-bearing age. Treatment options include vascular stent graft or embolisation depending on the position of the aneurysm and its relationship to the renal artery branches as well as the presence of a ‘neck’ [17, 18].

15.2.5 Renal Infarction

Renal infarction is a result of arterial occlusion mainly caused by thrombi, trauma, or polyarteritis nodosa. It is possible for thrombosis process to start in aorta and spread to the renal artery, causing unilateral or bilateral infarcts. It is more common that the small arteries are occluded, resulting in multiple small infarcts. The affected renal parenchyma undergoes necrosis, followed by fibrosis. If these areas are small, this process could be asymptomatic. Sudden, complete renal infarction could present with loin pain and haematuria. The patient could develop ‘epitheluria,’ caused by sloughing of renal tubular cells. CT with contrast may aid the diagnosis. DMSA scans will show the silent segment of parenchyma supplied by a segmental artery. When several segmental arteries are occluded, there is a very typical combination of a normal-appearing retrograde urogram, with a dramatic thinning of the renal parenchyma; however, an angiogram will show arterial occlusion (Figure 15.10).

Although immediate surgery has been suggested in the past, anticoagulation and conservative management is usually the first-line treatment.

15.2.6 Pathogenesis of Renal Hypertension

Renal artery stenosis causes narrowing of the arterial lumen. The lumen of the renal artery must be reduced by some 70% before there is a measurable reduction in blood flow [19], but the pressure gradient across the narrowing segment may be as much as 40 mm Hg [20]. The lowered arterial blood pressure leads to reduction in perfusion pressure, glomerular filtration, and in the amount of sodium that is filtered. As a result, the baroreceptor and macula densa systems release renin [21–23]. Renin is the first in a cascade of enzymes which successively liberate the two active polypeptides – angiotensin II and III – from their inactive globulin carrier ‘angiotensinogen’ (Figure 15.11). Both the angiotensins are vasopressors, but in addition, angiotensin II causes the adrenal to produce aldosterone, causing a rise in blood pressure to maintain tissue perfusion. In addition to renal hypertension, ischemic nephropathy can be seen at a later stage, causing deterioration in renal function.

The prevalence of renal hypertension is less than 1% of patients with mild or moderate hypertension [24]. Features raising suspicion of this disease include flank pain and diagnosis of hypertension before 30 years of age.
Several diagnostic methods have been used, such as peripheral renin activity assays, captopril testing, and radiouclide renal scanning. These tests have been replaced by Doppler ultrasound, MRI, and CT. Contrast angiography study remains the gold standard for diagnosis.

Medical treatment is the preferred method in the absence of ischaemic changes to the kidney. On the other hand, if patients show signs of progressive obstruction, angioplasty should be considered (Figure 15.12). The results of angioplasty are excellent in patients with fibromuscular hypoplasia.

Surgical revascularisation is rarely used. The block between aorta and renal artery may be bypassed with a graft of saphenous vein or internal iliac artery. On the left side, the splenic artery can be mobilised and anastomosed directly to the renal artery beyond the stenosis [25–27]. Nephrectomy is an alternative if the kidney is atrophic with poor function.
Figure 15.10 This patient had a sudden onset of hypertension, haematuria, and pain in the left loin. The angiogram shows occlusion of the left renal artery, only the upper segmental vessel is spared.

Figure 15.11 The renin-angiotensin cascade.
15.3 Disorders of the Renal Veins

15.3.1 Congenital Anomalies

Every surgeon should be aware of the retroaortic left renal vein. It is a common anomaly and can cause great difficulty when performing a left nephrectomy for live donor transplantation.

On the right side, a persistent post-cardinal vein results in a ‘vena cava’ which runs in front of the ureter and causes obstruction. The pyelographic appearances are typical and should contraindicate attempts at percutaneous pyelolysis. The open pyeloplasty is easy, and there is no need to attempt to remove the useless segment of ureter from behind the vena cava.

15.3.2 Renal Vein Thrombosis

Renal vein thrombosis is rare and usually associated with invasion of the renal vein by a tumour, nephrotic syndrome, and membranous glomerulonephritis. The vein becomes occluded causing the kidney to engorge. Patients present with flank pain and haematuria. Examination reveals tender mass. Thrombocytopenia may be noted. Contrast CT scan shows poor uptake of the contrast and a thrombus that may extend to the vena cava. Anticoagulation is usually the first-line treatment, although thromboembolisation has been reported.

Expert Opinion

Although vascular disorders of the kidney are rare, they can cause a significant detriment to the quality of life of the patient, and in some instances, increase mortality. Therefore, consideration of treatment and counselling of each patient is essential.

References

16

The Adrenal Glands

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Abstract

Managing patients with adrenal disease requires a detailed knowledge of endocrinology, pathology, radiology as well as both laparoscopic and major resectional surgery. It is important that patients are managed in a multidisciplinary setting. The principle tenets of adrenal surgery are to establish the presence or absence of endocrine dysfunction, determine the likelihood of adrenal malignancy, and assess the requirement for medical stability in the preoperative period. Laparoscopic surgery is the gold standard approach for benign tumours. Open surgery is mandatory for adrenocortical carcinoma.

Keywords  adrenal; cortex; medulla; Conn syndrome; Cushing syndrome; pheochromocytoma; adrenalectomy

Key Points

- Biochemical tests alone secure the diagnosis of adrenal endocrine dysfunction.
- A combination of cross-sectional imaging and positron emission tomography (PET) scan determine the likelihood of malignancy.
- Familial syndromes should be suspected in all patients with pheochromocytoma.
- Adrenocortical cancer is removed using an open surgical approach.

16.1 Principles of Endocrine Surgery

Management of patients with adrenal disease should be conducted within a multidisciplinary team. This team should involve an endocrinologist, a surgeon, a radiologist, a pathologist, a biochemist, an intensivist, and at times, access to a geneticist and an oncologist. Patients presenting with adrenal disease should be managed according to the five principles of adrenal surgery:

Confirm the diagnosis – Is the diagnosis confirmed? This is always a biochemical test and not a radiological one.

Render the patient safe – Hypertension and electrolyte imbalance should be controlled. Does the patient need steroid supplementation? Severe hypercortisolism may require medical treatment prior to surgery.

Consider localisation – Is localisation necessary, and if so, by what means?

Is surgery indicated? This may not be the case for many patients (i.e. small incidentalomas, cysts, myelolipomas, or bilateral adrenal hyperplasia).

If surgery is indicated – what approach? Although minimally invasive techniques may be feasible in many cases, they are not appropriate in others (e.g. adrenocortical carcinoma and malignant paraganglioma).
16.2 Anatomy

The adrenal glands are paired and lie superior to the kidneys, historically known as supra renal glands (Figure 16.1). The adrenal has two distinct parts: (i) the cortex, a busy endocrine gland subordinate to the pituitary, and (ii) the medulla, a specialised part of the sympathetic nervous system. Each adrenal measures about $5 \times 1$ cm and weighs about 5 g. They are not symmetrical. However, each adrenal gland is shaped like a cocked hat. Its cross-section resembles a triple sandwich: the outermost layer is the yellow zona glomerulosa, next the zona fasciculata, and third, the brown zona reticularis. Finally, there is a vascular filling – the medulla. (Figure 16.2). The triple layer of cortex is only a few millimetres thick – hence the term ‘suprarenal capsule’.

Each of the three layers of the cortex has a different function. The foamy cells of the outermost zona glomerulosa form aldosterone. The zona fasciculata – so called because its cells are lined up in orderly bundles – produces glucocorticoids, mainly cortisol. The zona reticularis produces androgens.

The medulla is made of pheochromocytes surrounded by spongy vascular spaces, rich in sympathetic ganglion cells. The pheochromocytes make the catecholamines adrenalin and noradrenalin. Because these turn brown when oxidised, this is called the ‘chromaffin reaction’.

16.2.1 Surgical Relations

Above each adrenal lies the diaphragm; medially are the aorta or the vena cava; laterally is the abdominal wall; inferiorly is the kidney to which the adrenal is so firmly attached that pulling down the kidney is a useful way of bringing the adrenal into a surgical incision. In front are the duodenum and colon: behind the diaphragm, 12th rib, and the pleural recess.

The right gland has a pyramidal shape and lies between the inferior vena cava and the right crus of the diaphragm. Its upper part lies in contact with the bare area of the liver, whilst its lower half has a peritoneal covering. The left gland is more crescentic in shape and lies on the medial border of the left kidney above the hilum, sandwiched between tail of pancreas and left crus of diaphragm.

16.2.2 Arterial Supply

The adrenal is supplied by small branches of the phrenic, renal, and lumbar arteries. Blood leaves the hilum through a single vein which flows into the renal vein on the left side and the inferior vena cava on the right. These adrenal veins are easily torn; on the right, such a tear may lead to daunting haemorrhage from the vena cava.
16.2.3 Nerve Supply

The adrenal medulla has a rich splanchnic nerve supply which is stimulated by sympathetic pre-ganglionic nerves of the aortic and renal sympathetic plexuses.

16.3 Physiology

16.3.1 Cortex

There are three distinct zones within the cortex (Figure 16.2), but they all synthesise and secrete steroid hormones derived from cholesterol. The cells of the zona glomerulosa make aldosterone – the 18-aldehyde of corticosterone, which is released under the action of angiotensin II, and by retaining water and salt in the distal tubules helps to sustain a rise in blood pressure by increasing blood volume.

The zonae fasciculata and reticularis are controlled by adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn responds to ACTH-releasing hormone of the hypothalamus.

The zona fasciculata forms the glucocorticoids cortisol and corticosterone, and the mineralocorticoid deoxycorticosterone. The glucocorticoids – all 17-hydroxycorticosteroids – can be measured in the urine. Cortisol can be measured in the plasma where it rises and falls according to the time of day, usually being lowest in the morning and highest in the evening.

Glucocorticoids are so named because they increase the production of glucose. Many synthetic glucocorticoids are available (e.g. prednisone, prednisolone, betamethasone, and dexamethasone), which all vary in the relative strength of their effects on inflammation and sodium retention.

The zona reticularis forms a little testosterone, and more of the androgen precursors dehydroepiandrosterone and androstenedione, which are converted into testosterone in tissue. The metabolic end product of all these androgens appears in the urine as the 17-ketosteroids. The androgens stimulate growth and the appearance of male secondary sexual hair.

16.3.2 Medulla

The adrenal medulla secretes the catecholamines adrenaline (80%) and noradrenaline (20%) and small amounts of dopamine (Figure 16.3). Unlike other adrenergic neurons, those of the medulla express phenylethanolamine-N-methyltransferase (PNMT) which catalyses the conversion of noradrenaline to adrenaline. Which are metabolised to normetanephrin and metanephrin. Their common metabolic end result in the urine is vanillyl mandelic acid (VMA). The effects of catecholamine excess include increased liver and skeletal muscle glycogenolysis, increased metabolic and respiratory rate, and greater force and rate of myocardial contraction. Noradrenalin raises the blood pressure by increasing peripheral resistance (by driving vasoconstriction) without changing the cardiac output. Adrenalin increases cardiac output by raising pulse rate and systolic pressure, without increasing peripheral vascular resistance (drives dilation of blood vessels in the liver and muscle). These effects are mediated by the hypothalamus (LHRH) and the anterior pituitary, which stimulates the release of adrenocorticotropic hormone (ACTH), which stimulates the zona fasciculata to secrete the corticosteroids, and the zona reticularis to secrete androgens.
by alpha-adrenergic receptors that bind both catecholamines and beta adrenergic receptors that preferentially bind adrenaline; it is the expression of alpha and beta receptors by different tissues that permits differing effects of both hormones when they are released simultaneously.

16.4 Pathology

Adrenal tumours are classified not only according to neoplasia but also regarding their endocrine function (Table 16.1).

16.4.1 Pathology of the Adrenal Cortex

16.4.1.1 Hypofunction

Loss of adrenal function will result in electrolyte disturbance, hypoglycaemia, and circulatory collapse. In the chronic variety serum ACTH levels are high, and the patient may become pigmented due to excess circulating melanocyte stimulating hormone (MSH). This occurs because ACTH and MSH are components of a common prohormone, pro-opiomelanocortin (POMC), and when ACTH is cleaved from POMC, MSH is also released.

16.4.1.1.1 Acute

There are a number of different scenarios for how this event might arise.

- Acute haemorrhage in the neonate due to difficult labour, that causes sudden loss of function.
- Septicaemia from meningococcus (and other bacteria) can result in a coagulopathy leading to adrenal haemorrhage and insufficiency – the Waterhouse Frederichsen syndrome.
- Primary adrenal haemorrhage in patients on anticoagulation can occur.
- Traumatic necrosis may arise following surgery – especially during nephrectomy.
- As a consequence of bilateral adrenalectomy, unless adequate steroid supplementation has been prescribed

16.4.1.1.2 Addison Disease (Primary Chronic Adrenal Insufficiency)

The most common cause is from primary disease of the adrenal itself. This is an autoimmune disease resulting in lymphocytic infiltration of the gland. Other causes include bilateral metastases, tuberculosis, sarcoidosis, and amyloid deposition.

16.4.1.1.3 Secondary Chronic Adrenal Insufficiency

This arises from failure of the hypothalamic pituitary axis. It might result from pituitary surgery, irradiation, tumour expansion, or infarction.

16.4.1.2 Hyperfunction

Three conditions result from overproduction of steroids.

16.4.1.2.1 Cushing Syndrome (Hypercortisolism)

ACTH-dependent hypercortisolism from an anterior pituitary tumour is defined as Cushing disease. Cushing syndrome arises from ACTH-independent hypersecretion of cortisol from tumours of the zona fasciculata, of which half are benign and half are malignant. Cushing disease accounts for 80% of all Cushing pathology and causes bilateral adrenal hyperplasia.

Clinical Features This typically affects young (30–40 years) women (4:1). The excess corticosteroid leads to proteolysis and glycogen deposition resulting in the ‘lemon-on-sticks’ appearance (Figure 16.4), buffalo humps, and moon face (Figure 16.5). Patients are affected

| Table 16.1 Classification of pathology of the adrenal gland. |
|---------------------|---------------------|---------------|---------------------|
| **Neoplasm**        | **Endocrine status**| **Cortex**    | **Medulla**         |
| Benign              | Functioning         | Hyperaldosteronism | Phaeochromocytoma |
|                     |                     | Cushing’ syndrome |                    |
|                     |                     | Virilisation syndrome |             |
|                     | Non-functioning     | Cyst           | Myelolipoma         |
| Malignant (primary) | Functioning         | Hyperaldosteronism | Pheochromocytoma |
|                     |                     | Cushing syndrome |                    |
|                     |                     | Virilisation syndrome |             |
|                     | Non-functioning     | Adrenocortical carcinoma |             |
| Malignant (secondary)| Non-functioning     | Adrenal metastases |                     |
with hypertension, thin skin, bruising, and depression. Other symptoms include hirsutism, myopathy, and oligomenorrhoea or impotence. Osteoporosis may be severe. Subclinically, Cushing syndrome refers to patients with mild autonomous cortisol excess in the absence of any clinical signs.

**Investigations**

*Endocrinology* Hypercortisolism is confirmed by demonstrating a nonsuppressible 8 a.m. serum cortisol following administration of 1 mg oral dexamethasone the night before (low-dose overnight dexamethasone suppression test) or the finding of raised salivary and urinary-free cortisol levels. Measuring the ACTH should distinguish pituitary and primary adrenal disease.

*Radiology* Cushing disease is imaged with pituitary magnetic resonance imaging (MRI) and bilateral inferior petrosal sinus venous sampling. ACTH-independent disease is investigated with an adrenal cross-sectional imaging (Figure 16.6). In addition to localising the tumour, features of malignancy should be carefully considered (see Sections 16.4.3.1 and 16.4.6).

![Figure 16.5 Caricature showing the principal clinical features of Cushing syndrome.](image)

![Figure 16.6 Unenhanced computed tomography (CT) scan showing primary cortical tumour of the right adrenal causing Cushing syndrome.](image)

![Figure 16.4 Patient with Cushing syndrome with typical ‘lemon-on-stick’ body habitus.](image)
Treatment Cushing disease is best managed with hypophysectomy. Adrenal surgery is only considered when pituitary surgery fails and the Cushing disease becomes severe. At that point, bilateral adrenalectomy is the operation of choice.

Cushing syndrome is managed with adrenal surgery. In the absence of suspicion for carcinoma, the laparoscopic approach is preferred. Preoperatively, optimisation of hypertension, diabetes, and muscle strength should be achieved. Severe hypercortisolism is best controlled medically (e.g. with ketoconazole or metyrapone; in severe cases, etomidate infusion may be necessary, but this requires intubation and ventilation in a critical care environment). The contralateral adrenal will be suppressed and adjuvant steroid supplementation must be prescribed pre- and postoperatively in liaison with the endocrinologist. These patients have delicate skin and brittle bones and so patients should be handled with the upmost care. Furthermore, surgery is associated with an increased risk of infection and thromboembolic disease, therefore, thromboprophylaxis is given.

Subclinically, Cushing syndrome may be associated with hypertension and impaired glucose tolerance, but the optimal treatment remains unclear. Typically identified as part of the investigation of an adrenal incidentaloma and may be an indication for adrenalectomy, but long-term follow-up data is scanty [1].

16.4.1.2.2 Primary Hyperaldosteronism (PA)
Clinical Features PA is a disorder with autonomous hypersecretion of aldosterone which leads to sodium and fluid retention, thereby causing hypertension (Figure 16.7). Hypokalaemia may be present, especially in severe and long-standing cases. Plasma renin is suppressed leading to a high plasma aldosterone to renin ratio (PARR). It is estimated that PA may account for between 5 and 18% of the general hypertensive population [2]. There are two major subtypes of PA. Bilateral adrenal hyperplasia (BAH) accounts for 50–70% [3]. Patients with BAH are generally older, have milder hypertension, and are more often normokalaemic. Aldosterone-producing adenoma (APA, also known as Conn adenoma) is unilateral and should be considered in younger patients with more severe disease. Adrenocortical carcinoma (ACC) accounts for about 1% of cases of PA.

Patients present with hypertension, which is often refractory to treatment (requiring three or more drugs). Fatigue, muscle cramps or weakness, thirst, and polyuria are secondary to hypokalaemia, but half of patients are normokalaemic.

Investigations
Endocrinology The established screening test is the PARR. In most patients, the renin is suppressed the plasma aldosterone concentration is raised and a ratio of >800 is diagnostic. Several antihypertensive agents interfere with the renin-angiotensin system and may affect the PARR. Beta-blockers and spironolactone should be stopped two weeks before testing. It is also advised to use a second confirmatory test (fludrocortisone suppression test) and the involvement of an endocrinologist is essential.

Localisation Once PA has been biochemically proven, it is essential to determine if this is unilateral or bilateral as it determines whether surgery is indicated. Conn tumours are nicknamed ‘canary tumours’ because they are small and yellow. In fact APAs may be as small as a few millimetres and beyond the resolution of available cross-sectional imaging. CT should be performed in all patients; however, normal CT does not exclude Conn tumours and the discovery of a tumour does not prove unilateral disease because it may be a nonfunctioning incidentaloma. Current guidelines recommend adrenalectomy without other localising tests in younger patients (<40 years) with an adrenal mass >10 mm on CT [4]. In all other patients, a functional test should be undertaken.

Adrenal Venous Sampling This is the gold standard. Each adrenal vein is catheterized via the femoral vein

![Figure 16.7 Principal features of Conn syndrome.](image-url)
Samples are drawn from the adrenal veins, the inferior vena cava (IVC) and the periphery. Assay for cortisol confirms the accurate placement of the catheter within the adrenal vein. Samples are taken for aldosterone and the aldosterone-to-cortisol ratios between adrenals are compared. A ratio greater than two confirms laterality (or a ratio of 4:1 if synacthen is given).

**Treatment**

Patients with BAH should be treated medically with a mineralocorticoid receptor antagonist; spironolactone, or eplerenone.

Laparoscopic adrenalectomy should be offered in cases of unilateral PA [5]. Hypertension may be cured in up to one-third of patients, but for the remainder, it becomes easier to control. The preoperative response to hypertension control by spironolactone is a good predictor for those whose hypertension will be cured [6].

**16.4.1.2.3 Virilising Tumours**

These are rare accounting for four cases per million of population. Up to 30% are malignant.

**Clinical Features**

Patients present with hirsutism, acne, and an enlarged laryngeal prominence (Figure 16.9).

**Diagnostic Tests**

The diagnosis is confirmed by measuring serum testosterone and its precursors androstenedione and dehydroepiandrosterone-sulphate (DHEAS). Elevation of DHEAS is observed in 80% of adrenocortical cancers. Either MRI or CT scanning will localise the tumour and identify risks for malignancy such as size, local invasion, and presence of metastases.

**Treatment**

Adrenalectomy will aim to cure the patient. In circumstances when malignancy is suspected, an open approach should be adopted (see Section 16.4.6.).

**16.4.1.3 Nonfunctioning Pathology**

**16.4.1.3.1 Incidentaloma**

**Definition**

An adrenal mass discovered incidentally during an imaging investigation for a nonadrenal disorder. Autopsy studies estimate the prevalence of adrenal tumours to be 6% [7], and so as imaging resolution improves the prevalence of adrenal incidentalomas on cross-sectional abdominal imaging nears 6% [8].

**Clinical Features**

Most (80%) patients are entirely asymptomatic when they have a nonfunctioning adenoma [9], but subclinically, Cushing syndrome (5%), pheochromocytoma (5%), and Conn tumours (1%) feature in the differential diagnosis.

**Diagnostic Tests**

The differential diagnosis of an adrenal mass is shown in Table 16.2. The purposes of investiga-

### Table 16.2 Differential diagnosis of an adrenal mass on imaging.

<table>
<thead>
<tr>
<th>Adenoma</th>
<th>Nodular hyperplasia</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganglioneuroma</td>
<td>Pheochromocytoma</td>
<td>Angiomyolipoma</td>
</tr>
<tr>
<td>Abscess</td>
<td>Amyloidosis</td>
<td>Cyst</td>
</tr>
<tr>
<td>Fibroma</td>
<td>Granulomatosis</td>
<td>Hamartoma</td>
</tr>
<tr>
<td>Haematoma</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Myelolipoma</td>
<td>Teratoma</td>
<td>Pseudocyst</td>
</tr>
</tbody>
</table>
tions are to identify functioning tumours or those that could be malignant. Patients are therefore screened for Conn tumours, Cushing syndrome, and pheochromocytoma. Factors that raise suspicion for malignancy include virilisation, rapid growth, certain radiological features on MRI/CT, and positive uptake on a positron emission tomography (PET) scan. The MRI/CT features to suggest malignancy include a large size (>6 cm), heterogeneous uptake of contrast, an irregular outline, and especially the presence of local invasion or metastases (Figure 16.10). The best modalities to predict malignancy are MRI and PET scan [10]. Biopsy should never be undertaken for a pheochromocytoma. Biopsy should not be undertaken for adrenocortical cancer as the histology report will be uncertain and biopsy risks tumour seeding. Biopsy might be considered when there is a known extra-adrenal primary malignancy as an investigation to diagnose metastasis.

Treatment Surgery is indicated for functional tumours, primary adrenal malignancy, and metastasectomy, if the disease is isolated. The risk of primary malignancy in unselected incidentaloma cases is 0.1% [9]. The risk of malignancy rises as the tumour size gets bigger (>4 cm: 10%, vs. >6 cm: 25–90%) [11]. But there is no benefit to excising all incidentalomas because it does not lead to an increase in the incidence of excising small cancers [12]. Surgery is recommended for tumours equal to or greater than 4 cm in maximum diameter. For the majority of patients found to have a smaller (<4 cm) nonfunctioning tumour, it is recommended that they undergo a further adrenal scan at a 3–6 months interval to exclude early growth. There is no consensus about follow-up beyond that period. However, there is evidence that a tumour greater than 3 cm has an increased risk of developing hyperfunction over time [13].

16.4.1.3.2 Cyst
Clinical Features Cysts in the adrenal may be so large as to be palpable. They rarely occur in infants [14]. They displace the kidney and are easily imaged by ultrasound and CT scanning. True cysts may be lymphangiomatous with milky fluid; pseudocysts are reported from degeneration or haemorrhage in a normal gland or tumour [15]. In adults, they are usually detected by chance, but occasionally become infected or give rise to retroperitoneal haemorrhage [16]. In the tropics they may occasionally be hydatid cysts [17].

Investigation Imaging by CT scan is usually diagnostic. Cysts have a smooth outline, are isodense, and appear fluid filled. Long-standing cysts may show calcification in the wall.

Treatment Cysts of the adrenal can usually be left alone unless they are causing discomfort by pressure on adjacent organs when they can be aspirated under radiological guidance. Recurrent cysts following aspiration can be considered for laparoscopic resection [18] or fenestration.

16.4.1.3.3 Myelolipoma
These are rare benign tumours composed of mature adipose and haematopoietic tissue. They can arise from either the adrenal cortex or medulla. Their size varies from millimetres to more than 20 cm.

Clinical Features Typically, they are discovered as incidental findings during abdominal imaging (ultrasound, CT, etc.). They account for 3–5% of all adrenal tumours and are commonest in the sixth decade of life. They are hormonally inactive but may coexist with functioning adrenal tumours. They are usually asymptomatic.

Investigations Myelolipomas appear as well-delineated heterogeneous masses with low-density mature fat (less than −30 HU) interspersed with more dense myeloid tissue
Fine-needle aspiration cytology should be considered when CT scanning is non-diagnostic.

Treatment Most of these tumours can be left alone. Surgery is only indicated when there is evidence of endocrine function or if the surgeon is convinced that a larger tumour (>70 mm) is the cause of local symptoms [19].

16.4.1.3.4 Adrenocortical Carcinoma (ACC)
This is a rare aggressive tumour with a poor prognosis. It affects about one to three people per million of population.

Clinical Features Nonfunctioning tumours will either present as an incidentaloma or with symptoms and signs of an abdominal mass. Functioning tumours will manifest with rapid onset of symptoms and signs of Cushing syndrome. Virilisation is highly suggestive of malignancy.

Diagnostic Tests
Endocrinology Patients must be screened for Cushing syndrome and pheochromocytoma. If negative, in the presence of hypertension, Conn tumours but should be considered (very rare). Plasma androstenedione, testosterone, and DHEAS should be measured. Analysis of urine from patients with ACC (urinary metabolomics) has demonstrated that there is a specific ‘signature’ for malignancy, whereby patients with malignant tumours exhibit increased urinary excretion of steroid precursors compared with patients with benign disease [20].

Radiology CT scanning will identify the hallmarks for malignancy – a large irregular mass with delayed wash-out of contrast (<50% at 10 minutes), uneven enhancement, possible local invasion, and distant metastases. PET scanning is effective at assessing metastatic disease.

Treatment Surgery offers the best chance of survival. There is no role for laparoscopic surgery in most cases, and even for small tumours that might be resectable via a laparoscopic approach, its use is controversial. The philosophy is to perform an R0 (clear margins) en-bloc resection. Traditionally invasion of the IVC (on the right) and superior mesenteric artery (SMA) (on the left) determined whether the tumour could be resected. Nowadays this surgery should be undertaken in specialist surgical centres with input from endocrine, hepatic (possibly transplant) and vascular surgeons. Even if R0 is not feasible, there may be merit in debulking the disease prior to chemotherapy. The multidisciplinary team should discuss adjuvant chemotherapy with mitotane by an oncologist familiar with this treatment and it should be considered in tumours with a Ki67 proliferation index >10% or those with incomplete resection or metastases. There is no conclusive evidence of benefit in those with complete resection and no known metastatic disease (Table 16.3) [21]. It is important to establish plasma levels within a defined therapeutic range. Mitotane can induce adrenal insufficiency necessitating steroid replacement.

16.4.1.3.5 Adrenal Metastases
Clinical Features The adrenal glands are the most common deposit for metastases. Common primary

<table>
<thead>
<tr>
<th>Stage</th>
<th>UICC/WHO</th>
<th>Adjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1, N0, M0</td>
<td>Minimal benefit in R0 resection unless Ki67 &gt; 10% in which case consider Mitotane&lt;sup&gt;a&lt;/sup&gt; therapy</td>
</tr>
<tr>
<td>II</td>
<td>T2, N0, M0</td>
<td>Minimal benefit if R0, consider Mitotane&lt;sup&gt;a&lt;/sup&gt; if Ki67 &gt; 10%</td>
</tr>
<tr>
<td>III</td>
<td>T3, N0, M0</td>
<td>Mitotane&lt;sup&gt;a&lt;/sup&gt; therapy probably beneficial</td>
</tr>
<tr>
<td></td>
<td>T1–2, N1, M0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>T4, N0–1, M0</td>
<td>Consider Mitotane&lt;sup&gt;a&lt;/sup&gt; in combination with cisplatin or etoposide chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Any M1</td>
<td></td>
</tr>
</tbody>
</table>

UICC, Union Internationale contre le Cancer.
T1: Tumour<5 cm; T2: >5 cm, T3: tumour infiltration into surrounding tissue, T4: Tumour invading adjacent organs. N0: no lymph node metastases, N1: lymph node metastases. M1: distant metastases.

<sup>a</sup> suggested duration of Mitotane, 2–5 years [21].
cancers that metastasise to the adrenal include lung, kidney, colon, prostate and breast. Synchronous metastases are defined as those with a disease-free survival of <6 m. Metastases diagnosed after 6 m are termed ‘metachronous’.

Diagnostic Tests (Endocrinology and Imaging) The diagnosis usually starts with staging tests for a known carcinoma. PET scanning is useful in selecting those with an isolated metastasis (Figure 16.12). Biopsy should only be considered when imaging is equivocal.

Treatment Adrenalectomy is considered in the rare circumstance when the metastasis is isolated without evidence of other spread. There is a paucity of data regarding the merits of this operation, but the evidence suggests that there is greater benefit for metachronous disease [22]. Laparoscopic adrenalectomy is the preferred approach, with open surgery being reserved for the presence of local invasion. In circumstances when a patient develops a second isolated adrenal metastasis, adrenal surgery will render the patient (who is possibly receiving chemotherapy) steroid dependent. Renal cell cancer is the most common scenario and the decision to operate should be judged on its individual merits by the multidisciplinary team. There is anecdotal evidence suggest that increasing size is associated with more difficult laparoscopic removal and greater risk of involved margins; therefore, if removal is contemplated, it should be carried out sooner rather than later.

16.5 Pathology of the Adrenal Medulla

16.5.1 Hypofunction

Patients who undergo a bilateral adrenalectomy do not suffer from any consequences of loss of the adrenal medulla.

16.5.2 Non-function

16.5.2.1 Adrenal Neuroblastoma

This malignant tumour originates from primitive nerve cells (neuroblasts) of the sympathetic nervous system, so they can be found anywhere along this system. It is the most common solid tumour of infancy, making up half of all tumours in this age group. Most occur younger than the age of five and half younger than the age of two. More than half arise in the neural crest tissues of the abdomen, 25% of them in the adrenal, the rest arise anywhere in association with the sympathetic trunk, thorax, and neck.

16.5.2.1.1 Clinical Features

Clinically, 75% of neuroblastomas present as a large fixed nodular lump, usually on the left. Most (80%) present before the age of five years. The child presents with weight loss and poor health. One in three younger than the age of two years already have metastases causing ‘joint pains’ and fever, prompting the misdiagnosis of

Figure 16.12 Fluorodeoxyglucose (FDG) sagittal, coronal, and cross-sectional fused positron emission tomography-computed tomography (PET-CT) scan demonstrating high uptake in a right adrenal tumour (metastasis).
rheumatic fever. Retro-orbital metastases cause malignant proptosis. If the tumour occurs in utero, it may cause hypertension in the mother.

16.5.2.1.2 Investigations
Bleeding into the tumour causes anaemia. Urinary catecholamines are elevated. Marrow aspiration may show infiltration by tumour. Alpha-fetoprotein and carcinoembryonic antigen are raised – the latter being a useful marker of response to chemotherapy. Ultrasound and CT confirms the mass (Figure 16.13).

16.5.2.1.3 Treatment
The International Neuroblastoma Staging System has identified distinct prognostic stages [23]. Patients can be assigned to low-, intermediate-, or high-risk groups. Patients with a low risk can be cured with surgery or just observed. Patients with an intermediate risk require surgery and chemotherapy. Patients with a high-risk require surgery, radiation therapy, intensive chemotherapy, bone marrow, or haematopoietic stem cell transplantation. Newer types of treatment include agents that target factors that have a role in proliferation and cell survival [24].

16.5.3 Hyperfunction
16.5.3.1 Pheochromocytoma and Paraganglioma
The tumours are uncommon with an incidence of two to eight per million of population. Tumours that arise from the neuroectodermal tissue of the adrenal medulla are termed pheochromocytomas (PHAEO) and those arising from the extra-adrenal parasympathetic and sympathetic ganglia are termed paragangliomas (PGL). PHAEO and sympathetic PGL are predominantly intra-abdominal, functioning tumours that secrete catecholamines and their metabolites. PGLs derived from parasympathetic ganglia of the head and neck PGL tend to be non-functioning. M:F preponderance is equal and median age at diagnosis is 55 years. About 70% of PHAEO and PGL are sporadic with the rest occurring as part of inherited endocrine tumour syndromes, including multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), and the inherited paraganglioma syndrome types 1, 3, and 4. About 10% are bilateral, 10% are extra-adrenal and less than 1% are malignant. Outside the adrenal these chromaffinomas occur in the retroperitoneum near the adrenals, mediastinum, carotid body, organ of Zuckerkandl (at the origin of the inferior mesenteric artery), and bladder, where paroxysmal hypertension occurs with micturition.

16.5.3.1.1 Clinical Features
Most patients present with one or all of the classical triad of sweating, palpitations, and episodic headache. These can be brought on by smoking, sexual intercourse, defaecation, pressure on the abdomen, pregnancy, and drugs such as morphine, ACTH, and parenteral methyldopa. Hypertension is observed in just more than two-thirds of patients and 2% of those with hypertension will have a PHAEO. Tumours may also present due to mass effect (abdominal pain, distension), as an incidental finding on imaging studies performed for other reasons, or as part of biochemical screening for familial disease.

16.5.3.1.2 Investigations
Most patients with symptoms will have increased levels of urinary or plasma fractionated catecholamines (i.e. adrenaline, noradrenaline, and dopamine) or metanephrines (i.e. metadrenaline, normetadrenaline, and 3-methoxytyramine). Metanephrines are produced as a result of intratumour conversion of catecholamines by the enzyme catecholamine-O-methyl-transferase (COMT), and measurement of plasma and urinary metanephrines (99 and 97% sensitive) is more sensitive than plasma and urinary catecholamine measurement (86 and 84% sensitive) [25]. Measurements of one or more of these substances, that are four times greater than the upper limit of the reference range is 100% diagnostic. Equivocal urinary biochemistry should prompt the use of an alternative test (e.g. plasma metanephrines) and because the results of metanephrine estimation may be affected by certain drugs (e.g. monoamine oxidase inhibitors, paracetamol, tricyclic antidepressants, sympathomimetics such as ephedrine and phenylephedrine, amphetamines, and levodopa), these

Figure 16.13 Enhanced computed tomography (CT) scan showing huge mass occupying the entire left side of the retroperitoneum. This neuroblastoma displaces the left kidney inferiorly and invades the renal pedicle.
should be discontinued prior to testing [26]. Tumours may exhibit characteristic biochemical profiles, classified as either noradrenergic or adrenergic. PGLs and PHAEOs arising in association with VHL disease are noradrenergic and predominantly secrete noradrenaline and normetadrenaline. Conversely, adrenergic PHAEOs secrete a mixture of adrenaline/metadrenaline and noradrenaline/normetadrenaline and may be sporadic or due to MEN2 or NF1.

16.5.4 Imaging and Localisation

16.5.4.1 CT and MRI
Positive biochemistry should be followed by imaging studies to determine tumour localisation. Abdomino-pelvic CT and MRI are most commonly used (sensitivity 90–100%, specificity 70–80%) [27] and will detect the majority of tumours particularly if they are symptomatic; however, they may lack the sensitivity to localise early screen-detected tumours (e.g. lesions <1 cm) (Figure 16.14). Contrast CT is quicker and often more readily available but requires exposure to radiation. Ionic contrast has been reported to precipitate catecholamine release from PHAEO, leading to 'PHAEO crisis', but non-ionic contrast media have been shown to be safe. MRI avoids radiation and can distinguish PHAEO (which appear hyperintense on T2-weighted images) from other types of adrenal mass (usually hypointense). Tumours appear vascular and frequently possess cystic areas or central necrosis.

Figure 16.14 Enhanced computed tomography (CT), magnetic resonance image (MRI), meta-iodobenzylguanidine (123I-MIBG) scan, and positron emission tomography (PET) scans show pheochromocytoma of a small renal mass.
Extra-adrenal PGL may occur in the head and neck (5%), along the sympathetic chain in the thorax (10%) and abdomen (75%), above (juxtaadrenal) or below the origin of the inferior mesenteric artery (organ of Zuckercandl) and the bladder (10%). If initial imaging is negative or reveals extra-adrenal disease, functional investigation with meta-iodobenzylguanidine ($^{123}$I-MIBG) – 80–90% sensitive) or $^{111}$In-octreotide scanning (50–70% sensitive) Routine use is not advocated in well-localised adrenal lesions. More recently, 6-$^{18}$F]fluorodopamine positron emission tomography-CT (PET-CT) scanning (Figure 16.15) have shown promise particularly in the setting of extra-adrenal PGLs, where conventional imaging and MIBG scanning are negative [28]. PET-CT is a nuclear medical scan combined with an x-ray CT scanner. It acquires sequential images from both devices in the same session, which are superposed (Figure 16.15). Thus, functional imaging depicts the spatial distribution of metabolic or biochemical activity in the body. Selective adrenal vein sampling has proved misleading in the case of PHAEO and is probably of very limited use.

16.5.4.2 Management
Biochemical diagnosis and localisation of PHAEO or PGL should be followed by medical preparation to control blood pressure and prompt surgical excision.

16.5.4.2.1 Preoperative Control of Blood Pressure
Surgery in the presence of undiagnosed PHAEO is associated with a mortality of between 25 and 100%; therefore, preoperative preparation to protect against catecholamine excess and triggers of secretion such as induction of anaesthesia is essential for a successful outcome. Although practice varies, alpha-adrenergic blockade with or without the addition of beta-adrenergic blockade is most commonly used. Supervised initiation of alpha blockade using oral phenoxybenzamine to control blood pressure is the first step. Once alpha blockade has been established (good blood pressure control with a postural drop >10 mm Hg and nasal stuffiness) beta blockade to control tachycardia may be commenced (e.g. propranolol). This order is important to avoid dangerous elevations in blood pressure that occur if beta blockade is commenced without blockade of alpha-induced vasoconstriction. Pharmacological treatment reduces blood pressure, allows restoration of depleted circulating volume, and takes two to four weeks. In the week prior to surgery, admission, and supervised blood pressure monitoring allows further optimisation of alpha and beta blockade to ensure normal blood pressure with a postural drop and abolition of compensatory tachycardia. Other regimens have been described, for example alpha blockade with doxazosin or prazosin, with and without beta blockade, using calcium channel blockers alone, and using the catecholamine synthesis blocker, metyrosine in the setting of cardiac failure. However, familiarity and experience with a particular pharmacological regime are probably more important than the regime itself. At this point surgery is safe to proceed.

16.5.4.3 Treatment
PHAEO and intra-abdominal PGL account for 95% of tumours and can be dealt with by laparotomy or laparoscopic surgery.

16.5.4.3.1 Adrenalectomy for PHAEO
Laparoscopic adrenalectomy is the ideal management for all PHAEOS up to 10–12 cm. In large tumours (>10–12 cm) make a transverse or vertical abdominal incision. Display the right adrenal by mobilising the colon and duodenum and retracting the liver and gallbladder upwards (Figure 16.16). On the left side, mobilise the splenic flexure and duodenum downwards and medially (Figure 16.17). For a very large left tumour a thoracoabdominal approach is used.

In common with ACC, diagnosis of malignancy requires the presence of direct invasion or metastases on preoperative imaging; if there is direct invasion, laparotomy, and en bloc excision of involved adjacent organs offers the best chance of cure. In the presence of metastases, excision of the primary tumour is still recommended to improve symptom control and improve the sensitivity of adjuvant radio-labelled MIBG and octreotide therapy.

16.5.4.3.2 Surgery for PGL
Tumours along the sympathetic chain can be technically challenging due to their posterior relationship to the great vessels and visceral arterial branches, which may hide smaller lesions. Furthermore, Type 4 hereditary PGL are associated with increased risk of local recurrence. For this reason, minimally invasive surgery may not be feasible, open surgery is the preferred option.

16.5.4.3.3 Adrenal Surgery
Preoperative Preparation As previously described, patients with functioning tumours should be managed in a multidisciplinary setting to prepare the patient for a safe operation. This team should include endocrinologist, anaesthetist, and surgeon and in some circumstances an intensivist and biochemist. The surgeon should be skilled in both the open and laparoscopic approaches and should maintain a prospective audit of outcomes. The anaesthesists should have experience in managing patients with functioning adrenal tumours. When appropriate patients should be consented about invasive monitoring and bladder catheterization.
Figure 16.15 Positron emission tomography-computed tomography (PET-CT) showing 'hot' area of pheochromocytoma.
Figure 16.16 Exposure of the right adrenal in pheochromocytoma. The liver is retracted upwards and the colon and duodenum mobilised medially.

Figure 16.17 Exposure of the left adrenal for pheochromocytoma. After taking down the splenic flexure, (a) the colon and (b) the duodenum and retracted medially.
Consideration should be given to thromboprophylaxis, prophylactic antibiotics and the probability of blood transfusion. In patients with Cushing syndrome should receive steroid supplementation.

Surgery The gold standard for adrenalectomy is laparoscopic surgery because of the advantages of smaller incisions, less pain, shorter hospital stay, and improved cosmesis [29]. There are two approaches – transperitoneal and retroperitoneal. Most surgeons favour the transperitoneal route because the surgeon is familiar with the peritoneal cavity. The retroperitoneal approach is technically more challenging, but this approach has advantages for patients with bilateral adrenal tumours and in the presence of previous extensive intra-abdominal surgery. Primary adrenocortical cancer is an absolute contraindication to either minimally invasive approach. Relative contraindications include a large size and previous abdominal surgery. Tumours greater than 5 cm are difficult to extract via the retroperitoneal route whereas the cut-off for the transperitoneal approach is around 8–10 cm.

Postoperative Care Monitoring: in addition to the standard observations, there are specific issues to consider. After removal of a pheochromocytoma the blood glucose may fall precipitously. Patients with Cushing syndrome require steroid support (either intravenous or oral). A synacthen test should be done to test the function of the contralateral gland. In Conn tumours and pheochromocytoma all antihypertensives should be stopped in the postoperative period and the blood pressure monitored.

Patients with Cushing syndrome are vulnerable to most complications including haematoma, bruising, infection, and peptic ulcer formation and complications.

References


16.6 Congenital Disorders of the Adrenals

Haemorrhage into the adrenals on one or both sides may follow a difficult labour or childbirth asphyxia. The diagnosis is usually made postmortem, the child having died of exsanguination and hypoadrenalism. Sometimes Gerota fascia will tamponade the bleeding and control it, and the child then survives with a mass which displaces the kidney downwards and may calcify later on. There may be late adrenal insufficiency.

16.7 Trauma

The adrenal is often torn during nephrectomy, when there may be bleeding from the venous sinuses of the medulla, which may need suture ligature.

16.8 Inflammation

Spontaneous haemorrhage into the adrenals occurs in the Waterhouse–Fridrichsen syndrome in septicaemic shock. Calcification in the adrenals from old tuberculosis was in former times an important cause of Addison disease – hypoadrenalism.
Part III
17

Bladder and Urethra Structure and Function

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Abstract

The embryology and anatomy of the bladder and urethra are well understood; however, the details of physiological function are an area of active research. We outline the essential points in our current understanding of bladder and urethral anatomy and physiology.

Keywords bladder anatomy; physiology; muscarinic receptors; adrenergic receptors; bladder contraction

Key Points

- The bladder and urethra develop from the caudal part of the hindgut.
- The bladder is an extraperitoneal pelvic organ.
- The bladder urothelium is distensible along with the bladder muscle and forms an effective blood–bladder barrier to prevent uraemia.
- Arterial supply is from branches of the internal iliac artery; drainage is via rich venous plexuses.
- Lymphatics drain to internal and external iliac nodes and obturator nodes.
- The urethral sphincter is deficient posteriorly.
- Relevant regions within the central nervous system are the frontal cortex, the pontine micturition centre (PMC) and Onuf’s nucleus (S2–4).
- The main purpose of the urinary bladder is to receive urine from the kidneys and act as a compliant pouch to store that urine, until such time as it is socially appropriate and convenient to void.

17.1 Anatomy

17.1.1 Gross Anatomy of the Bladder

The bladder is an extraperitoneal pelvic organ. Only the dome and part of the posterior wall of the bladder are covered by parietal peritoneum, with coils of small bowel and sigmoid above. However, when full, the bladder rises out of the pelvis and may reach the level of the umbilicus. The bladder has no anatomical capsule.

The bladder lies posterior to the symphysis pubis, separated from it by the space of Retzius or retropubic space. In the male, the bladder lies anterior to the rectum, with the fused fold of peritoneum in between (known as Denonvilliers fascia). Infero-posteriorly on each side lies the ureter, the seminal vesicle, and the vas deferens (Figure 17.1). In the female, the bladder lies anterior to the vagina and uterus, with the vesicouterine pouch (of Douglas) in between. Again, the ureter lies infero-posteriorly on either side. The female urethra lies within the anterior vaginal wall (Figure 17.2).

Laterally to the bladder are extraperitoneal fat and connective tissue, containing venous plexuses, superior and inferior vesical vessels, obturator vessels, obturator nerves, and prostatic, vaginal, or uterine vessels. Further laterally are the obturator internus muscles covered by the obturator fascia.

Inferiorly, in the male, is the prostate. Below the prostate or directly below the bladder (in the female) is the levator ani complex covered by pelvic fascia. The
levator ani comprises of the pubococcygeus, iliococcygeus, ischiococcygeus, and the coccygeus, supporting all pelvic organs and contributing to sphincteric function. Additional support is derived from various ligaments and fasciae: pubourethral ligaments in the female, puboprostatic ligaments in the male, urethropelvic ligaments running laterally, and pubocervical fascia and cardinal ligaments and uterosacral ligaments in the female.

### 17.1.2 Bladder Wall

Structurally the bladder is made up of interwoven fibres of smooth muscle (detrusor) that make up the body of the bladder (Figure 17.3). Distinct layers can only be defined at the trigone and around the bladder neck. Each detrusor muscle cell is separated from its neighbour by a basal lamina, but ‘pegs and sockets’ permit electrical excitation to pass from one cell to another. There is a rich lymphatic plexus within the detrusor muscle.

The muscle layers are lined internally by the lamina propria and an inner urothelium that acts as a protective layer. The bladder urothelium is distensible along with the bladder muscle and forms an effective blood–bladder barrier to prevent uraemia [1].

In the empty bladder, the urothelium is some six cells thick, but when distended it is only one or two cells thick. A superficial layer of umbrella cells with numerous tight junctions results in separation of solutes in the urine from the intracellular and intravascular compartments.

The lamina propria lies deep to the urothelium and consists of connective tissue and microvasculature of varying thickness. It contains the muscularis mucosae, a thin layer of myofibroblasts or suburothelial ‘interstitial cells’ distinct from the detrusor muscle.
17.1.3 Trigone, Ureters, and Bladder Neck

The base of the bladder forms the trigone, outlined by the interureteric bar, the ureteric orifices (2–3 cm apart), and the bladder neck.

The ureters enter the bladder through oblique tunnels, approximately 1.5 cm in length, which prevent vesicoureteric reflux. These tunnels have a lubricated sleeve of connective tissue allowing movement up and down through the detrusor. Outside this sleeve is a sheath of muscle – Waldeyer’s sheath – whose muscle fibres run on the outside of the trigone down to the urethra (Figure 17.4). They have fewer cholinergic nerves and more adrenergic ones than the rest of the detrusor. During micturition they contract to elongate the ureters and prevent reflux (Figure 17.5).

In the male, the bladder neck is a collar of smooth muscle which merges distally with the muscle fibres of the prostate. Both are adrenergic and contract on stimulation of the sympathetic nerves (Figures 17.6 and 17.7). There are a few elastic fibres around the bladder neck.

In the female, the bladder neck fibres merge obliquely into the wall of the urethra. They are cholinergic rather than adrenergic and play no active part in continence; indeed, in women with normal continence, the bladder neck is often found to be slightly open (Figure 17.8).

17.1.4 Arteries, Veins, and Lymphatics

The bladder is primarily supplied by branches of the internal iliac artery which divides into an anterior and posterior division (Figure 17.9). The posterior division gives the iliolumbar, lateral sacral, and superior gluteal, while the anterior division supplies three branches to the bladder (i.e. superior vesical, obliterated umbilical, and inferior vesical arteries), three to the viscera (i.e. middle rectal, vaginal, and uterine), and three parietal branches (i.e. obturator, inferior gluteal, and internal pudendal). Branches to the prostate and seminal vesicles are from the inferior vesical arteries.

The veins of the bladder drain into the vesicle plexus, which communicates with the prostatic, vaginal, or
uterine plexus, and the internal iliac, ovarian, and superior haemorrhoidal and sacral veins, providing a direct route to the bones of the pelvis and vertebrae.

The lymphatics of the bladder drain to the external and internal iliac nodes and obturator groups of nodes.

### 17.1.5 Female Urethra

The female urethra is 4 cm long and is made up of an epithelial lining, spongy submucosa full of microvasculature, a smooth muscle layer, and an outer connective tissue layer. Closure is largely achieved by the combined occlusive pressure of all four layers. The striated sphincter creates a ‘horseshoe shape’ or ‘signet ring configuration’ around the urethra at the level of the pelvic floor; it is deficient posteriorly.

### 17.1.6 Male Urethra

The male urethra measures about 20 cm in length, divided into posterior urethra and anterior urethra. The posterior urethra comprises of the prostatic urethra and membranous urethra. The anterior urethra comprises of the bulb urethra, penile (or pendulous) urethra, and fossa navicularis. The anterior urethra is surrounded by the corpus spongiosum along its entire length. Closure of the male urethra is achieved at the level of the bladder neck, prostate, and at the distinct external sphincter just below the apex of the prostate gland.
17.1.7 Neuroanatomy Relevant to the Bladder and Urethra

This will be considered in more detail in another Section (17.2.2), but by means of a summary, regions within the central nervous system which are relevant to bladder and urethral function are the frontal cortex, the pontine micturition centre (PMC) and Onuf’s nucleus (sacral micturition centre) (S2–4). The PMC is subdivided into a medial (M) and lateral (L) region. The sympathetic (T10–L2), parasympathetic (S2–4), and somatic nervous system (S2–4) all interact in the control of urine storage and voiding function.

The parasympathetic supply originates from nerve cells from the intermediolateral columns of the second to fourth sacral spinal segments (S2,3 mainly), pass through the spinal cord through the anterior primary division, called the ‘nervi erigentes’, which join the pelvic plexus. Fibres pass through the splanchnic nerves to the inferior hypogastric plexus and supply the bladder and urethra. These nerves supply cholinergic excitatory input to the smooth muscles. The parasympathetic ganglia for the bladder are located in the adventitia of the bladder and bladder base (50%) and within the bladder wall itself (50%) [2].

The sympathetic supply originates from nerve cells from the intermediolateral columns of the 10th thoracic to the 2nd lumbar segments. Fibres pass through the sympathetic chain as the hypogastric nerve and supply the bladder, prostate, and urethra. Afferent fibres convey painful stimuli such as that seen with bladder overdistention. Hence the vasovagal effect seen with a full bladder. These nerves supply inhibitory input to the smooth muscles.

The hypogastric plexus are autonomic nerves lying inferior to the bifurcation of the aorta. It is a continuation of the intermesenteric plexus of nerves. Fibres from the superior hypogastric plexus enter the pelvis and descend in front of the sacrum and merge with the pelvic splanchnic nerves on either sides of the rectum, forming the inferior hypogastric plexuses and continue descent as the pelvic plexus. The pelvic splanchnic nerves supply parasympathetic fibres. Pelvic nerves can be damaged during pelvic operations, especially bowel surgery.

The somatic innervation is via the pudendal nerve (S2,3,4) originating from the second to fourth sacral spinal segments, specifically from Onuf’s nucleus, which lies in the medial part of the anterior horn of the spinal cords, in addition to nerves from the inferior hypogastric plexus. These nerves supply the skeletal muscles of the pelvis and the muscles of the sphincter mechanism. Afferent sensory fibres from the urethra travel via the pudendal nerve.

17.2 Physiology

17.2.1 Overview

Normal bladder function is divided into storage and voiding. However, this is a purely academic division. The urinary bladder is a quintessential organic ‘machine’; once trained, it usually goes about its business with very little fuss. A ‘normal’ bladder will come to its owner’s attention for little more than one or two minutes a day.

The main purpose of the urinary bladder is to receive urine from the kidneys and act as a compliant pouch to store that urine, until such time as it is socially appropriate and convenient to void. The normal bladder fills with urine at a rate determined by input via food and drink, and fluid loss in sweat, faeces, and respiration. As it fills, there is no increase in pressure within normal bladder capacity. This is due to the compliance of the bladder wall, which is the relationship between change in bladder volume by change in detrusor pressure (expressed by the formula \( \Delta DV/\Delta DP \)). The bladder is highly compliant (minimal change in pressure despite large changes in volume) due to the bladder connective tissue’s elasticity and the smooth muscle’s ability to increase their length without any change in tension.

A sensation of filling is appreciated by most people when the bladder contains about 250 ml. At this stage, micturition can normally be postponed for a considerable time. Intra-detrusor pressure does not normally rise until the bladder contains 500 ml or more, and only then ‘urgency’ is perceived. The exact volume at which this takes place varies considerably from one patient to another.

Although the lining of the bladder is virtually water-proof, some ions and small molecules can be absorbed. Absorption by the bladder may also be altered in some diseases (e.g. bladder pain syndrome).
17.2.2 Neurological Control of Urine Storage and Micturition

There are a number of reflexes controlling urine storage and voiding, including essential coordination from the PMC. Higher centres in the frontal cortex play a largely inhibitory role during storage and activate the micturition reflex at a socially convenient time and place. The input from higher centres can override reflex activity to store or to void (i.e. micturition can be postponed despite reaching the person’s individual usual bladder capacity, and equally they can choose to void despite a fairly empty bladder).

At least four functionally relevant reflexes are known [3], all of which start with afferent impulses originating from the urothelium, the lamina propria, or the detrusor (Figure 17.10):

1) Detrusor contraction: stimulation is channelled to the PMC and then to Onuf’s nucleus. There, activation of parasympathetic neurons occurs to cause detrusor contraction via acetylcholine and M muscarinic receptors on detrusor muscle cells (M2–3 with M3 being most potent).

2) Reciprocal relaxation of the urethral sphincter: stimulation is again channelled to the PMC, Onuf’s nucleus, and parasympathetic neurons, but release of nitric oxide onto purinergic receptors in the bladder neck and urethra causes relaxation of smooth muscles.

3) Urethral pressure increase during bladder filling: stimulation is channelled directly to the sacral spinal cord, where nerves are stimulated to cause increased contraction of urethral smooth muscle.

4) Facilitation of further bladder filling: stimulation is channelled through sympathetic nerves and hence the thoracolumbar spinal cord, to then inhibit pelvic parasympathetic postganglionic neurons, preventing detrusor contraction. Sympathetic activity also directly causes detrusor relaxation via β receptors (β1–3 with β3 being most potent).

Reflexes 1 and 2 ensure complete bladder emptying. Reflexes 3 and 4 create a gating mechanism, whereby small amounts of afferent input are prohibited from being transmitted to efferent fibres.

The origin of afferent impulses and the neurotransmitters involved are an area of active research [3]. As a summary, the urothelium and myofibroblasts are linked by a nervous plexus, which together act as a stretch receptor releasing adenosine triphosphate (ATP). The majority of these afferent impulses are carried along parasympathetic nerves to the PMC as well as the cerebral cortex and communicate normal bladder filling. Afferents from the trigone travel along sympathetic nerves to the PMC and cerebral cortex, communicating definite fullness. Afferents from the urethra travel in the pudendal nerve to the same centres communicating urgency. However, M2 and M3 muscarinic receptor activity of myofibroblasts have also been found to correlate with urgency scores [4], indicating a much more complex situation in disease.

17.2.2.1 Smooth Muscle Contraction in the Urinary Tract

Smooth muscles contractions result from an increase in $Ca^{2+}$ in the sarcoplasm from either within cellular...
stores or entrance from extracellular channels. The increase in Ca\textsuperscript{2+} combined with calmodulin (abbreviation for calcium-modulated protein) forming the Ca\textsuperscript{2+}-calmodulin complex, activates myosin light chain kinase (MLCK) leading to the phosphorylation of myosin and leading to myosin contraction (i.e. smooth muscle contraction). Relaxation occurs by dephosphorylation of myosin by myosin light chain phosphatase (MLCP), which is induced by protein kinase A (PKA).

Bladder contraction is thought to be mainly mediated by acetylcholine (ACh) neurotransmission through the parasympathetic and somatic motor nerves. Muscarinic receptors are targets for ACh and are expressed throughout the urinary tract. Five muscarinic receptor subtypes are identified (m1–5); however, in the bladder M2 and M3 are predominantly expressed. M2 receptors are expressed nearly nine times as much as M3, but M3 seem to have a more pivotal role in normal bladder contractions, and M2 may have a more active role in pathological bladder contractions [5]. Similarly, adrenergic receptors (namely β receptors) mediate bladder relaxation, with β3 being the driving receptor.

M3 receptors are coupled with G\textsubscript{i} proteins, which activate phospholipase C enzyme (PLC). This, in turn, converts phosphoinositides (PIP\textsubscript{2}) to inositol triphosphate (IP\textsubscript{3}) and diacylglycerol (DAG). DAG activates protein kinase C (PKC) leading to opening of the gated calcium channels and inhibits relaxation, while IP\textsubscript{3} binds to receptors on the sarcoplasmic reticulum releasing Ca\textsuperscript{2+} from intracellular stores leading to an overall increase in intracellular Ca\textsuperscript{2+} which binds with calmodulin leading to activation of MLCK leading to myosin light chain (MLC) contraction (Figure 17.11). In the urethra, α-adrenoceptors share a common final pathway with the muscarinic receptors to lead to muscular contractions.

M2 receptors are coupled with G\textsubscript{i} protein, reduce cAMP production by influencing adenylate cyclase activity. However, β-receptors are the main drivers behind bladder smooth muscle relaxation. Stimulation of these receptors leads to increase in conversion of ATP to cAMP by activating adenylyl cyclase. Adenosine 3’5’-cyclic monophosphate (cAMP) drives calcium into the sarcoplasmic reticulum leading to muscular relaxation (Figure 17.12).

Purinergic receptors (P2 receptors) also contribute to smooth muscle function in response to release of ATP. Although contraction is mainly through ACh release, in pathological bladders, purinergic receptor-mediated contraction increase. P2 receptors are classified into families of metabotropic G protein coupled (P2Y) and ionotropic ligand-gated nonspecific cation channels (P2X) [6]. The metabotropic receptors cause bladder relaxation of smooth muscles, via cAMP-dependent PKA activity, while the ionotropic receptors cause contraction by increasing Ca\textsuperscript{2+} influx into the cell through Ca\textsuperscript{2+} channels.

Nitric oxide synthase (NOS) is formed in three tissue types, neuronal NOS, inducible NOS from macrophages, and endothelial NOS, all present in the lower urinary tract and lead to increase in nitric oxide (NO). The production of NO leads to muscle relaxation, by stimulating

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**Figure 17.11** Muscarinic and adrenergic pathways to muscular relaxation.
nitrergic receptors leading to an increase in cyclic GMP (cGMP) leading to a decrease in intracellular calcium and the ensuing smooth muscle relaxation.

The trigone, bladder base and neck, and urethra (especially in men, including the prostate) are mainly regulated by adrenergic receptors to cause muscular contractions with relative absence of muscarinic and β receptors.

References

18

Bladder Congenital Anomalies

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Abstract

This chapter will cover the breadth of congenital anatomical and functional abnormalities of the bladder and urinary tract infection (UTI) in children.

Keywords bladder abnormalities; urinary tract infection (UTI)

Key Points

- Bladder embryology
- Exstrophy-epispadias complex
- Urachal anomalies
- Bladder diverticula and bladder ears
- Megacystis
- Bladder duplication-septations-agenesis
- Urinary tract infection in children
- Urinary incontinence in children
- Nocturnal enuresis

18.1 Embryology [1, 2]

The development of the bladder takes place between the fourth and seventh weeks of gestation. The cloaca is the section of the primitive hindgut into which the embryonic ureters and the mesonephric ducts drain. A transient membrane, the cloacal membrane covers the medioventral part of the cloaca. Mesodermal ingrowth between the ectodermal and endodermal layers of the bilaminar cloacal membrane results in formation of the lower abdominal musculature and pelvic bones. Between the fourth and sixth weeks of gestation, the cloaca is compartmentalised by the descending urorectal septum and the ingrowth of the folds of Rathke laterally into the urogenital canal (or primary urogenital sinus) anteriorly and the anorectal canal posteriorly. The primary urogenital sinus then develops into the vesicourethral canal which forms the bladder and the prostatic part of the urethra and the definitive urogenital sinus which forms the urethra, with differences between males and females. During this period, the mesonephric ducts migrate caudally, and their fusion forms the vesical trigone before they join the prostate forming the ejaculatory ducts. The detrusor is the smooth muscle that constitutes the bladder wall, and it is created by the differentiation of the adjacent mesenchyme of the pelvis (i.e. splanchopleural mesoderm) in response to induction with contact with the embryonic urothelium. The dome of the bladder is in continuation with the allantois which progresses into the urachus. Later on, the urachus obliterates and forms the medial umbilical ligament. When the descending urorectal septum reaches the cloacal membrane, their fusion creates the perineal body. The cloacal membrane eventually ruptures, forming the urogenital and anal orifices.

18.2 Exstrophy-Epispadias Complex

The failure of development of the lower abdominal wall during early foetal development is believed to give rise to a spectrum of abnormalities, which are described as exstrophy-epispadias complex. Three distinct anomalies comprise this complex: bladder exstrophy, epispadias, and cloaca exstrophy.

Their pathogenesis is believed to depend on the stage of development when the cloacal membrane ruptures.
This premature rupture is attributed to the failure of the migration of the mesoderm between the layers of the endoderm and the ectoderm of the cloacal membrane. If the membrane ruptures before the completion of the urorectal septum's descent, the distal bowel, bladder, and urethra are not compartmentalised giving rise to the anomaly of cloacal exstrophy. Rupture of the membrane later on, after the separation of the urogenital and anal canals is believed to lead to an open bladder and urethral plate, and if it occurs later in development, only the urethra and bladder neck remain open, giving rise to the epispadias anomaly. Various theories have been proposed to explain this embryological anomaly; however, it remains a source of controversy [2, 3].

18.2.1 Bladder Exstrophy

Bladder exstrophy is very rare. Its incidence is 1:50000 with a male to female ratio of 3:1 [4]. Antenatal diagnosis is difficult with characteristic non-visualisation of the bladder, accompanied by a low-set umbilical cord, a short phallus, and an irregular lower abdominal wall (Figures 18.1 and 18.2). Antenatal counselling of the parents is necessary so that they understand the nature and implications of bladder exstrophy, the surgical management, and long-term outcome [2].

The clinical features of bladder exstrophy is related to its pathogenesis (Figure 18.1–18.4): [4]

1) The bladder is open to external environment along with the anterior abdominal wall, and so is the urethral plate with a visible verumontanum in males and a short open urethra running between the open bladder and the vagina in females. The ureters drain directly onto the open bladder plate; the ureteric orifices are laterally placed which can lead to vesicoureteric reflux (VUR). If neglected, the exposed urothelium undergoes intestinal metaplasia.

2) There is a low-set umbilicus cranially with associated umbilical hernias, split (diversification) rectus abdominis muscles laterally, and an open pelvic ring caudal to the open bladder plate.

3) The symphysis pubis diastasis (widening) can vary, reaching a defect of up to 5 cm in newborns with severe forms of exstrophy. This is due to external rotation of the pelvic bones along the sacroiliac joints.

4) The corpora are separate and attached to the inferior border of the ipsilateral inferior pubic rami. This leads to a shortened, broad, and open penis with deficiency of dorsal foreskin in males, and separate, bifid clitoral bodies and the urethra barely present, short vaginal canals, and can lead to uterine prolapse in females.

5) The anus is anteriorly placed due to the abnormal development of the anterior abdominal muscles. There might be associated rectal prolapse, compounding faecal incontinence.

6) In the male, the urethra is represented by a strip of urothelium on the dorsum of a short, broad, up-turned penis. The testicles are undescended. Inguinal hernias are a common association (80% in boys, 15% in girls).

7) Superior vesical fissure: Here the exstrophy is restricted to the apex of the bladder. The remainder of the bladder is correctly formed (Figure 18.5).
18.2.1.1 Management

The suspected defects can be seen on prenatal ultrasound, which can help with parental counselling and planning of delivery and further management.

After birth, the bladder plate is covered with cling-film, the umbilical cord clamp is replaced with a suture tie to avoid trauma to the bladder plate, and the neonate is transferred to appropriate paediatric urology referral centre. Closure is advisable in the first few days of life; however, it can be delayed in cases of premature babies that need a long period of stabilisation and growth.

Preoperative work-up should include a baseline renal ultrasound and routine blood tests. Other congenital abnormalities are not common with bladder exstrophy. Vitamin K should be administered to the neonate and antibiotic cover is not necessary. As neonates with this condition are usually healthy otherwise, intravenous access is not required preoperatively and the babies can breastfeed [4].

18.2.1.2 Surgery

18.2.1.2.1 Primary Closure of Bladder Plate and Reconstruction of the Lower Abdominal Wall

The primary closure of bladder exstrophy is performed under general anaesthesia and an epidural catheter is preferable because it provides excellent postoperative analgesia.

The primary bladder closure, lower abdominal wall reconstruction, and approximation of the pubic bones are generally achievable without osteotomies in early closure. For delayed closures (which is practiced in several centres across the world) or in cases with wide pubic diastasis, pelvic osteotomies with external fixators are needed. Inguinal hernias are repaired during this procedure when present. Complications after bladder closure include partial or complete wound dehiscence, a tight closure with outflow obstruction, and upper tract dilatation, which in combination with UTIs, may lead to renal damage [4, 5].
18.2.1.2.2 Continence Procedures

In females, the primary closure is rarely adequate to achieve continence, and in the majority of patients with bladder extrophy, secondary procedures will be necessary for continence and genital reconstruction to achieve continence and cosmesis [6].

Three surgical approaches are currently followed in various part of the world:

1) Complete primary repair of bladder extrophy (CPRE) [7–16]. Mitchell suggested a complete anatomical reconstruction at the time of the primary closure. The bladder plate is fully mobilised and the bladder neck, urethra, and penis are reconstructed in one setting. This technique is thought to create a bladder outlet resistance early in life, allowing for bladder cycling and growth. The division of the intersymphyseal ligaments allows the appropriate anatomic placement of the bladder neck and posterior urethra deep into the pelvis in its orthotopic position.

Patients whose bladder does develop will likely undergo fewer procedures than in a staged fashion. Continence has been reported after CPRE to be 76%, defined as dry intervals longer than two hours and spontaneous voiding without catheterization. However, a significant percentage of patients will likely still require a formal bladder neck procedure to achieve continence. There are concerns with this technique related to a high-pressure lower urinary system and VUR, urinary tract infections (UTIs), and renal scarring and damage. There is also rare risk of penile injury with loss of glans or penile skin or tissue with penile reconstruction at such a young age, and requirement for multiple procedures despite the name ‘complete repair’. Approximately 36–68% of patients will be left with a hypospadias after CPRE that will require further penile surgery.

2) Modern Staged Reconstruction of Exstrophy (MSRE) [16–24]. Jeffs and Gearhart advocated MSRE, which has been the standard approach for many centres for many years. It includes an initial primary closure followed by a modified Cantwell-Ransley epispadias repair in the first 6–12 months of life. The bladder is mobilised (Figure 18.6). The edges of the mobilised bladder and urethra are rolled in to make a new bladder and urethra. The tissues on either side of the bladder neck are mobilised and sewn together. To help closure, an osteotomy is performed through the iliac bone just lateral to the sacroiliac joint. A second operation may be necessary a few years later to achieve continence (Figure 18.7).

The ongoing incontinence is considered to preserve renal function and at the same time, the bladder may develop with the presence of some outlet resistance. The bladder neck repair (i.e. Young-Dees-Leadbetter) for continence is performed between five and nine years of age, when an adequate bladder capacity is achieved, and the patient and family desire continence. Ureteric reimplantation is carried out at this stage through long submucosal tunnels to prevent reflux.

If the bladder capacity is not good, the patient is left incontinent until the bladder grows and maturity improves or diversion with augmentation with a catheterisable channel and bladder neck closure when necessary, which is also the procedure of choice in the case of failed bladder neck reconstruction, is used.

Day and night-time continence of can reach about 75%, with the patients voiding per urethra without augmentation or intermittent catheterization. Social continence, defined as dry for more than three hours during the day but damp at night, was found in a further 10%. Patients with a mean capacity greater than 100 ml at the time of the bladder neck reconstruction had better outcomes. In males after closure, epispadias, and bladder neck reconstruction, the total complication rate was 41.7%, and in females after bladder closure and bladder neck reconstruction, the total complication rate was 19.5%. In a series of successful bladder growth 19.4% of males and 17% of females had failed bladder neck reconstruction and have undergone or will require an augmentation with a catheterisable stoma and bladder neck closure as indicated. Major complications are reported at 11% (e.g. bladder dehiscence or prolapse, orthopaedic or neurological complications) and minor complications again at 11% (i.e. bladder outflow obstruction [BOO], urethrococutaneous fistula, surgical site infection, UTIs, etc.).

3) The Kelly procedure (radical soft-tissue mobilisation) [4, 5, 25, 26]. This surgical technique for continence that was first advocated by J. H. Kelly in the 1980s. Its concept is that continence in bladder extrophy can be achieved by repairing the disorganised pelvic floor musculature involved in normal continence. An examination under anaesthesia and cystoscopy is carried out at three months after bladder closure to assess the anatomy, capacity, and outlet. The Kelly operation is carried out after the age of nine months. It is performed irrespective of bladder capacity. The bladder is opened in the midline and bilateral ureteric reimplantation (Cohen) is performed. The pelvic floor, penile corpora bodies, and urethra are radically mobilised. The penile corpora along with the perios- tum are mobilised off from the lower border of the inferior pubic rami with great care to the pudendal nerves and vessels that must be preserved as they run through Alcock canal. Then the penile corpora can be completely mobilised towards the midline, thus increasing their length and protrusion. The urethral
Figure 18.6 Jeffs’ method of closure of exstrophy. First stage – performed in the neonate. (a) The skin incision excises the necrotic umbilicus. (b) The incision is carried round the margin of the bladder. Two flaps are formed inferiorly. The urogenital diaphragm is separated from the symphysis on each side and the corpora cavernosa are mobilised. (c) The skin flap on the left is sewn to the edge of the prostatic urethra. (d) The skin flap on the right is sewn to the prostate. (e) The mobilised bladder and prostate is rolled in (f) and reinforced by the urogenital diaphragm. (g) The incision is closed leaving an epispadiac urethra.
plate is dissected from the corpora and glans. A bladder neck repair is performed with excision of two small mucosal triangles lateral to the verumontanum. The tubularisation continues distally, and if the penile length is not compromised, a complete reconstruction of the penis and urethra could be carried out. However, the urethra is usually deemed short, and therefore, brought to a perineal position in males. The perineal muscle is wrapped around the proximal urethra, in an attempt to recreate the sphincter. The corpora are externally rotated to correct the dorsal chordee and joined in the midline. The glans is reconstructed and the shaft skin cover provided. The abdominal wall is closed.

In girls, the clitoral corpora are similarly mobilised, with the labia minora attached. The pelvic floor is mobilised and the pudendal nerves are again identified and preserved. After the bladder neck repair, the pelvic muscle is wrapped around the urethra and vagina. The clitoral bodies are brought together in the midline.

The hypospadiac meatus in boys can be repaired in two stages with the use of buccal, labial, or posterior auricular grafts in the future. In girls, no further genital reconstruction is required.

Although published follow-up data are limited, good continence outcomes in patients with spontaneous voiding are reported with the Kelly procedure. Continence (complete or partial) is reported in 63.5–70%. In a not as yet published series that was presented at the European Society for Paediatric Urology (ESPU) conference 2015, the Paediatric Urology team of Great Ormond Street Hospital reported 64% spontaneous voiding continence in boys and 79% in girls five years after the Kelly operation in patients who also underwent the primary closure of bladder extrophy at the same institution. Pelvic floor exercises and biofeedback is applied to the patients when they are old enough to cooperate to enhance the function of the pelvic floor muscles. Complications after this procedure include fistula formation (10%), vulval scarring and dehiscence (5%), recurrent UTIs (59%), urethral stricture (7%), wound dehiscence (11%), and infective bladder calculi (7%). Renal scarring on nuclear medicine scans was 10%, urethral clean intermittent catheterization (CIC) was performed in 3.5%, and bladder augmentation was carried out in 10% of patients in the Great Ormond Street Hospital series. Penile injury and glans loss is extremely rare and erectile dysfunction has not been reported [25–29].

The complexity of bladder extrophy and its surgery mandates that the management of patients with this condition should be done at extrophy centres of excellence and by multidisciplinary teams with standardised assessments and management regimens.
18.2.2 Epispadias

When the cloacal membrane is less extensive (Figure 18.8), its dissolution leaves a defect in the urethra that may be restricted to the glans or may form a strip along the short curved penis. The urethral meatus opens onto the dorsal penis, either in the glans, penile shaft, or in the penopubic region (Figure 18.9).

In males, epispadias is associated with dorsal chordee with incomplete foreskins, dorsally. The leads to an upward curvature and a hooded glans. In females, there is a bifid clitoris and poorly developed labia. There is associated urethral sphincter disruption leading to incontinence. Incidence in males is 1:120,000 and in females 1:400,000.

18.2.2.1 Surgery of Epispadias

Surgical repair of these genital anomalies are usually performed during the first two years of life. The aims of epispadias surgery in boys are to correct the dorsal chordee, to reconstruct the urethra and relocate it ventrally, and to redistribute the skin around the penis to cover the dorsal skin defect at 6–18 months of age. The most commonly used techniques are those described by Ransley, Mitchell, and Kelly.

The Cantwel-Ransley epispadias repair is widely used. The incision begins in the midline above the urethral opening and is extended dorsally on each side of the urethral plate and ventrally circumferentially the penis is degloved and the urethral plate, the neurovascular
bundled and each corporal body are fully mobile except for their granular part. The urethral plate is tubularised and a MAGPI type plasty (i.e. IPGAM) of its distal end allows ventralisation of the future urethral meatus. The corpora are then rotated and approximated. The skin shaft cover is performed with a transverse flap of ventral skin dissected with its pedicle and transferred to the dorsal side of the penis [30–32].

Mitchell’s technique is based on a complete disassembly of the penile structures which allows a tubularisation and ventralisation of the entire urethra, and a more complete release of the corporal rotation. The corpora cavernosa are completely separated from each other with their corresponding hemiglans. The urethral plate is dissected off of the corporeal bodies, tubularised, and transferred ventrally. The corpora entirely separated and independent are rotated to correct the dorsal chordee and sutured together. The glans halves are subsequently brought together [33–36].

In the severe forms of epispadias, where the bladder neck is inadequate, and the phallus short and severely curved, the Kelly procedure is more appropriate. At the same time, it offers penile lengthening and protrusion because the postoperative cosmetic appearance of the penis which often looks short and buried. In girls, the open urethral plate extending from the bladder neck to the medial aspect of both hemi-clitori anteriorly, and to the anterior vaginal edge posteriorly, is separated from the adjacent structures up into the perineal muscles and subsequently tubularised. The perineal muscles located in front of and between the neo-urethra and the vaginal orifice are both sutured together. This manoeuvre significantly increases the bladder outlet resistance and aids to social continence in most cases. The Kelly procedure is also used to offer continence and external genital reconstruction simultaneously [37].

18.2.2.2 Continence Surgery

The degree of incontinence is quite variable in children with epispadias and is analogous to the severity of the epispadias. Often, patients who have had epispadias repair require additional procedures to become continent. The injection of biocompatible substance in the bladder neck may offer a less invasive but usually transient solution, with only 30–40% continence rates reported with several years of follow-up. Although immediate results can be encouraging, continuous deterioration with increased leakage is common. It does not seem that the type of bulking agents used makes a significant difference [38].

Bladder neck reconstruction (i.e. Young-Dees-Leadbetter) is usually performed after the age of three or four years, if the bladder capacity is deemed adequate (usually >100 ml). Experience shows that this challenge is rarely achieved in the exstrophy group, although results are better in the epispadias group because the bladder behaviour is probably more normal. This technique often leads to ‘obstructive’ micturitions and retrograde ejaculations related to the deficient sphincter mechanism [39, 40].

The artificial urinary sphincter insertion around the exstrophy-epispadias complex bladder neck has also been used with poor results. There is a much higher risk of erosion in a reconstructed bladder neck and urethra. The artificial sphincter is therefore not a front-line solution in the exstrophy-epispadias complex [41]. For persistent incontinence, bladder neck closure with urinary diversion in the form of a Mitrofanoff channel with or without bladder augmentation (depending on bladder capacity and compliance) is the final continent procedure [40, 42–44].

18.2.3 Cloacal Exstrophy

Cloacal exstrophy is the most severe abnormality in the exstrophy spectrum that is compatible with viability. It is extremely rare, occurring in 1 in 200000–400000 live births. The male to female ratio has been reported in a large contemporary study to be equal between the sexes, 1:1 [4, 45].

Prenatal diagnosis is possible and based on major criteria (i.e. non-visualisation of the bladder, a large midline infra-umbilical anterior wall defect or a cystic anterior wall structure, an omphalocele and a myelomeningocele) and minor criteria (i.e. lower extremity anomalies, renal anomalies, ascites, widened pubic arches, narrow thorax, hydrocephalus, and a single umbilical artery) [46].

When a prenatal diagnosis is made, parents should be counselled by an experienced exstrophy surgeon and referred to an exstrophy centre of excellence for delivery whenever possible [47].

Cloacal exstrophy includes findings of exstrophy of the hindgut and bladder complex (Figure 18.10), bifid phallus, wide pubic diastasis, prolapsing terminal ileum and proximal colon, imperforate anus, and an omphalocele (Figure 18.11). When seen coexisting with omphalocele, imperforate anus, and spinal defects it is considered part of the OEIS complex [48]. The lower urinary tract is typically composed of two hemi-bladders exstrophy on either side of the midline each with its ureteric orifice and rudimentary phallus. Between them, a length of intestine with two openings represents the ileocaecal region a characteristic elephant trunk appearance. The upper opening leads into the ileum and discharges small bowel content; the lower one leads into a loop of large bowel, which ends blindly in front of the sacrum. There maybe one or two appendices. The anus is imperfect, and there is usually spina bifida. Variations, however, are frequent.
Abnormalities from other systems are common and involve the nervous system (spina bifida), skeletal anomalies, gastrointestinal anomalies (e.g. omphalocele, malrotation, bowel duplication, duodenal atresia, duodenal web, Meckel’s diverticulum, and short gut syndrome), upper urinary tract anomalies (e.g. pelvic kidneys, renal agenesis, hydronephrosis, hydroureter, multicystic dysplastic kidney (MCDK), fusion anomalies, ectopic ureter, ureteric duplication, congenital stricture, and megaureter), genital tract anomalies (e.g. uterine duplication, bicornuate uterus, vaginal duplication, vaginal agenesis, and undescended testes) and cardiovascular and pulmonary anomalies (e.g. cyanotic heart disease, aortic duplication, vena caval duplication, bilobed lung and an atretic upper lobe bronchus) [4, 45, 49–51].

Management of these complex patients should be carried out in a specialised exstrophy centre. The bowel and bladder plates should be kept covered with a clear cling film wrap as for bladder exstrophy. Often the severity of cloacal exstrophy is enhanced by the nature and severity of the associated anomalies and these in turn may delay the surgical management for several months. Immediate management is intended to medically stabilise the newborns that are usually premature.

A renal and spinal ultrasound (and if needed a spinal magnetic resonance image [MRI]) should be carried out early along with full blood tests and assessment for cardiac anomalies [52]. Optimal feeding to establish growth is necessary. Evaluation should involve a multidisciplinary team to perform an assessment of all the comorbidities and plan the short- and long-term reconstruction. Decisions should only be made after appropriate parental counselling and education. This often will require a chromosomal analysis. As surgical techniques for phallic reconstruction have evolved, a functional and cosmetically acceptable phallus can now almost always be constructed, and it is the general consensus amongst experts that it is important to assign gender that is consistent with karyotype [51].
In patients with spinal conditions, a neurosurgical evaluation and closure should be undertaken as soon as the infant is medically stable. Long-term follow-up is important because up to 33% of children can have symptomatic spinal cord tethering [53].

One of the important decisions to make during the initial operative planning is whether to perform a one- or two-stage closure [54–56]. A one-stage repair is preferred, if possible, to minimise the number of neonatal procedures necessary and also allow the bladder to be closed, reducing the risk of trauma and polyp formation, and potentially improve its chances at normal development. During either a one- or two-stage procedure, an omphalocele if present, is excised; the extrophy plate is dissected from the skin and rectus abdominis muscles laterally; and the bowel is carefully separated from the hemi-bladders. The hindgut is tubularised and brought out as an end colostomy usually onto the left iliac fossa. The location of the stoma should be such to allow for an effective placement of an appliance. Ileostomies have been widely used in previous years, but they have been associated with malabsortion and nutritional problems. The hemi-bladders are approximated in the midline to create a single bladder plate, which may then be closed as in primary bladder extrophy closure. Bilateral ostetomies are performed because usually the closure is delayed and the pubic diastasis is wide. These should allow for a tension-free closure, but if this is not possible, then the use of a silo to cover the residual abdominal wall defect is advisable. In cases where a two-staged approach is decided (i.e. in the presence of a large omphalocele defect and respiratory or haemodynamic instability etc.), bladder closure and osteotomy may be delayed until respiratory and gastrointestinal stability are achieved [57, 58].

Preserving as much bowel tissue possible is essential to enhance absorption and avoid complications of short bowel, thus helping the survival rate of these patients [59]. Parenteral nutrition is necessary until enteric feeds are established. Also, any possible distal bowel and appendices should be preserved because they may be used for future reconstruction and stoma formation. When the child is older and if an adequate hindgut exists and there are no neurologic deficits, then a pull through procedure could be performed via the posterior sagittal approach. The majority of these patients however have been reported incontinent of faeces [4, 45].

Patients with cloacal extrophy are incontinent for urine. Intermittent catheterization is likely to be needed for emptying especially in the presence of spinal defects. Surgery to produce a continent reservoir should be delayed until the child is old enough to participate in self-care. The choice between a catheterisable urethra and catheterisable stoma should be made according to the adequacy of the urethra and bladder neck, bladder capacity, gender, and orthopaedic status [60, 61].

In males with cloacal extrophy, reconstruction of the penis is challenging. However, when adequate corporal tissue is present, epispadias repair can be performed at the same time of initial closure or later [62]. Also, when performed by experts, the Kelly procedure offers a great perspective in the cosmetic appearance of the external genitalia of boys [4]. Genital reconstruction in girls is usually done at the time of bladder closure and osteotomy. It is acceptable to leave the vaginas in situ, but further surgery will be needed to bring one of these to the perineum.

### 18.3 Urachal Anomalies

The progressive obliteration of the urachus is usually complete by the 28th week of gestation. A small remnant proximal to the bladder may be present in 10% of adults [63]. This is called a vesico-urachal diverticulum and is asymptomatic; very rarely it can be cause of infection or stone formation due to urinary stasis within. After its obliteration, the urachus represents the median umbilical ligament. Should the process of obliteration fail, then urachal anomalies occur (Figure 18.12). These are rarely seen in 1% of paediatric population (1 in 5000–7000 births), and they present as a patent urachus (20%), a urachal sinus (35%) or a urachal cyst (45%), depending on whether there is complete or partial patency of the urachus [64].

#### 18.3.1 Patent Urachus

There causes continuous or intermittent drainage of sero-sanguineous or purulent fluid from the umbilicus. If the umbilicus becomes infected, then there is perumbilical swelling, tenderness, and drainage. It is correlated to a BOO in 14% of cases, and in these cases, it acts as a ‘pop-off’ mechanism. The diagnosis of a patent urachus can be done with ultrasonography and Micturating cystogram, which is also necessary to exclude BOO (Figure 18.13). A patent urachus needs to be excised. The excision is done through an extraperitoneal approach and the urachus needs to be excised completely, including a part of the bladder dome.

#### 18.3.2 Urachal Sinus

This represents incomplete closure of the urachus with an ‘opening’ distally towards the umbilicus. Episodic infections of the sinus can lead to purulent drainage from the umbilicus and periumbilical tenderness. Usually it presents as a ‘wet’ umbilicus or a persistent granuloma after multiple cauterisation with silver nitrate. It can be diagnosed with ultrasonography or sinography is possible. In difficult diagnostic cases, a computed tomography
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(CT) or MRI maybe required. Treatment is again complete excision if the sinus persists for more than two months [65, 66].

18.3.3 Urachal Cyst

This presents as a fluid-filled structure between the two obliterated ends of the urachus and is usually located in the distal third of the urachus. It is usually an incidental finding, or it can present as a suprapubic mass with fever, pain, and dysuria. In delayed diagnosis, the cyst may rupture towards the peritoneum, causing acute abdomen and peritonitis. The most common organism isolated is *Staphylococcus aureus* (in >50% of cases) [67]. The diagnosis is again set with ultrasonography, CT, or MRI, and the treatment is surgical excision. For very inflamed cysts, initial incision and drainage (two-stage approach) is preferable [67, 68].

The surgical excision of urachal anomalies can be done through an open or laparoscopic approach [68–70]. Lately robotic-assisted surgery has also been used [71]. The decision relates to the surgeon’s experience and the degree of inflammation [72–75]. The treatment of asymptomatic remnants remains controversial, but it is suggested that the presence of microcalcifications seen in imaging is in favour of excision [67, 75]. These calcifications seem to be related to chronic inflammation, which maybe in turn a predisposing factor for carcinogenesis. Urachal cancer is very rare (0.35–0.7% of bladder cancer) and extremely rare in childhood. Carcinoma of the urachus in the adult presents with haematuria. Cystoscopy shows a cherry-sized lump at the air bubble, and a much larger mass outside it; biopsy reveals adenocarcinoma. Primary urachal rhabdomyosarcoma has been reported and carries a poor prognosis. It is more

Figure 18.12 Complications of a persistent urachus. (a) It may cause a urinary fistula if associated with outflow obstruction from urethral valves. (b) There may be a midline cyst which may become infected. (c) Carcinoma arising in the urachus presents in the bladder at the apex and erodes early into the peritoneal cavity.

Figure 18.13 (a) and (b) Patent urachus. Source: Courtesy Prof Sandesh Parelkar, K.E.M Hospital, Mumbai.
common in childhood and especially older than the age of 40 [76–79]. Therefore, many surgeons favour preventive removal of urachal remnants when diagnosed.

### 18.4 Bladder Diverticula

The incidence of bladder diverticula is 1.7%. They represent a herniation of the bladder mucosa through the detrusor [80]. They can be congenital or acquired. Congenital diverticula are usually solitary and usually located near the ureteric orifice [81]. Acquired diverticula are usually multiple, and they are secondary to BOO, recurrent infections, or can be iatrogenic. The most common causes are urethral valves, urethral strictures, neuropathic bladders, detrusor-sphincter dys-synergy, or can occur after anti-reflux surgery. Bladder diverticula are also associated with Ehlers-Danlos syndrome [82].

Diverticula can present with UTIs, VUR (8–13%), ureteric obstruction (5%), or BOO. The presentation depends on their site and size. The cases of the ureteric orifice situated within the diverticulum are associated with VUR, and in 15–33% of cases, there is some degree of renal dysplasia. Diverticula are also related to voiding dysfunction, but there is always a dilemma of cause versus effect correlation. Urinary stasis within the diverticulum may cause the formation of stones or epithelial dysplasia [81, 83].

The diagnosis is set with ultrasonography, Micturating cystogram and cystoscopy (Figure 18.14). Treatment is mandatory when diverticula are symptomatic, and it includes open or laparoscopic or vesicoscopic excision of the diverticulum with ureteric reimplantation where indicated. BOO must always be excluded and treated prior to any surgery for the diverticulum [80–83].

#### 18.4.1 Bladder ‘Ears’

Innocent protrusions of the bladder are normal in male infants and common in women. In the adult male, they commonly accompany an inguinal hernia into the inguinal canal.

#### 18.4.2 Megacystis

This is a very rare abnormality that can present antenatally, postnatally on ultrasound, or with UTIs. It is associated with high-grade VUR. It can also be related to other conditions such as posterior urethral valves, Ehlers-Danlos syndrome, and urethral diverticula. It can also be a manifestation of megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), which is characterised by neonatal abdominal distension due to bowel dilatation, severely dilated bladder, and severely dilated ureters. The causes of this rare syndrome are not known. Myogenic, neurogenic, or hormonal factors may be involved. It presents more commonly with functional neonatal intestinal obstruction and urinary retention [84]. There is clear preponderance of females, 70.6 vs. 29.4% in 227 MMIHS cases [85]. The survival rate is about 20% with the oldest survivor being 24 years old. Outcomes seem to be improving with the introduction of long-term total parenteral nutrition (TPN) and multi-organ transplantations.

Bladder duplication is extremely rare. It can be partial or complete, with the duplication being in the sagittal or coronal plane. In complete duplication, there are two hemi-bladders usually in a sagittal plane, with the corresponding ipsilateral ureter draining within each hemi-bladder and in continuation with a duplicated urethra. Associated anomalies include a duplicated penis, duplicated vagina and uterus, vertebral anomalies (usually lumbar), and hindgut anomalies. Often rectovesical, vesicovaginal, or vesicourethral fistulae are present.

Figure 18.14 (a) and (b) Bladder diverticulum before and after bladder emptying.
Diagnosis can be made with ultrasound, micturating cystourethrogram (MCUG), and cystoscopy, and treatment is necessary if there are symptoms such as urinary incontinence, UTIs, or upper tract obstruction [80, 86, 87].

Bladder septations are fibromuscular or mucosal septations that divide the bladder into equal or unequal compartments. They are diagnosed when they are symptomatic because of complications such as upper tract drainage impairment. They are diagnosed with MCUG and ultrasound.

Bladder agenesis is extremely rare and incompatible with life. Twenty-three cases have been reported in live births, and all were female infants. In the absence of the bladder, the ureters are seen draining into the urethra, vagina, Gartner’s duct in girls, or the rectum. The urachus may stay patent. They are associated with hydrourteronephrosis, renal dysplasia or agenesis, agenesis of the prostate, seminal vessels, penis, or vagina, and spinal, orthopaedic or hindgut anomalies. Diagnosis is made with ultrasound, MCUG, and MRI. In infants that survive, diversion is essential as initial management, and later in life, a neo-bladder can be constructed [88–90].

18.5 Disorders of Development of the Sacrum

18.5.1 Sacral Agenesis

These are exceedingly rare and represent a variation on the theme of failure of development of the neural canal. The child is born with an absence of most of the sacrum, and a lesion of the cauda equina leading to a neuropathic bladder. The diagnosis is obvious from a plain radiograph of the pelvis, but it is all too easy to miss the absence of the sacrum.

18.5.2 Presacral Dermoid

A congenital neural canal defect leads to the formation of a dermoid cyst between the sacrum and the rectum. Clinically, they may present with bizarre symptoms, few of which are serious unless the cyst becomes infected. On rectal examination, a large mass is found. Surgical intervention is only required if the cyst is causing obstruction or is associated with a cauda equina lesion and carries a high risk of producing a neuropathic bladder even if not already present.

18.6 UTI in Children [91, 92]

UTI is one of the most common causes of referral to paediatric urology unit. As such, standard guidelines have been developed to aid management [91–93]. Epidemiology and pathophysiology [91–93]:

UTIs in the first 3 months of life occurs in 4% of boys and 2% of girls; in the first 10 years the incidence changes to 1% in boys and 3% in girls; and changing to 0.5% in boys and 5% in girls during school years. Uncircumcised boys have a higher incident of UTIs.

Though majority of UTIs are successfully treated with no long-term consequences, a minority will develop renal scarring, especially infants. This can lead to hypertension, proteinuria, renal impairment, or even renal failure in adult life.

Most common organism is *Escherichia coli* and is responsible for >90% of UTIs; however enterococcus, *Pseudomonas, Klebsiella*, and *Proteus* spp. and *Staphylococcus epidermidis* can all be causative agents.

The infection of the urinary tract is most commonly due to ascending infection and any condition predisposing for this increases the risk of infection.

Risk factors for UTIs:

- previous UTI.
- premature birth (due to immature immune system), poor growth, or malnutrition.
- congenital anomalies (e.g. pelvic-ureteric or vesicoureteric obstruction, ureterocele, VUR, posterior urethral valves, enlarged bladder, or spinal anomalies).
- functional anomalies (voiding dysfunction and chronic constipation).

18.6.1 Classification

UTIs can be divided based on site:

- Lower urinary tract (LUT) or cystitis: dysuria, frequency, urgency, malodorous urine, enuresis, haematuria, or lower abdomen or suprapubic pain.
- Upper urinary tract (UUT) or pyelonephritis: fever, chills, or flank, back, or lower chest pains. Symptoms of LUT may also be present.

Classified according to severity:

- Typical UTI: could be asymptomatic or symptomatic;
- Simple UTI: low-grade pyrexia with mild dehydration; generally, well.
- Severe UTI: high-grade pyrexia (>39°C), vomiting, moderate to severe dehydration; unwell.

Atypical UTI: seriously ill, non-*E. coli* infection, poor urinary flow, deranged renal function, abdominal or bladder mass, septicaemia, and failure to respond to treatment within 48 hours.

Classification according to episode:

- A single infection is treated successfully and does not recur. However, it can be a sign an underlying condition.
- Recurrent UTIs could be due to bacterial persistence, unresolved infection (due to noncompliance with treatment, subtherapeutic antimicrobial level, malabsorption,
or resistant organism), or reinfections and must be one of the following:

- one episode of cystitis with one episode of pyelonephritis.
- ≥2 episodes of pyelonephritis.
- ≥3 episodes of cystitis.

The clinical presentation of the UTI in children varies and is summarised in Table 18.1 [91].

<table>
<thead>
<tr>
<th>Age group</th>
<th>Symptoms and signs Most common &gt; Least common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants younger than 3 months</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
</tr>
<tr>
<td>Infants and children, Preverbal 3 months or older</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>Frequency</td>
</tr>
<tr>
<td></td>
<td>Dysuria</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

Source: From NICE guideline.

A urine culture is the gold standard for diagnosis of UTI; however, it is only as good as the collection method. It is important to take into consideration the sample collection method while interpreting the culture reports (Tables 18.2 and 18.3).

A clean catch urine sample is the recommended method for urine collection. If a clean catch urine sample cannot be obtained, other noninvasive methods such as urine collection bags should be used. When it is not possible or practical to collect urine by noninvasive methods, catheter samples or suprapubic aspiration (SPA) under ultrasound guidance should be used.

In an infant or child with a high risk of serious illness, it is highly preferable that a urine sample is obtained; however, treatment should not be delayed if a urine sample is unobtainable.

If urine is to be cultured and it cannot be cultured within four hours of collection, the sample should be refrigerated or preserved with boric acid immediately.

18.6.3.2 Clinical Differentiation between Acute Pyelonephritis (Upper Urinary Tract Infection) and Cystitis (Lower Urinary Tract Infection) [91]

Infants and children who have bacteriuria and fever of 38°C or higher should be considered to have acute pyelonephritis or upper UTI. Infants and children presenting with fever lower than 38°C with loin pain or tenderness and bacteriuria should also be considered to have acute pyelonephritis or upper UTI. All other infants and children who have bacteriuria but no systemic symptoms or signs should be considered to have cystitis or lower UTI.

18.6.3.1 Urine Collection and Interpretation [91]

Urinary dipstick testing is only a screening test for UTI. It has poor sensitivity and specificity, especially in children younger than three years of age.

18.6.2 History and Examination

The history is focused on enquiring about symptoms to distinguish between primary or recurrent infection. Also looking for risk factors for UTIs. The child should be examined from head to toe, looking for palpable masses, lymph nodes, tenderness, phimosis, labial adhesions, and stigmata of spina bifida or sacral agenesis.

18.6.3 Investigations

Infants and children presenting with unexplained fever of 38°C or higher with or without the symptoms and signs suggestive of UTI should have a urine sample send for culture irrespective of the urine dip and microscopy result.
18.6.4 Radiological Investigation

(Table 18.4)

18.6.4.1 Ultrasonography
In presence of UTI acute ultrasound (within 24 hours) is indicated in all of the following situations (to rule out obstruction specifically):

a) Sick child needing hospital admission and or parenteral antibiotics.

b) Deranged renal function test.

c) Not responding to suitable oral antibiotics within 48 hours.

If the child has responded well to oral antibiotics, then a planned ultrasound should be arranged. Ultrasound can identify anatomical anomalies such as hydronephrosis, renal duplication, or renal scars and urinary stones.

18.6.4.2 Nuclear Medical Scans
Nuclear medicine scans should be done for split renal function and renal scarring four to six months following the acute infection in following situations:

a) Recurrent infections.

b) Deranged renal function test.

c) Ultrasound showing dilated ureter and or kidney.

Static scan: Dimercaptosuccinic acid (DMSA) labelled with metastable technetium-99 (Tc-99m) bind to the basement membrane of the proximal renal tubules, with a half-life of nearly six hours and has a radiation dose of 1 millisieverts (mSv). These scans help determine the split function of the kidneys as well as duplex kidneys, in addition to the accurate diagnosis of cortical scarring. The scan is avoided during an infection because the infection interferes with the uptake of the radiotracer by the renal tubules.

18.6.4.3 Cystourethrography
MCUG (with antibiotic cover) is indicated in children up to one year of age in following situations (i.e. MCUG is difficult to perform after the age of one year because of practicality and in such situation MAG-3 with indirect radiography is recommended).

Table 18.2 The interpretation of urine dip test for children three years or older [91].

<table>
<thead>
<tr>
<th>If both leukocyte esterase and nitrite are positive</th>
<th>The child should be regarded as having UTI and antibiotic treatment should be started. If a child has a high or intermediate risk of serious illness or a past history of previous UTI, a urine sample should be sent for culture.</th>
</tr>
</thead>
<tbody>
<tr>
<td>If leukocyte esterase is negative and nitrite is positive</td>
<td>Antibiotic treatment should be started if the urine test was carried out on a fresh sample of urine. A urine sample should be sent for culture. Subsequent management will depend upon the result of urine culture.</td>
</tr>
<tr>
<td>If leukocyte esterase is positive and nitrite is negative</td>
<td>A urine sample should be sent for microscopy and culture. Antibiotic treatment for UTI should not be started unless there is good clinical evidence of UTI (e.g. obvious urinary symptoms). Leukocyte esterase may be indicative of an infection outside the urinary tract which may need to be managed differently.</td>
</tr>
<tr>
<td>If both leukocyte esterase and nitrite are negative</td>
<td>The child should not be regarded as having UTI. Antibiotic treatment for UTI should not be started, and a urine sample should not be sent for culture. Other causes of illness should be explored.</td>
</tr>
</tbody>
</table>

UTI, urinary tract infection.

Table 18.3 Guidance on the interpretation of microscopy results [91].

<table>
<thead>
<tr>
<th>Microscopy results</th>
<th>Pyuria positive</th>
<th>Pyuria negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriuria positive</td>
<td>The infant or child should be regarded as having UTI</td>
<td>The infant or child should be regarded as not having UTI</td>
</tr>
<tr>
<td>Bacteriuria negative</td>
<td>Antibiotic treatment should be started if clinically UTI</td>
<td></td>
</tr>
<tr>
<td>Urine from Suprapubic puncture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any number of cfu ml(^{-1}) (at least 10 identical colonies)</td>
<td>≥10(^3)–10(^5) cfu ml(^{-1})</td>
<td>≥10(^4) cfu ml(^{-1}) with symptoms</td>
</tr>
<tr>
<td>Urine from catheterisation</td>
<td></td>
<td>≥10(^5) cfu ml(^{-1}) without symptoms</td>
</tr>
<tr>
<td>Urine from midstream void</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: From NICE guideline.
cfu, colony-forming unit; UTI, urinary tract infection.
radionuclide cystography [IRC] can be useful in selected situations):

a) Bilateral hydronephrosis or hydronephrosis in solitary kidney.
b) Unilateral or bilateral hydroureter.
c) Known spinal dysraphism.
d) Children with voiding difficulties.
e) Other known uropathies on case-to-case basis.

MCUG is the most commonly used scan to investigate the urinary tract especially in UTIs, with nearly 25% revealing VUR. Dynamic scans are used to assess obstructive uropathy, such as pelviureteric junction (PUJ), as well as split function and with indirect cystogram for VUR. Mercapto-acetyltriglycine (MAG-3) labelled with Tc-99 m, is the radiotracer use, it is excreted by the renal tubules (90%) and the glomeruli (10%), its radiation dose is 0.4 mSv.

18.6.4.4 Urodynamics
Urodynamic evaluation is indicated in patients with voiding dysfunction, incontinence, residual urine, and increased bladder wall thickness.

18.6.5 Management
The main goals of investigating and treating UTIs is to eliminate symptoms and eradicate the causative organism in the acute episode, prevention of renal scarring, recurrent UTIs, and correction of associated urological anomalies or abnormalities.
Management if UTIs is aimed at treating the acute scenario, then diagnosing the cause followed by treating of the underlying cause if present.

18.6.5.1 Acute Management [91–93]
Finding a UTI in a sick child does not exclude another site of serious infection (e.g. meningitis). Remember that 2% of young children will have asymptomatic bacteriuria, and this may not be the cause of this acute presentation.

Infants and children with a high risk of serious illness and younger than three months with a possible UTI should be referred immediately to the care of a paediatric specialist for treatment with parenteral antibiotics.

For infants and children three months or older with acute pyelonephritis or upper UTI:
- Consider referral to a paediatric specialist.
- Treat with oral antibiotics for 7–10 days.
- If oral antibiotics cannot be used, treat with an intravenous (IV) antibiotic agent such as cefotaxime or ceftriaxone for 2–4 days followed by oral antibiotics for a total duration of 10 days.
- Fluid resuscitation: 20 ml kg⁻¹ bolus of fluid, followed by 4 ml kg⁻¹ h⁻¹ as maintenance.

For infants and children three months or older with cystitis or lower UTI:
- Treat with oral antibiotics for three days. The choice of antibiotics should be directed by locally developed multidisciplinary guidance. Trimethoprim, nitrofurantoin, cephalosporin, or amoxicillin may be suitable.
- The parents or carers should be advised to bring the infant or child for reassessment if the infant or child is still unwell after 24–48 hours.

If an infant or child is receiving prophylactic medication and develops an infection, treatment should be with a different antibiotic, not a higher dose of the same antibiotic and should be tailored as per clinical response and sensitivity report.

18.6.5.2 Prevention of Recurrence
Dysfunctional elimination syndromes and constipation should be addressed in infants and children who have had a UTI. Children who have had a UTI should have ready access to clean toilets when required and should not be expected to delay voiding, and should maintain adequate amount of fluids.

18.6.5.3 Antibiotic Prophylaxis
Antibiotic prophylaxis should not be routinely recommended in infants and children following first-time UTI. However, it may be considered in infants and children with recurrent UTIs. In addition to those with increased risk of UTIs, such as VUR, trimethoprim 2 mg kg⁻¹ is the usual prophylaxis.

Asymptomatic bacteriuria in infants and children should not be treated with prophylactic antibiotics. Cranberry juice or tablets and probiotics might help in preventing recurrent infections.

18.6.6 Follow-Up [91]
Infants and children who have recurrent UTI or abnormal imaging results should be assessed by a paediatric specialist.

Assessment of infants and children with renal parenchymal defects should include height, weight, blood pressure, and routine testing for proteinuria.

Infants and children with a minor, unilateral renal parenchymal defect do not need long-term follow-up unless they have recurrent UTI, family history, or lifestyle risk factors for hypertension.

Infants and children who have bilateral renal abnormalities, impaired kidney function, raised blood pressure, or proteinuria should receive monitoring and appropriate management by a paediatric nephrologist to slow the progression of chronic kidney disease.

Infants and children who are asymptomatic following an episode of UTI should not routinely have their urine retested for infection.

Asymptomatic bacteriuria is not an indication for follow-up.

18.6.7 Information and Advice for Children, Young People, and Parents or Caregivers
Healthcare professionals should ensure that when a child or young person has been identified as having a suspected UTI, they and their parents or caregivers as appropriate are given information about the need for treatment, the importance of completing any course of treatment, and advice about prevention and possible long-term management [91].

Healthcare professionals should ensure that children, young people, and their parents or caregivers, as appropriate, are aware of the possibility of a UTI recurring and understand the need for vigilance and to seek prompt treatment from a healthcare professional for any suspected reinfection.

Healthcare professionals should offer children, young people, and their parents or caregivers appropriate advice and information on:
- prompt recognition of symptoms.
- urine collection, storage and testing.
- appropriate treatment options.
- prevention.
- the nature of and reason for any urinary tract investigation.
- prognosis.
- reasons and arrangements for long-term management if required.
18.6.7.1 Lower Urinary Tract Symptoms in Children

18.6.7.1.1 Definitions
Daytime LUT conditions encompasses symptoms including urgency, urge incontinence, poor flow, hesitancy, frequency, and UTIs. All children with incontinence are also included in this new terminology; however, night-time incontinence is known as ‘enuresis.

Bowel disturbances can be seen in more than 50% of children with bladder disturbances; therefore, concomitant bladder and bowel disturbances is known as bladder bowel dysfunction (BBD).

18.6.7.1.2 Normal Physiology
In neonates, the trigger to void is from the sacral spinal cord and is a reflex when the bladder is full. As the infant develops, the voiding reflex when the bladder is full is suppressed, the bladder capacity increases, and the voiding frequency decreases. Eventually the child learns to control voiding and understands bladder sensation to void.

18.6.7.1.3 Urinary Incontinence in Children
More than 95% of cases of incontinence are functional and tend to resolve spontaneously or with conservative treatment. Organic causes such as ectopic ureter, epispadias, posterior urethral valves, or spina bifida need to be closely monitored to ensure protection of the renal function.

Definitions and types of incontinence in children [94]
- Urgency with or without incontinence: detrusor overactivity gives rise to an overactive bladder.
- Stress incontinence: usually seen in neuropathic children and in those with cystic fibrosis.
- Underactive or hypotonic bladder: either secondary to spinal anomalies, poor voiding habits of ‘holding it in’ (voiding postponement), or as part of urological congenital anomalies such as posterior urethral valves.
- Extraordinary daytime urinary frequency: self-limiting, the child voids small amounts and frequently.
- Voiding postponement: usually behavioural or psychological disturbances whereby the children habitually postpone micturition, leaving voiding too late, which leads to incontinence. Seen mainly in girls, and they tend to use holding manoeuvres to postpone voiding, such as leg crossing and squatting (i.e. Vincent’s curtsy). Over time, the bladder may become hypreflexive and sensation decreased. This may lead to overflow or stress incontinence and leave the child prone to recurrent UTIs due to high postvoid residual volumes.
- Laughing or giggling incontinence: affects girls, whereby incontinence occurs when laughing or giggling, probably due to a week pelvic floor. Resolves with age.
- Vaginal reflux: urine reflexes into the vagina and leaks out at a later time. Labial adhesion could be the culprit, which can be divided.
- Dysfunctional voiding: the external urethral sphincter contracts during voiding either intermittently or continuously. This results in residual urine, which can lead to recurrent UTIs.

History and Examination
The history should focus to rule out underlying pathology and establish toilet habits. History should include voiding habits, family history, bowel habits or problems, and social, behavioural, and psychological history.

Incontinence from birth is classified as primary incontinence, whereas if incontinence has developed after a period of being continent for at least six months, it is secondary. Primary incontinence is more likely due to an organic cause, while secondary incontinence more likely to be due to functional causes. Continuous incontinence might be caused by an ectopic ureter. Incontinence shortly after voiding may indicate vaginal reflux. Voiding habits may indicate holding it until the last minute (i.e. voiding postponement).

In addition to the general examination of the whole patient, a focused external genitalia examination for congenital anomalies, such as bifid clitoris, epispadias, meatal stenosis, phimosis (increased risk of infections), as well as a neurological examination should be carried out, looking for pigmented or hairy lesions over the midline indicating spinal anomalies. Sacral agenesis typically presents with a flattening of the buttocks.

Investigations
Similarly, to adults: should include
- Urine dip sticks to rule out infection.
- Frequency volume charts, bladder voiding diaries to establish voiding timing and habits, as well as the expected bladder capacity: for <2 years of age is 7.5 ml kg⁻¹, while that of >2 years of age is 30 ml X (age + 2).
- Uroflowmetry: bell-shaped curve is the normal flow pattern.
- Ultrasound: for postvoid residuals and PUJ obstruction.
- MCUG for VUR
- Videourodynamics: for neuropathic bladders or those that do not respond to treatment or where the diagnosis is not clear.
- Spinal MRI for neurological causes.

Management

Conservative Management
Conservative therapy can be successful in up to 80% of children. Child and parent education is as important as all other measures. Behavioural and psychological therapies might be needed. Many children respond to conservative approaches, including bladder retraining, timed voiding,
appropriate voiding posture (for vaginal reflux), avoiding holding manoeuvres and avoidance of bladder irritants such as any caffeinated drinks, blackcurrant, or medication. Lifestyle modification, regular fluid intake, and preventing constipation with diet modification or laxatives are also key points.

**Specific Management** These are focused on treating the underlying cause, including physiotherapy for supervised pelvic floor exercises, biofeedback, alarm therapy, medication, and neurostimulation.

If for overactive bladder syndrome, conservative measure fail, antispasmodics, anticholinergics, or beta agonists are indicated. Neuromodulation, Botox injection, and ileocystoplasty procedures are other modalities used in a stepwise manner.

For laughing or giggling incontinence, anticholinergics, imipramine (a tricyclic antidepressant with anticholinergic and antispasmodic properties), and methylphenidate are recommended.

For underactive bladder, intermittent self or parental catheterisation (ISC) is used.

For dysfunctional voiding, antispasmodics, anticholinergics, ISC, and counselling are recommended.

**18.6.7.2 Nocturnal Enuresis [94]**

Nocturnal enuresis (NE) is intermittent incontinence during sleeping and is divided into:

- Mono-symptomatic nocturnal enuresis (MNE): NE without any other lower urinary tract symptom (LUTS) and without a history of bladder dysfunction.
- Non-Mono-Symptomatic NE (NMNE): has associated voiding dysfunction.

NE is classified into either:

- Primary NE: incontinence since birth, never been dry for more than a six-month period.
- Secondary NE: incontinent emerging after a period of dryness for at least six months.

**18.6.7.2.1 Prevalence**

More common in girls, NE affects 15% of five year olds and 10% of seven year olds with nearly 15% spontaneous resolution per year, and 0.7% continue to adulthood.

**18.6.7.2.2 Pathophysiology**

NE is a results of three processes:

- Altered antidiuretic hormone (ADH) section: the normal circadian reduction in urine output during sleep is diminished in nearly 60% of these children because of decreased ADH levels at night causing increased urine production.
- Altered sleep or arousal mechanism: impairment of the natural arousal from sleep response to a full bladder.
- Reduced nocturnal functional bladder capacity with or without overactive bladder (OAB) symptoms.

Risk factors that worsen NE:

- Family history, any siblings, or other family members have or had NE.
- Psychological and behavioural factors: vicious circle as NE can be caused be psychological factors; however, NE can be a stressful condition causing a huge psychological burden on the child leading to low self-esteem.
- UTIs.
- Constipation.

History and examination are similar to that of incontinence aimed at establishing an underlying pathophysiology.

**18.6.7.2.3 Investigations**

Diagnostic evaluation is largely from the history and examination, especially for monosymptomatic NE.

- Voiding diaries to assess nocturnal polyuria and estimated functional bladder capacity. Diaper weighing in the morning to estimate night-time volumes.
- Urinalysis to exclude infection, diabetes, or renal disease.

**18.6.7.2.4 Management**

Conservative Treatment is usually commenced after five years of age because of a high chance of spontaneous resolution in those younger than five.

Behavioural or supportive measures:

- Reassurance, positive reinforcement, and counselling of children and parents is vital to understand the problem, and its management course aides a more rapid positive response.
- Motivational techniques and reward systems can improve child’s confidence and self-esteem.
- Bladder training: regular daytime toileting, emptying the bladder before bed, avoiding bladder stimulants, and reduced fluid intake in the hours before sleep. Avoid constipation through modifying diet or laxatives.
- Conditioning therapy: first-line treatment modality, especially beneficial for arousal disorder. An enuritic alarm connected to the child’s underwear, triggered with the first few drops of urine, wakes the child up. This is affective in 60–80% of cases.

**Medical Therapy**

- Desmopressin: given just before bedtime with no further drinking; producing an antidiuretic response. Success rates of 70% can be seen: with nearly 30% achieving full response and 40% having partial
response. The recommended forms are either tablets (200–400 ug) or sublingual (120–240 ug).

- Anticholinergics or antispasmodics can help with small bladder capacity.
- Imipramine might help in resistant cases; however, response rates are 50%, with caution of overdose, which can cause cardiotoxicity or death.

A full response is considered with 14 consecutive dry nights or a 90% improvement in the number of wet pads. Patients with nocturnal polyuria and normal bladder function have a good response to desmopressin.

Patients with functionally reduced bladder capacity benefit from a combination of enuresis alarm, bladder training, and anticholinergics with or without desmopressin.

### Expert Opinion

Congenital bladder disorders can carry significant long-term morbidity for the patient and their family. Therefore, each case should be tailored around the patient’s condition and appropriate counselling at each stage of management and each stage of development is crucial.

### References


91 www.nice.org.uk/guidance/cg54/chapter/1-Guidance
92 www.rch.org.au/clinicalguide/guideline_index/Urinary_Tract_Infection_Guideline/)
Bladder Trauma

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Abstract

The bladder is the most commonly injured organ in the urinary tract. Bladder injuries are usually associated with other injuries, and the patient should be assessed thoroughly. The main cause of traumatic bladder injuries is pelvic fracture, whereas iatrogenic injuries are caused by surgical procedures. Early diagnosis can lead to successful treatment; however, an undiagnosed bladder injury can lead to significant morbidity. A cystography can accurately diagnose the injury. Extraperitoneal injuries are more common and could be managed conservatively. Intraperitoneal injuries often require surgical repair.

Keywords bladder injury; trauma; intraperitoneal; extraperitoneal; cystography

Key Points

- Extraperitoneal injuries are more common.
- In blunt noniatrogenic injuries, visible haematuria is the cardinal sign triggering further investigations.
- Cystography is the main diagnostic test.
- The bladder should be filled with at least 350–400 ml of diluted contrast.
- Extraperitoneal bladder injuries are more common and could be managed conservatively.
- Intraperitoneal bladder injuries usually need surgical repair and placement of urinary catheter.

19.1 Bladder Injuries

The bladder is located deep in the pelvis; hence an empty bladder is protected from external trauma. Bladder injuries are usually associated with other injuries and patients should be carefully assessed.

19.1.1 Classification of Bladder Injuries

Bladder injuries could be classified based on the type of injury:

1) Noniatrogenic or traumatic injury (blunt or penetrating trauma)
2) Iatrogenic (secondary to open, minimally invasive, or endoscopic procedures)

Alternatively, bladder injuries could be classified into intraperitoneal injury, extraperitoneal injury, or a mix of both.

19.1.1.1 Traumatic Bladder Injury

Pelvic fractures secondary to road traffic incidences involving motor vehicles are the most common cause of traumatic bladder injury followed by falls, industrial injuries, and direct blows to the suprapubic lower abdomen (Figure 19.1) [1–3]. Although, 4–10% of patients with pelvic fractures have associated bladder injuries, 60–95% of patients with bladder injuries have associated pelvic fractures [1–11]. Up to 45% of patients with bladder injuries are associated with at least one other intra-abdominal injury, and about 10–30% have associated urethral injuries [2, 6, 11–13].

Pelvic fracture associated bladder injuries are invariably always extraperitoneal [3]. The injury happens as a result of shearing the bladder, usually at the base, when the pelvic ring is disrupted (>1 cm) or as a result of a direct penetration of a sharp bony edge (Figure 19.2).

Although a sudden blow to a distended bladder will likely be intraperitoneally because the weakest point of the bladder is the base, extraperitoneal injuries typically happen as a result of penetrating trauma or as a result of shearing the bladder base (Figure 19.3).
the bladder is the dome, and a sudden rupture here will shear the overlying peritoneal surface [2, 11].

### 19.1.1.2 Iatrogenic

The bladder is the most common organ subjected to iatrogenic injuries, with obstetric and gynaecological procedures being the most common culprit [2]. This includes caesarean section, hysterectomy, and surgical procedures for management of urinary incontinence or prolapse.

Internal iatrogenic bladder injuries on the other hand are most commonly caused by urological procedures, such as transurethral resection of bladder tumours (TURBTs) with a reported incidence rate of 4–60% depending on the surgeon’s experience [14, 15]. Risk factors include elderly, previous resection, previous intravesical instillation, and size and site of the tumour [16, 17]. Resecting a tumour on the lateral wall using monopolar diathermy without muscle relaxation carries the risk of stimulating the obturator nerve (obturator kick). More often than not, internal bladder injuries are usually extraperitoneal; however, resecting at the anterior area or at the dome can lead to intraperitoneal injury due to the anatomical layout of the peritoneum and its contents over the bladder at these areas.

Foreign bodies such as meshes, stents, catheters, clips, or sutures used in pelvic surgery could cause an injury by erosion. Spontaneous bladder rupture can occur in neuropathic bladders who have had an augmentation enterocystoplasty, and rarely in patients with continent reservoirs when performing intermittent self-catheterisation [10].

### 19.1.2 Diagnosis and Investigations

#### 19.1.2.1 Clinical Assessment

Rupture of the bladder without fracture of the pelvis is classically seen in the elderly drunk who has been injured (Figure 19.1). The patient seldom remembers the cause and the diagnosis may be difficult because leakage of uninfected hypotonic urine into the peritoneal cavity at first excites little reaction [18, 19]. There is no tenderness on palpation; bowel sounds persist. Only a very astute doctor will suspect a vesical injury, when there is any doubt the patient should be admitted for observation.

 Nonetheless, gross haematuria is present in >80% of patients; if this is coupled with a pelvic fracture, then at least 30% of patients will have a bladder rupture and immediate imaging is warranted [2, 3, 8, 9, 20]. Therefore, other signs of injury need to be sought for, such as suprapubic or abdominal tenderness, inability to void, suprapubic bruising, clots in the urine, or signs of peritonitis if intraperitoneal rupture.

Extraperitoneal ruptures causes extravasation of urine which can track down to the scrotum causing it to enlarge or down the thighs or even anterior abdominal wall between the transversalis fascia and the peritoneum [2, 11].

Intraoperative bladder injuries are usually noticed when excessive clear fluid appears in the surgical field, when the laceration or the urinary catheter is seen, or when blood is noted in the urinary catheter bag, while air inflation of the urine bag is seen during laparoscopic or robotic procedures. If there is a high suspicion of a bladder injury, despite absence of overt signs, then the instillation of methylene blue into the bladder might illicit the injury site.

If an injury is missed at the original operation (e.g. hysterectomy), urine can leak from the vagina a few days later, forming a vesicovaginal fistula. However, the patient can slowly develop ileus and peritonitis if the injury was intraperitoneal. If injured extraperitoneally, urine collection with pain and or sepsis can develop.

Endoscopic iatrogenic bladder injuries are diagnosed when seeing extra vesicle fat, a dark gap between the detrusor muscles or bowels [14]. One can also notice that the bladder fails to distend despite adequate irrigation.
with low return of irrigation fluid and abdominal distention.

If an intraperitoneal injury is not recognised, the patient gradually develops a chemical peritonitis, the abdomen becomes swollen and tender, and bowel sounds disappear. Eventually, there may be fat necrosis and sloughing of omentum and bowel. When in any doubt, it is safer to perform a laparotomy and close the rent in the bladder and drain it because these injuries carry a high mortality (nearly 15%) if left untreated [1].

Patients with an intravesical foreign body may present with recurrent infections, dysuria, pelvic pain, frequency, and urgency and can lead to bladder stone formation.

19.1.2.2 Blood Tests
Renal function test: Elevated creatinine and urea levels could be found in patients with intraperitoneal ruptures as a result of the reabsorption of urea, nitrogen, and creatinine.

The fluid leaking from the vagina may be shown to be urine by measuring its creatinine concentration; no other body fluid can have a creatinine concentration greater than that of the plasma postoperatively [21].

19.1.2.3 Imaging

19.1.2.3.1 Cystography
Cystograms are the gold standard for diagnosing bladder injuries and are highly accurate when performed appropriately (>95% accuracy) (Figure 19.3). The absolute indication is visible haematuria associated with pelvic fracture or penetrating injuries. The relative indication for cystogram after blunt trauma is visible haematuria without pelvic fracture or microscopic haematuria with pelvic fracture.

Computed tomography (CT) cystogram is comparable to plain X-ray cystogram; however, it can diagnose other injuries and is therefore considered more efficient (Figure 19.3) [1, 2]. Whether a CT cystogram or a plain film cystogram is obtained, a stress cystogram should be performed. During a stress cystogram, the bladder is filled with 350–400 ml of diluted contrast and three images obtained: a precontrast plain film, a film when bladder is full, and a postcontrast image for detection of posterior extravasation.

Extraperitoneal bladder injury in a plain cystogram gives a flame-shaped collection of contrast medium in the pelvis. In intraperitoneal injuries, the contrast medium will freely flow to the abdominal cavity and outline the loops of bowel or other abdominal organs.

Clamping the catheter in an attempt to antegrade fill the bladder and obtaining delayed images is considered to be inadequate [22].

19.1.2.3.2 Ultrasonography Scan
Ultrasound may demonstrate fluid in the abdomen or the presence of extra peritoneal collection; however, ultrasounds are not sufficient to diagnose bladder injury [2].
19.1.2.3.3 Cystoscopy
Cystoscopy can diagnose intraoperative bladder injury by direct visualisation of the defect or failure to distend the bladder during TURBT. Ureterograms are done on both sides to rule out concomitant ureteric injury. Cystoscopy should ideally be performed after suburethral sling insertion to ensure the trocar has not gone through the bladder wall (Figure 19.4).

In noniatrogenic injuries, it is too difficult to see the tear during cystoscopy because of bleeding and is seldom worthwhile to do.

19.1.3 Management
All injuries recognised during surgery should be primarily closed. However, if the injury is missed or occurred during a TURBT procedure, management will depend on whether the perforation was intraperitoneal or extraperitoneal. For all intraperitoneal injuries, the standard is surgical exploration and repair of the injury. If the injury was extraperitoneal, then the vast majority can be treated conservatively with adequate drainage and antibiotics, with <1% requiring further intervention [1].

19.1.3.1 Conservative Management
Conservative management is the standard treatment for extraperitoneal bladder injury. The principles include adequate bladder drainage using a wide-bore catheter, clinical observations, and antibiotics prophylaxis given to prevent the infection of the extravesicle haematoma [4, 7]. Conservative management may also be considered in intraperitoneal injuries that were not recognised at time of TURBT if the patient is stable and in the absence of peritonitis and ileus [6].

The catheter is left on free drainage for 7–14 days, at which point cystography should be carried out to confirm complete healing.

19.1.3.2 Surgical Management
Intraperitoneal injury and all penetrating trauma should be managed by exploration and surgical repair.
For extraperitoneal injury, surgical repair is indicated where there is bladder neck injury, if the patient is having exploratory laparotomy for other injuries (associated rectal or vaginal injuries or if the patient is undergoing internal fixation of pelvic fracture), if the bladder is entrapped between two bone fragments, or a bone spike has penetrated the bladder wall [2].

19.1.3.2.1 Surgical Approach
Exploration is carried out through a lower midline abdominal incision. Any pelvic haematoma should not be disrupted. The anterior bladder wall is opened between stay sutures, and the whole of the bladder wall should be carefully inspected. The ureteric orifices should be identified and inspected for efflux (Figure 19.5). Injuries are often larger than they appear on imaging.

The bladder wall is then closed in two layers. The bowels should be examined to rule out any concomitant injuries. Injuries sustained during laparoscopy could be repaired laparoscopically if the surgeon is experienced in this technique. A large drain is left in situ. Either a suprapubic or urethral catheter is left on free drainage [9, 23]. The catheter could be removed 7–14 days after the repair; cystography should be done before removing the catheter to ensure bladder integrity.

If vaginal or rectal injuries are present, they should be repaired separately, and viable tissue should be interposed between the two repaired organs to reduce the risk of fistula formation.

19.1.4 Variant Injuries
19.1.4.1 Silent Rupture of the Bladder
After bladder tumours on the dome have been coagulated with diathermy, especially in patients who are elderly, the coagulated part of the thin wall of the bladder

Figure 19.5 (a) Extraperitoneal bladder perforation, and (b–d) intraperitoneal bladder perforation with contrast outlining bowel.
may give way and allow urine to escape into the peritoneum. The early physical signs are minimal: the urine gives rise to too little irritation and it is only after two or three days that the patient develops abdominal pain and distension. With prompt catheterization, the condition is easily remedied and laparotomy can be avoided.

19.1.4.2 Catheter Trauma
A catheter may be forced through the wall of the bladder, usually one that is already severely contracted. The diagnosis is as difficult to make as in the other groups of ‘silent’ perforation but should always be suspected.

19.1.4.3 Cather Balloon Rupture
A diabolically dangerous method for bursting a Foley catheter balloon used to be to inject ether down the side channel. Before it burst, the balloon could rupture the bladder. Unless great care was taken in every case to wash the bladder out, bits of rubber from the balloon could be left behind on which stones can subsequently form.

19.1.4.4 Gunshot Wounds
It is necessary to distinguish between gunshot injuries caused by high- and low-velocity missiles [2-4]. In both types of injury, if there is any suspicion of trauma to the rectum, a diverting colostomy will avoid the risk of the havoc caused by gas gangrene with its consequent massive loss of tissue [5, 24, 25].

High-velocity bullets produce an enormous spherical blast injury with devitalization of all lining tissue within its radius. In the few who survive, all devitalized tissue must be excised. Primary repair must not be attempted [25]. Free drainage is provided. Delayed primary or secondary suture can be carried out 5–10 days later. Low-velocity missiles, bullets, and shrapnel fragments call for more conservative debridement, but primary closure should not be performed; delayed primary or secondary suture is safer [25]. In bladder injuries, the main requirement is to provide free drainage.

<table>
<thead>
<tr>
<th>Expert Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simply put, CT cystogram should be done early in suspected bladder injuries, and regardless of cause, bladder injuries are either intraperitoneal or extraperitoneal. If the injury is intraperitoneal, then surgical repair is the gold standard. If extraperitoneal, then conservative management can be attempted. However, if the patient deteriorates and if the injury involves the bladder neck, a bone spike is present, bladder tissue is compressed between two bone fragments, or other organs injured, then a surgical exploration must be done. Aftercare is as important as the primary care. If the injury was during bladder resection, then a catheter should be left in place for at least five days; a cystogram with the catheter clamped is obtained, if no contrast extravasation is seen, then the catheter can be removed. If the injury was intraperitoneal and repaired, drainage with a catheter should be for at least 7–14 days, followed by a cystogram. Antibiotic prophylaxis administered for the duration of recovery, mainly until the catheter is removed.</td>
</tr>
</tbody>
</table>

References

References


20

Bladder Inflammation

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² Urology Department, University Hospital of Wales, Cardiff, UK

Abstract

Inflammation of the bladder is known as cystitis. It is a common condition. Acute cystitis is usually caused by bacterial infection, and these cases make up the majority of patients presenting in both acute and clinic settings. Chronic inflammatory conditions of the bladder are much rarer and present challenges in both definitive diagnosis and management. Most patients require a multidisciplinary approach and need ongoing support to manage their symptoms. Parasitic infections are rare and should only be considered if working in high-risk areas or with at-risk populations.

Keywords bladder; inflammation; bacterial cystitis; chemical cystitis; viral cystitis; ketamine bladder; schistosomiasis; bilharzias; painful bladder syndrome

Key Points

This chapter covers the following:

- Bacterial cystitis
- Viral cystitis
- Chemical cystitis
- Radiation cystitis
- Tuberculosis cystitis
- Schistosomiasis
- Rare bladder inflammatory conditions

20.1 Introduction and Definitions

Inflammation or infection of the bladder is termed cystitis. There are a variety of causes such as bacteria, viruses, and chemicals. The term ‘acute cystitis’ or inflammation of the bladder, is commonly used to denote a lower urinary tract infection (UTI).

Bacteriuria is the presence of bacteria in the urine, irrespective of being symptomatic or asymptomatic.

Pyuria is the presence of white blood cells in the urine, representing the presence of an inflammatory response. It can be associated with bacteriuria, implying an infective cause, or without bacteriuria (i.e. sterile pyuria).

Sterile pyuria is seen with carcinoma in situ, urinary calculi, tuberculosis (TB), or schistosomiasis infections, and inflammatory conditions, such as interstitial cystitis, or after bladder treatments.

Bacteriuria without inflammatory cells (i.e. pyuria) implies bacterial colonisation, such as that seen in patients with long-term catheters.

An uncomplicated UTI is an infection occurring in patients who have physiological and anatomical normal urinary systems.

A complicated UTI is an infection occurring in patients who have an underlying abnormality. Inherently all men with prostatic enlargement giving rise to infection complications are deemed to have a complicated UTI, although the majority of uncomplicated UTIs happen in women.

Simple UTI is an infection that occurs sporadically and is successfully treated with antibiotics with no complications and does not reoccur for at least a six-month period.

Recurrent UTI is either ≥2 or more culture proven UTI episodes within six months or ≥ 3 within a year.
Recurrent UTIs are either caused by reinfection by a different organism or persistence of the original organism. Bacterial persistence is usually seen in patients where the cause of the infection persists, such as with stones, fistulas, atrophic chronic infected kidneys, or chronic prostatitis. An unresolving infection may be the result of inappropriate antibiotic use, such as bacterial resistance.

### 20.2 Acute Cystitis or Lower UTI

Acute cystitis is common, affecting 50% of women during their lifetime; however, either sex can be affected at any age [1]. Causes are commonly due to bacterial gut flora, viruses, parasites, or chemicals.

#### 20.2.1 Bacterial Cystitis

This is the most common cause of acute cystitis, typically caused by an enteric organism such as *Escherichia coli* (*E. coli*; 70–95% of cases). Other species include *Klebsiella*, *Proteus mirabilis*, or *Streptococcus faecalis* and less frequently *Chlamydia trachomatis*, *Neisseria gonorrhoea*, and *Staphylococcus saprophyticus*. About 50% of infections can extend into the upper urinary tract [2]. Risk factors for lower UTIs are listed in Table 20.1.

#### 20.2.1.1 Pathogenesis

The urinary tract is normally a sterile environment; however, pathogens can reach the bladder urothelium by ascent up the urethra, haematogenous, and lymphatic spread, or translocation of organisms from the colon. Host defence mechanisms and bacterial virulence play a multifactorial role in the development of lower UTIs.

Bacteria can increase their virulence in several ways, such as avoidance of host defences, antimicrobial resistance, and mechanisms for adhesion to the urothelium. *E. coli* has an extracellular capsule which can resist phagocytosis and reduce the humoral and cell-mediated immune responses. *E. coli* can also release endotoxins which can destroy host erythrocytes. *Proteus* species have developed the ability to produce ureases which split urea into ammonia and leads to struvite stone formation.

Antimicrobial resistance of bacterial can occur through a number of mechanisms. Bacteria can alter their cell membrane permeability, preventing antibiotics from entering the cell. Similarly, bacteria can alter antibiotic binding sites on their surface membrane via genetic alteration. β-lactam antibiotics (i.e. penicillin, carbapenems and cephalosporins) can be inactivated by bacteria producing β-lactamase (enzyme) such as *Staphylococcus aureus*, enterobacteria, and *N. gonorrhoeae*.

Bacteria can adhere to cells through binding of a bacterial ligand to a host cell receptor. These ligands, which surround the organism in the form of pili, are antigenically specific for epithelial receptors (Figure 20.1). Pili have the ability to mediate haemagglutination. The number of pili can range from 100 to 400 and are usually 5–10 nm in diameter and up to 2 μm in length [3]. Pili express adhesins that allow the organism to adhere to tissue [3]. Type 1 (Mannose-sensitive, associated with cystitis mainly), P (Mannose-resistant, associated with pyelonephritis, and S pili (seen with both bladder and kidney infections) are the most well described pili. Organisms can express either one type of pili, multiple types, or are un-piliated (Dr adhesin-associated UTIs, seen in pregnancy and children).

The vagina may be colonised with piliated organisms several days before the clinical onset of infection. Vaginal cells from women who seldom contract urinary infection do not allow pathogenic strains of bacteria to adhere to

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**Table 20.1 Risk factors for developing bacterial cystitis.**

<table>
<thead>
<tr>
<th>Promote colonisation</th>
<th>Reduced urine flow</th>
<th>Facilitate ascent</th>
<th>Impaired host defences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual activity, increased inoculation</td>
<td>Outflow obstruction (e.g. benign prostatic hyperplasia, prostatic carcinoma, urethral stricture, foreign body [calculus])</td>
<td>Catheterisation</td>
<td>Haematological disorders</td>
</tr>
<tr>
<td>Spermicide, increased binding</td>
<td>Neurogenic bladder</td>
<td>Urinary and faecal incontinence</td>
<td>Chemotherapy immunosuppression</td>
</tr>
<tr>
<td>Antimicrobial agents, decreased indigenous flora</td>
<td>Dehydration</td>
<td>Residual urine</td>
<td>(i.e. malignancy, transplantation, steroids)</td>
</tr>
<tr>
<td>Oestrogen depletion, increased binding</td>
<td></td>
<td></td>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>

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**Figure 20.1** Diagram of a bacterium showing pili. These enable a bacillus to adhere to urothelial cells.
them, unlike those from women who become frequently infected. Similar differences occur in the mouth and may be determined by the human leucocyte antigen (HLA)-A3 antigen.

Unpiliated organisms may be less adherent to host cells but also are less susceptible to phagocytosis. The process of change in pili is called ‘phase variation’ and is usually in response to the milieu. Through a symbiotic relationship, organisms, such as lactobacilli, act as a secondary defensive mechanism for the urinary tract by produce a protective biofilm, preventing competing pathogenic bacteria from contact with the urothelium [4–8].

### 20.2.1.2 Clinical Features

Symptoms often described are dysuria, pain, frequency of micturition, and urgency. Occasionally haematuria, strangury, offensive smelling urine, and suprapubic and lower back pain may be present. In women, following sexual intercourse or menstrual periods, symptoms of dysuria and frequency are often the only symptoms experienced.

Clinical signs are usually suprapubic discomfort and cloudy urine (in un-centrifuged urine, microscopy will show abundance of white cells with bacteria in the edges), occasionally accompanied by a palpable bladder if the patient is unable to void. Other signs can include warm peripheries due to sepsis, confusion, and if pyrexia, rigours and loin pain develop and can indicate an ascending infection (pyelonephritis).

### 20.2.1.3 Investigations

A urine dipstick test is a quick and simple first-line investigation that can provide useful information whether pyuria or bacteriuria is present within urine [9, 10].

Microscopic urinalysis and culture of urine identifies the underlying pathogen and provides antibiotic sensitivities. Results can take up to 48 hours. Empirical treatment can be given without the results, but urine culture should be sent in all patients to exclude resistant bacterial strains [11, 12]. In practice, many women with urinary infection and pus in their urine have what is reported as sterile urine. Table 20.2 shows organisms that cause UTI.

A mid-stream urine (MSU) specimens can be contaminated by bacteria as urine leaves the urethra, particularly in women and following urethral catheterisation. False-positive urinalysis can also occur if a urine specimen has been left for several hours. Specimens should be refrigerated immediately and cultured within 24 hours.

Suprapubic aspiration of urine from the bladder provides the most accurate assessment of urine because it is least likely to be contaminated; in practice, this is rarely performed because it is invasive and requires a full bladder.

Recommended bacterial count that indicates significant bacteriuria: [14]

### Table 20.2 Classification of bacteria causing urinary tract infection.

<table>
<thead>
<tr>
<th>Gram positive</th>
<th>Aerobes</th>
<th>Cocci</th>
<th>Streptococcus</th>
<th>Non-haemolytic:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enterococcus faecalis</td>
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<td></td>
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<td></td>
<td></td>
<td>Haemolytic:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>β-haemolytic streptococcus</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viridans streptococci</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Staphylococcus</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Staphylococcus epidermidis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Staphylococcus saprophyticus</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>Rods (Bacilli)</td>
<td>Corynebacteria</td>
<td>Corynebacterium urealyttium</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mycobacteria (acid fast)</td>
<td>Mycobacterium tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Gram negative</td>
<td>Aerobes</td>
<td>Cocci</td>
<td>Clostridium</td>
<td>Lactobacillus crispatis/Lactobacillus jensenii</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(vaginal commensal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neisseria</td>
<td>Clostridium perfringens</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enterobacteriaceae</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Escherichia coli</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Klebsiella spp.</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>Rods (Bacilli)</td>
<td>Non-fermenters</td>
<td>Pseudomonas agruginosa</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacteroides</td>
<td>Bacteroides fragilis</td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted from [13].
- $10^3$ colony-forming units (cfu) ml of pathogens in a MSU sample in acute uncomplicated cystitis in women or recurrent UTIs.
- $10^4$ cfu ml$^{-1}$ of pathogens in an MSU in acute uncomplicated pyelonephritis in women or complicated UTIs in men.
- $10^5$ cfu ml$^{-1}$ of pathogens in an MSU in complicated UTI in women or asymptomatic bacteriuria in two consecutive MSU cultures more than 24 hours apart.

When urine is obtained from a catheter, cystoscope, or needle aspiration of the bladder, any organism signifies an infection. The concept of the colony count only applies to voided urine specimens.

In lower UTI cases, imaging studies are not required because clinical and urinalysis findings provide for accurate diagnosis. Lower UTIs in men, febrile infections, recurrent infections, suspicion of urinary tract obstruction, and the patient who is immunocompromised warrant further investigation.

Imaging modalities to consider are ultrasound, plain X-ray, or computed tomography (CT).

Renal tract ultrasound can identify urinary retention, poor bladder emptying, and hydronephrosis. Plain film X-ray of the kidneys, ureter, and bladder (KUB) is of little value in these patients but can help identify renal or bladder stone disease as well as for follow-up purposes.

CT, with or without contrast, can rule out causes for renal obstruction and stone disease. Cystoscopic visualization of the bladder can be performed for assessment of recurrent UTIs confirmed on urinalysis.

### 20.2.1.4 Management

Prevention is paramount. Conservative measures such as fluid advice, voiding urine following coitus, preventing constipation, and maintaining good genital hygiene can be helpful.

In the last few decades, the number of antimicrobial-resistant organisms in the community and hospital have increased; therefore, it is important that all UTIs are treated adequately and appropriately guided by culture sensitivities and knowledge of pathogen strains within an area. Antimicrobial therapy of uncomplicated cystitis in premenopausal women are depicted in Table 20.3.

In women, continuous or postcoital antimicrobial prophylaxis for prevention of recurrent lower UTIs should be considered if conservative measures fail [11]. Any previous UTI should be adequately treated should be confirmed by a negative urine culture one to two weeks following treatment before starting antimicrobial prophylaxis.

Follow-up is recommended in persistent recurrent cystitis or suspected underlying abnormalities.

### Table 20.3 Recommended antimicrobial therapy in uncomplicated cystitis in premenopausal women [11].

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Daily Dose</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosfomycin</td>
<td>3g sd</td>
<td>1 day</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50mg qd</td>
<td>7 days</td>
</tr>
<tr>
<td>Nitrofurantoin microcrystal</td>
<td>100mg bd</td>
<td>5–7 days</td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>400mg bd</td>
<td>3 days</td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>200mg bd</td>
<td>7 days</td>
</tr>
<tr>
<td>Alternatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>250mg bd</td>
<td>3 days</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>250mg bd</td>
<td>3 days</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400mg bd</td>
<td>3 days</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>200mg bd</td>
<td>3 days</td>
</tr>
<tr>
<td>If local resistance pattern is known (Escherichia coli resistance &lt;20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-sulphamethoxazole</td>
<td>160/800mg bd</td>
<td>3 days</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>200mg bd</td>
<td>5 days</td>
</tr>
</tbody>
</table>

sd: single dose.
bd: twice a day.
qd: four times a day.

#### 20.2.1.5 Recurrent UTI

Nearly 30% of women will have two UTIs in a six-month period, and 3% will have a third in the same period [15]. Table 20.4 summarises the pathophysiology and management of recurrent UTIs in men and woman.

Bacterial persistence is usually related to an underlying pathology in both men and women such as renal stone disease or fistulas. These people have relapsing UTI symptoms within days or weeks of stopping antibiotic therapy. Definitive management is to treat the underlying cause.

Women who suffer with reinfection usually do not have an underlying cause, and it is not always possible to cure them of this condition. Men on the other hand usually display signs of bladder outflow obstruction (BOO). The common causes are benign prostatic enlargement (BPE) or urethral stricture disease. For both men and woman, symptoms reoccur weeks or months after initial treatment of the infection and usually the same organism is to blame. Management for men is treatment of their underlying BOO. For women a number of antibiotic strategies can be deployed (Table 20.4).

#### 20.2.1.5.1 UTI in Pregnancy

Pregnancy in itself does not increase the incidence of UTI in women, but due to anatomical and physiological changes, there is a higher chance of infections progressing quickly or becoming recurrent. Physiological
<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Sex</th>
<th>Pathology</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial persistence</td>
<td>Short time interval between infective episodes (days/weeks)</td>
<td>Male</td>
<td>Kidney stones, Infected prostate, Stone disease, Obstructed kidney, Urethral diverticulum, Vesicovaginal/colovesical fistula, Vesicoureteric reflux</td>
<td>X-ray KUB, Renal ultrasound, Flexible cystoscopy, PVR and flow testing, CT urogram/KUB</td>
<td>Correct underlying Pathology</td>
</tr>
<tr>
<td></td>
<td>Same organism for each infective event</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usually underlying abnormality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reinfection</td>
<td>Time interval between infective episodes (weeks/months)</td>
<td>Male</td>
<td>BOO (BPE/stricture)</td>
<td>Flexible cystoscopy, Urodynamics, PVR measurement, Rule out bacterial persistence (as above)</td>
<td>Correct underlying pathology</td>
</tr>
<tr>
<td></td>
<td>Different organism for each infective event</td>
<td>Female</td>
<td>No underlying pathology</td>
<td>Rule out bacterial persistence (as above)</td>
<td>Conservative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increase oral fluids, Voiding after penetrative sexual intercourse, Cranberry juice/tablets, Avoid spermicides, Natural yoghurt, Alkalisation of urine, Oestrogen supplementation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antibiotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low-dose prophylaxis, Postintercourse prophylaxis, Self-start therapy</td>
</tr>
</tbody>
</table>

BOO, bladder outflow obstruction; BPE, benign prostatic enlargement; CT, computed tomography; KUB, kidney, ureter, and bladder; PVR, postvoid residual.
hydronephrosis leading to stasis of urine in the renal collecting system can lead to UTI. Up to 10% of women will have asymptomatic bacteriuria, which can lead to severe infections such as pyelonephritis in 20–40% of cases.

*E. coli* remains the most common causative organism. UTI’s are more common in women who suffered with recurrent infection before pregnancy, those with known anatomical or voiding abnormalities, and diabetics.

As with any infection, UTIs can develop into and present with severe sepsis (see Chapter 12 for physiology of sepsis syndrome). More specifically, UTIs during pregnancy increase the risk of preterm delivery and are associated with interuterine growth retardation (IUGR) and low foetal weight.

Cultural- and sensitivity-based management is paramount. Antibiotic treatment must also be tailored according to gestation (Table 20.5). Urine screening and antibiotic treatment is encouraged in asymptomatic women given the high risk of severe infections and detrimental effects on the pregnancy. Treatment should last for three to five days and a follow up urine culture should be taken one week after treatment or at a specified time before delivery.

### 20.2.1.6 UTI in Children

UTI is a common ailment in children of all ages, but it is not commonly seen by the urologist. The risk in the first decade of life is 1% in males and 3% in females [16]. Younger than age three months, UTI is more common in boys than girls, but after this, the trend reverses and girls are three times more likely to suffer with infections [17].

Figure 20.2 outlines the pathophysiology and risk factors for UTIs in children.

Investigations are warranted in girls who have two or more infective episodes and boys who have just one episode.

Management is dependent on underlying pathology.

### 20.2.2 Viral Cystitis

Lower UTIs caused by viruses are uncommon and are found in patients who are immunocompromised. The increase in tissue transplantation, use of chemotherapy agents, and acquired immunodeficiency syndrome have also led to increased cases of viral cystitis. Viruses such as adenovirus, cytomegalovirus, and BK virus are often found as the causative pathogen in solid organ and stem-cell transplantations [18–20]. Herpes zoster involving

### Table 20.5 Antibiotics to avoid in pregnancy by trimester.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Mechanism of Action</th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
<th>Risk to foetus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Prevents cell wall synthesis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>Prevents cell wall synthesis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Inhibits ribosomal protein synthesis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Prevents DNA replication by inhibiting dihydrofolate reductase</td>
<td>✠</td>
<td>✓</td>
<td>✓</td>
<td>Teratogenic (folate antagonist)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Inhibits ribosomal protein synthesis</td>
<td>✠</td>
<td>✠</td>
<td>✠</td>
<td>Maternal hepatotoxicity Effects skeletal development</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Causes DNA damage by its reduced form which is highly reactive and damages ribosomal proteins, DNA, pyruvate metabolism and others</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Avoid at term due to severe effects of nausea and vomiting</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Prevents DNA replication by inhibiting DNA gyrase</td>
<td>✠</td>
<td>✠</td>
<td>✠</td>
<td>Neonatal haemolysis Arthropathy</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>Prevents DNA replication by inhibiting dihydropteroate synthase</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Neonatal haemolysis Methaemoglobinanaemia</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Inhibits ribosomal protein synthesis</td>
<td>✠</td>
<td>✠</td>
<td></td>
<td>Neonatal ‘grey’ syndrome</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Inhibits ribosomal protein synthesis</td>
<td>✓</td>
<td>✠</td>
<td></td>
<td>Vestibular and auditory nerve damage</td>
</tr>
</tbody>
</table>
Acute Cystitis or Lower UTI

the S2, S3 segments can often be identified on cystoscopy by a well-defined patch of bladder inflammation and the rest of the bladder is unaffected [21].

Polymerase chain reaction (PCR) is used to diagnose and quantify the viral load. Treatment is by an antiviral agent, such as Cidofovir. Specialist microbiological advice should be sought.

20.2.3 Noninfectious Cystitis

Noninfectious cystitis is rare. The most important types to be familiar with are chemical and radiation cystitis.

20.2.3.1 Chemical Cystitis

Chemicals introduced into the bladder by iatrogenic, self-inflicted, or accidental means can induce varying degrees of inflammation, from mild irritation to gross bladder necrosis. Diagnosis is based on history, high index of suspicion, and negative urine culture. Historically, ether was used to rupture Foley catheter balloons that would not deflate. Leakage of ether from the ruptured balloon was reported to cause severe chemical necrosis and bladder contracture [22]. Silver nitrate used for treatment of recurrent UTIs occasionally led to severe chemical cystitis.

Cyclophosphamide is commonly used in the treatment of malignancies (e.g. leukaemia) and autoimmune diseases (e.g. rheumatoid arthritis). Its metabolite, acrolein, is excreted in the urine, and with prolonged contact, commonly causes bladder inflammatory reactions leading to mucosal oedema and vasodilation resulting in increased friable capillaries (i.e. haemorrhagic cystitis), and in severe cases, full-thickness bladder necrosis. On cystoscopy, no single bleeding vessel can be seen, but the haemorrhage may be persistent and even exsanguinating. The development of squamous cell carcinoma, adenocarcinoma, and leiomyosarcoma have been reported as the long-term sequelae of cyclophosphamide use [23].

Other drugs and chemicals implicated to cause haemorrhagic cystitis or bladder neoplasm are depicted in Table 20.6.

20.2.3.1.1 Management

Stopping or reducing the dose of the drugs and promoting diuresis by aggressive rehydration can help reduce toxicity within the bladder. Continuous bladder irrigation by urethral catheter can help reduce the concentration and length of exposure of acrolein to the bladder urothelium. Intravenous sodium 2-mercaptoethane sulfonate (mesna) has been used to prevent haemorrhagic cystitis following ifosfamide and cyclophosphamide use, although its use is controversial. Some promising results in controlling chemotherapy-induced haematuria with agents such as amifostine, glutathione, N-acetylcysteine, and L-2-oxothiazolidine-4-carboxylate (Procysteine) have recently emerged [24].

20.2.3.1.2 Ketamine Bladder

Another cause of chemical cystitis is ketamine, which is a noncompetitive N-methyl-D-aspartate receptor antagonist used for induction and maintenance of anaesthesia and is also used as a recreational drug. Ketamine abuse has been linked with the development of lower urinary tract symptoms that resemble interstitial cystitis and
hypersensitive bladder syndrome, often referred as ‘ketamine bladder syndrome’ [26–28].

The pathophysiology is not entirely clear however; the metabolites are concentrated in the urine and cause intense inflammatory reaction throughout the urinary tract. In the kidneys, ketamine can cause papillary necrosis and renal failure. In the ureters, the inflammation can cause stricture formation leading to hydronephrosis. Although the bladder is the most common end site, can cause significant storage lower urinary tract syndromes, painful urination or suprapubic pain, or haematuria.

Urodynamics show detrusor overactivity and reduced bladder compliance; flow rates are normal. Cystoscopic appearances can include inflammation, denuded urothelium, petechial haemorrhages, and a small capacity bladder. CT urogram can show upper tract involvement.

Management of ketamine bladder syndrome can be challenging because often patients cannot stop taking the drug. However, the first step is to stop usage. Counselling and support groups are vital.

Taking ketamine more than three times per week is associated with lower voiding volumes, while those using for more than two years are associated with significantly worsening symptoms than those using for less than two years [29]. Furthermore, symptom improvement is directly proportional to the length of abstinence from using and functionality can potentially normalise after one year of stopping ketamine use [29].

Medical treatment is based on a symptom control, early referral to pain team, indwelling catheters, or intermittent self-catheterisation for drainage of small capacity bladders, anticholinergics, or beta-agonists for overactive bladder (OAB) symptoms.

Surgical treatment is reserved for patients who have stopped using and have developed complications of ketamine use. For ureteric stricture: nephrostomy insertion with or without ureteric stenting can be done until ureteric stricture treatment can be done. Augmentation cystoplasty might be required if the bladder’s compliance does not improve. Cystectomy with or without neobladder reconstruction if symptoms persist and are affecting quality of life (QoL).

### 20.2.3.2 Radiation Cystitis

Nearly 15–20% of patients who received radiotherapy for pelvic malignancies develop bladder complications [30]. It usually develops after 90 days from starting radiotherapy but can develop several years later [31].

Radiotherapy induces a progressive microscopic obliterator endarteritis that causes bladder mucosa ischaemia resulting in ulceration and bleeding. In injured areas, development of new friable blood vessels occurs which readily bleed after mucosal trauma, irritation, or distension. Cystoscopic features of a vascular blush on the bladder mucosa are typical of acute radiation injury. Severity tends to become less over time.

Delayed radiation injuries are progressive and irreversible. Histological features include cellular depletion, fibrosis, and obliterator arteritis [32]. Symptoms include dysuria, frequency, and urgency (small bladder capacity secondary to fibrotic changes). Treatment is aimed at symptoms (e.g. analgesia, anti-muscarnics, or indwelling urethral catheters for small capacity bladders). Treatment for refractory radiation cystitis can be difficult but luckily is rare. Modalities include intravesical alum, formalin (will require anaesthetic as can be very painful), hyperbaric oxygen, iliac artery embolisation, or even palliative radiotherapy or even cystectomy.

### 20.2.4 Chronic Bacterial Cystitis

Repeated episodes of acute cystitis can lead to chronicity. Particularly in women, chronic cystitis can manifest in continuous symptoms of constant pain, dysuria, and frequency. Cystoscopic biopsy will show cystitis follicularis or glandularis or a mixture of both. These patients are often unusually anxious and kind; empathy, and sympathy are no less important in therapy than accurate diagnosis and treatment.
20.2.5 Cystitis Follicularis

Cystitis follicularis is commonly found in elderly women and is often accompanied by a narrow, stiff urethra possibly due to depleted oestrogen levels. There is no obvious aetiological cause, and the causative organism is often difficult to identify requiring several urine cultures. Cystoscopic appearances are of an irregular mucosa resembling a cobblestone appearance (Figure 20.3). Histopathology shows collections of lymphocytes with germinal follicles in the lamina propria, and lymphocytes and plasma cells outnumber the number of leucocytes [33].

Adequate fluid intake to promote diuresis, frequent voiding, and prolonged course of the appropriate antibiotic based on culture sensitivities. When this fails, a short course of bactericidal antibiotics given intravenously, if necessary, may eradicate the infection. It should be followed up with a prolonged course of a lowered dose antibiotic.

20.2.6 Cystitis Cystica

Cystitis cystica is usually associated with inflammation and chronic obstruction but is also a common finding in normal bladders [34]. Irritative voiding symptoms and haematuria are the most common clinical features. It has a characteristic cystoscopic appearance of glistening bubbles under the mucosa, occasionally blackened by haemosiderin accumulation. Histopathological findings are of cystic nests lined by cuboidal or columnar cells and von Brunn's nests. They arise when small islands of epithelium become buried and form small vesicles.

Persistent cystitis can develop into cystitis glandularis, which may develop into intestinal metaplasia characterised by the presence of goblet cells similarly found on colonic epithelium. These areas of intestinal metaplasia may have malignant potential, and it is recommended that these patients have regular endoscopic assessments [35].

Treatment is by a transurethral resection (TUR) and relief of any underlying BOO. A variant is nephrogenic adenoma. A long-term sequelae of persistent irritation and infection and can be seen with stones or treated tuberculosis. Rarely might follow cystoscopic procedures.

20.2.7 Eosinophilic Cystitis

The aetiology is unclear, although immunological diseases and allergies may be associated. Cystoscopic features are of a grossly inflamed bladder. Symptoms include dysuria, haematuria, urinary retention, and suprapubic pain. Histopathological findings are of eosinophil infiltration through all layers of the bladder.

TUR combined with corticosteroids, antihistamines, or antibiotics have been found to provide benefit in all age groups [36]. Rarely, cystectomy may be required because of ureteric obstruction or contraction of the bladder. However in children, the disease can be observed because it is usually self-limiting.

20.2.8 Malakoplakia

Malakoplakia is an unusual inflammatory disease first described in 1902. Its aetiology is unclear but may be caused by repeated coliform infections causing an abnormal macrophage function in response to bacteria [37]. It can be associated with systemic disorders, immunodeficiency syndrome and autoimmune disease, and cancer.

Patients, usually in their fifth decade, present with symptoms of chronic cystitis and haematuria, with no organisms found on cultures. Cystoscopic findings are of light brown plaques indistinguishable from cancerous lesions; ureteric involvement can lead to obstruction. Histopathologic findings show large histiocytes known as von Hansemann cells and tiny calcified spheres (basophils) built up around bacteria like pearls on a grain of sand in an oyster, called ‘Michaelis-Gutmann bodies’, which are pathognomonic of this disease.

Preventing UTI will help avoid progression of the disease. Trimethoprim, sulphonamides, doxycycline, and rifampicin have been found to be beneficial because of their intracellular bactericidal activity [38].

20.2.9 Emphysematous Cystitis

Several intestinal organisms produce gas by fermentation of glucose. People who are diabetic infected with
these organisms are at risk of producing gas bubbles within the bladder wall, which produces a characteristic appearance on X-ray film (Figure 20.4). These changes resolve after treatment with the appropriate antibiotics.

20.2.10 Alkaline-Encrusted Cystitis

*Proteus mirabilis* infection around an indwelling catheter can invade all layers of the bladder wall, resulting in deposition of calcium salts. The urothelium can become ulcerated and covered with a crust of calcified debris. Presentation is of haematuria. Treatment includes appropriate antibiotic therapy and urine acidification. The sequela usually is a small, contracted bladder that may require cystoplasty or urinary diversion.

20.3 Chronic Interstitial Cystitis and Bladder Pain Syndrome

These topics are covered in Chapter 23.

20.4 Tuberculosis

Chapter 12 gives information about TB in the kidney and also other genitourinary systems. *Mycobacterium tuberculosis* infection of the bladder is common in Asia and usually affects young adults. It is often accompanied with renal tuberculosis. Use of bacillus Calmette-Guerin therapy (BCG) for bladder cancer can also cause bladder tuberculosis. Symptoms are usually atypical but can include persistent frequency and painful urination similar to cystitis.

Urine will contain pus cells but is sterile on routine culture; at least three early morning samples are needed. Ziehl-Neelsen staining of the urine may detect acid-fast bacilli but requires culture on Lowenstein-Jensen medium to confirm the presence of *M. tuberculosis*. In some cases, this can take up to eight weeks due to the slow doubling time of the bacterium (16–20 hours). Polymerase chain reaction of urine can hasten the diagnosis.

Cystoscopic features are usually of generalised erythema with no discernible features. Classical tubercles are rarely seen, even in the early stages, and any ‘tubercles’ are more likely to be lymphoid follicles on biopsy. TB should be suspected if one ureter is seen to be oedematous and not to move up and down with expulsion of urine. Occasionally ulcers and papillomatous granuloma resemble a carcinoma and this requires biopsy, which speeds up the diagnosis. The lungs should also be assessed for pulmonary TB.

Medical treatment follows a similar course to that of renal TB (see Chapter 12). As the granulomas in the bladder respond to the antibiotics, they heal with fibrous tissue, resulting in a small, contracted fibrosed bladder that may require cystoplasty. All treatment should be directed by specialist in the field of TB [39].

20.5 Parasitic Infections

20.5.1 Introduction

Parasitic infections of the bladder are extremely rare in European and North American countries, but with the ease of foreign travel and migration of different populations, parasitic infections need to be considered in a list of differential diagnoses (Figure 20.5). The only true parasitic infection of the bladder is Schistosomiasis.

20.5.2 Schistosomiasis

20.5.2.1 Introduction

Urinary schistosomiasis is caused by blood flukes of the genus *Schistoma*. Although it was known to the ancient Egyptians [40], Theodore Bilharz (a German pathologist) described these worms in the mesenteric veins in 1852 and also found evidence of eggs in the faeces of infected people [41]. It is one of the most prevalent infections worldwide with almost 243 million people requiring treatment for schistosomiasis infection in 2011 [42].

20.5.2.2 Aetiology

There are a number of different species distributed across the world (Figure 20.6 and 20.7) [42]. Lack of access to clean water and sanitation systems are the major source of the infection.
20.5.2.3 Pathology and Pathophysiology

Infection comes with exposure to larva (cercariae), which are released by freshwater snails (cercariae). The life cycle is complex in which there is a sexual generation in human, and an asexual stage in snails (Figure 20.6 and 20.7). Cercariae are able to penetrate the skin, and once inside the human body, mature in to adults. The pairs of adult worms, about 1 cm long (Figure 20.8), live in veins of abdominal viscera (bowel and bladder) attached by the sucker on the head of the male fluke and can live for 30 years, producing up to 400–500 eggs per day.

The body reacts to the worms and their eggs by forming a granuloma, mainly in the lamina propria, and later amongst the muscle bundles of the detrusor. The eggs secrete a histolytic antigen which evokes a cell-mediated immunological response, attracting eosinophils. The granulomas may project into the lumen of the bladder.

The inflammatory response to the eggs leads to ischaemia and loss of overlying urothelium, which now undergoes metaplasia, squamous or glandular; changes often made worse by bacterial infection.

Dead eggs provoke foreign body giant cell reaction and calcification. Healing is succeeded by reinfection, and the repeated cycle of healing, granuloma, and ulceration leads to carcinoma in situ and overt cancer (squamous cell).

20.5.2.4 Clinical Features

Ten seconds contact between the skin of an adult or child and water containing cercariae allows them to penetrate the skin where they enter the lymphatics and within
24 hours may set up an irritation (swimmers’ itch) and is sometimes accompanied by a papular rash which lasts a few days.

The infective process (two weeks after penetration) is known as Katayama fever. This is an acute immune reaction to egg laying. Symptoms include pyrexia, headache, sweating, urticarial, and coughing. This initial phase lasts 12 weeks, during which the flukes are migrating via the bloodstream to their final destination in veins anywhere in the body (i.e. brain, eyes, skin, bowel, and bladder).

The active inflammatory phase occurs when eggs become deposited into tissues, giving rise to visible haematuria and lower urinary tract symptoms such as frequency, urgency, and dysuria.

Untreated, the chronic active phase develops where egg-laying activity reduces but due to deposition of immune-complex’s nephrotic syndrome can occur in up to 25% of patients [43]. Chronicity leads to polyplody or fibrotic lesions which can cause an obstructive uropathy leading to permanent renal dysfunction.

### 20.5.2.5 Investigations

Diagnosis may be difficult during the initial phase because there is no way of detecting worm couples. After 12 weeks, the terminal-spined eggs are shed into the urine and can be easily be seen with a microscopy of a mid-day urine sample Figure 20.9. The severity of the disease is done by counting the number of eggs/10 ml of urine [43, 44].

- < 100 = Mild infection
- 100–400 = Moderate infection
- >400 = Severe infection

Cystoscopy will show minute yellow specks, the bilharzial tubercles, sometimes surrounded by a halo of hyperaemia (Figure 20.10). Later, these granulomas enlarge and form polyps which may or may not calcify. Calcified eggs glisten under the surface like specks of sand (the sandy patches), more obvious from the loss of the vascular pattern of blood vessels, commonly found in the trigone.

Ulceration may extend deep into the tissues outside the bladder, especially anteriorly. Histological features of all the forms of chronic cystitis are to be found: cystitis cystica and glandularis, von Brunn’s nests, squamous metaplasia, and frank leucoplaikia.

Radiology may demonstrate calcification of the visceral walls or an obstructed renal collecting system (Figure 20.11).

### 20.5.2.6 Management

#### 20.5.2.6.1 Public Health and Prevention

Sewage systems for urine and faeces would prevent schistosomiasis. Individuals who are travelling to endemic areas should avoid contact between bare skin and contaminated freshwater. If there is contact, then skin should be immediately dried and rubbed with alcohol.
20.5.2.6.2 Medical Management
Drugs are used to reduce and eradicate in situ worms but will not change the prognosis of nonreversible fibrotic and malignant lesion [44, 45]. Praziquantel 40 mg kg⁻¹ as a single dose or divided doses is sufficient to eradicate the parasite. During the Katayama fever stage, steroids can help alleviate symptoms.

20.5.2.6.3 Surgical Management
The surgical management calls for TUR of any polyps or ulcers in the bladder and removal of any calculi formed.

Contracture from healing of granulomas in the bladder neck is often accompanied by weakness of the damaged detrusor. Reconstructive procedures may be required.

Figure 20.7 (a and b) Pair of adult schistosome worms (miracidea and cercaria) removed from a vein.
Scarring draws the ureters onto the trigone calling for caution when resecting the bladder neck.

### 20.5.2.7 Bilharzial Cancer of the Bladder

Characteristic features:

1) Two-thirds are squamous cell cancers.
2) The age incidence is relatively young (average 46.7 years).
3) Dense fibrosis surrounds the bladder/Neither TUR nor partial cystectomy is applicable to these large tumours, which often present late.
Radical cystectomy is the gold standard.

### 20.5.2.8 Other Complications of Schistosomiasis

#### 20.5.2.8.1 Urethra

Stricture usually involves the bulb and in part may be the result of instrumentation rather than the infestation.

#### 20.5.2.8.2 Prostate

Secondary infection and prostatitis are common. In the prostate, the ova are distributed throughout the stroma, and fibrosis may cause outflow obstruction.
20.5.2.8.3 Seminal Vesicles
The seminal vesicles are frequently chalked out on the X-ray by the calcified ova. The inflammation can cause haemospermia and painful ejaculation, ova being found in the semen. It may be necessary to remove the vesicles.

20.5.2.8.4 Bilharziasis in the Female
The uterus, fallopian tubes and ovaries are often involved. Large painful polyps of the urethra and vulva give rise to distressing dyspareunia. Bilharzial fibrosis and ischaemia make repair of obstetrical fistulae more difficult; therefore, drug treatment should always be given first.

20.6 Amoebiasis

*Entamoeba histolytica* may travel from the bowel into the bladder through a fistula, but more probably is blood-borne. Clinically, it causes cystitis with haematuria and frequency. Cystoscopy shows inflammation, ulceration, and polypoid elevations of the urothelium. Balanitis, vaginitis, and vulvitis may be complications.

Figure 20.10 Cystoscopy appearance of schistosoma nodules in the bladder.

Figure 20.11 Computed tomography (CT) showing ureteric and bladder calcification secondary to schistosomiasis. Source: Photographs courtesy of Dr. Des Alcorn Queen Elizabeth University Hospital.
20.7 Worm Infestations

Eustrongylas gigas, the legendary 'giant kidney worm', is said to be the largest nematode known to infect humans. Its life cycle is ill-understood. It invades the renal pelvis and destroys the renal parenchyma.

Even more bizarre is vesical sparganosis, which is caused by eating raw frogs. The worms make a nest of tunnels in the wall of the bladder, causing a mass that must be excised. Antibody titres for Sparganum are raised.

20.8 Catfish

The Carnero or candiru is a catfish 5 cm long and 4 mm wide which is attracted by urine and said to swim up the urethra of unwary people bathing in the Amazon.

References


Abstract

Bladder cancer is the most common urothelial malignancy. More than 90% arise from the transitional cell lining of the urinary tract. The remainder of the histological variants include squamous cell cancer, adeno carcinoma, and other rare tumours. Urothelial cancer is associated with smoking and exposure to industrial carcinogens. This cancer generally affects people who are older and who have many comorbidities, which makes their management more challenging.

More than two-thirds of the urothelial cancers are non-muscle-invasive bladder cancer (NMIBC) confined to the mucosa or submucosal layers of the bladder wall and remainder are muscle-invasive bladder cancer (MIBC). NMIBC have tendency to recur, and the risk of recurrence varies between 15 and 80% and the majority of the recurrences occur within 6–12 months. Hence, intensive surveillance with cystoscopy and imaging of the urinary tract is required, which in turn incurs a high cost to the healthcare systems. The NMIBC cancers are classified based on their risk of recurrence and progression into low, intermediate, and high risk to tailor subsequent management and surveillance. In addition to the initial transurethral resection, intravesical therapies in the form of chemotherapy, immunotherapy, or a combination are used to reduce recurrence or progression of the disease.

For MIBC or high-risk NMIBC, radical cystectomy and urinary diversion is the mainstay of treatment. Radical cystectomy is a life-changing operation and is associated with significant perioperative morbidity and mortality. Therefore, experts in the field are striving to minimise the morbidity of the procedure by using minimal invasive techniques of laparoscopy or robotic surgery in combination with enhanced recovery pathways to expedite recovery.

There remains a risk of recurrence even after radical cystectomy due to micrometastasis. Various chemotherapy regimens have been used to decrease this in the neoadjuvant and adjuvant settings. Neoadjuvant chemotherapy has so far provided 5–8% absolute survival benefit at the expense of significant morbidity. In patients unfit or unwilling to undergo radical cystectomy, bladder preservation is an alternative which includes external beam radiotherapy and chemotherapy after transurethral resection. There is not enough evidence to prove the equivalence of this to radical surgery.

In those with advanced or metastatic disease, patients are put on palliative care pathway because the natural history of the disease is poor with four to six months expected survival. However, some newer immuno-therapies that inhibit the interaction between programmed death ligand 1 (PD-L1), present on the surface of tumour or antigen-presenting cells, and programmed death 1 (PD-1), present on the surface of activated lymphocytes, are offering new hope to the patients with advanced disease. In some cases of locally advanced cancer, palliative cystectomy can be performed for control of recurrent bleeding.

Keywords: bladder cancer; transitional cell carcinoma; non-muscle-invasive bladder cancer; muscle-invasive carcinoma; diagnosis and management of bladder cancer

Key Points

- Cystoscopy remains the gold standard for diagnosis of bladder tumours.
- Photodynamic cystoscopy and Narrow Band imaging improve the sensitivity of cystoscopic assessment.
- Imaging should be obtained before transurethral resection (TUR).
The technique of TUR of the tumours must be meticulous to avoid staging errors.

Single instillation of Mitomycin-C remains standard of care in patients suspected to have papillary noninvasive tumours.

Pathological evaluation should be preferably performed by expert uro-pathologists and subsequently discussed in a multidisciplinary meeting.

Tumours should be risk stratified as per EORTC tables.

Adjuvant therapies should be tailored to individual needs.

High-risk disease must be managed in a multidisciplinary setting and radical surgery offered to high-risk groups.

**21.1 Bladder Neoplasm**

**21.1.1 Incidence**

Bladder cancer is the ninth-most common cancer worldwide. Nearly 429,800 new cases were diagnosed in 2012, accounting for 3% of all the cancers [1]. It is the fifth-most common cancer in Europe. About 151,000 new cases were diagnosed in 2012, accounting for 4% of all cancers diagnosed that year. The highest incidence of bladder cancer in males is found in Belgium and amongst females in Hungary. In the UK, bladder cancer incidence is the lowest of all males in Europe and 13th lowest in females.

**21.1.2 Aetiology**

**21.1.2.1 Modifiable Risk Factors**

1) Carcinogens: Amongst the numerous causative factors for bladder cancer, the most significant are smoking and occupational exposure to carcinogens. Risk of bladder cancer is 3.8 times higher in current smokers compared with never smokers [2]. Some 37% of bladder cancers in the UK are linked to tobacco smoking [3]. Smokers who develop bladder cancer are incapable of detoxifying the tobacco-tar carcinogens (4-aminobiphenyl and 2-naphthylamine) due to deficiency of N-acetyl transferase and glutathione S-transferase M1 (GSTM1) in the liver [4]. The toxic effect of smoking reduces slowly over time with consequences lasting up to nearly 20 years after ceasing smoking. However, the risk is reduced by 40% after four years after smoking cessation.

Industrial carcinogens have been known to cause bladder cancer since 1895 when Rehn first observed carcinogenesis in aromatic hydrocarbons industry such as the aniline dye workers [5]. Nitrosamines-linked occupational bladder cancer has led many first-world countries to stop the use of naphthylamines. It is estimated that about 7% of male and 2% of female bladder cancers can be attributed to occupational exposure [6]. There is a long latency interval of 20–40 years between carcinogen exposure and development of subsequent disease. Therefore, it is often difficult to identify the potentially offending chemicals [7]. Vitamins A and C may play a role in blocking nitrosamine formation from everyday consumables.

Other occupations that may also be relevant include [8]:

1) Rat-catchers (alpha-naphthylthiourea contaminated with 2-naphthylamine)
2) Textile workers (carcinogenic dyes)
3) Polyurethane plastics industry – car bumpers and soles of shoes (methylenebis(2-chloroaniline) [MBOCA])
4) Laboratory workers (benzidine)
5) Leather work
6) Printing (used car oil)
7) Aluminium refining
8) Machine turning (mineral oil)
9) Lorry drivers (diesel)
10) Hairdressers (dyes)
11) Amateur anglers (maggots stained with chrysoidine)

2) Social deprivation and ethnicity: Poor socioeconomic conditions are known to be associated with higher risk of bladder cancer [9]. Age-standardised rates (ASR) for white males are higher (approximately 20 per 100,000) compared to Asian males (6.5–10.1/100,000) and black males (5.6–9.6 per 100,000) [10].

3) Obesity: Bladder cancer incidence is reported as being 9% higher in patients with body mass index >30. This association is more likely to be limited to males and may be confounded by smoking in this patient population [11, 12].

4) Chronic irritation: Spinal cord injury predisposes one to bladder cancer due to chronic irritation caused by indwelling urinary catheters, urinary tract infections (UTIs), or bladder calculi [13]. About 1% of patients with spinal cord injuries with indwelling catheters develop bladder cancer [14]. There is well-known association of

**Muscle-Invasive Bladder Cancer (MIBC)**

- Neoadjuvant chemotherapy should be offered to all suitable candidates.
- Surgical modalities include open, laparoscopic, and robotic surgery.
- Extended lymphadenectomy is the current standard of care.
- Urinary diversion should be tailored to individual situations.
- Enhanced recovery protocols should be employed perioperatively.
schistosomiasis infection with bladder cancer (squamous cell carcinoma [SCC]) and in countries with high prevalence more than 40% of patients with bladder cancer have schistosomiasis [15].

5) Radiation of the pelvis: approximately 3% of bladder cancers in the UK are attributable to radiation exposure, predominantly diagnostic radiation [3].

6) Chemotherapy: Bladder cancer risk in women is twice higher due possibly to cyclophosphamide therapy for systemic sclerosis [16]. The tumours can occur years after cyclophosphamide exposure (>10) and is due to the irritation and damage from its metabolite acrolein. Bladder cancer risk is also reported to be threefold greater amongst renal transplant recipients [17].

7) Human papillomavirus: Bladder cancer risk is up to 2.8 times higher amongst those with human papillomavirus infection. Incidence is three times more common in men who have viral Condylomata acuminata [18, 19].

8) Diabetes mellitus: Risk of bladder cancer is 20% higher in people with Type 2 diabetes who have been on long-term therapy with pioglitazone. This increased risk is not associated with other people who do not have diabetes [20]. The risk of bladder cancer in patients with Crohn’s disease has doubled [21]. Excessive analgesic consumption [8] and nitrosamines are considered risk factors for bladder cancer. A high index of suspicion should be held for patients who often have a long history of chronic urinary infection and chronic cystitis [22].

### 21.1.2.2 Nonmodifiable Risk Factors

Some nonmodifiable risk factors include:

**Age:** Bladder cancer is more common in the elderly, probably due to the long latency period needed for carcinogenesis with some of the modifiable risk factors.

**Sex:** Although this was mainly due to exposure of men more than women to the modifiable risk factors, now the incidence is equalising.

**Race:** People of Afro-Caribbean descent are less susceptible to bladder cancer than Caucasians; however, people of Afro-Caribbean descent have a poorer prognosis.

**Genetic:** Genetic abnormalities have been linked to increase bladder cancer; these include deletions of chromosomes 9 (p16 gene), 11, 13 (retinoblastoma [Rb] gene), and 17 (p53 gene) leading to inactivation of tumour suppressor genes such as p53 mutations, Rb gene mutations, and p16 cyclin-dependent kinase inhibitor gene. In addition, but to a lesser degree, activation of oncogenes such as p21 ras, c-myc, c-jun, and erbB-2, and increased expression of vascular endothelial growth factors (VEGF), leading to increased angiogenesis, also have a role. Deletion of chromosome 9 is associated with low-grade superficial cancer, while p53 mutations and RB loss with high-grade disease.

### 21.1.3 Clinical Features

Visible haematuria (VH) is the presenting symptom in nearly 80–90% of patients. Nonvisible haematuria (NVH) accounts for 5–15% of patients and about 10–15% patients present with lower urinary tract symptoms such as frequency, urgency, dysuria, and suprapubic pain and recurrent UTIs. About 5% have symptoms of advanced or metastatic disease such as anaemia, uremia obstructive uropathy with renal failure, lower limb oedema due to lymphatic or venous obstruction, bone pain, weight loss, or cachexia. Pneumaturia is highly suggestive of a colovesical fistula. In the early phase of the disease, very few to no signs can be found. While in late cases, induration or mass in the suprapubic region may be felt on rectal examination [23].

### 21.1.4 Investigations

As the main presenting feature is haematuria, all patients with VH and NVH with symptoms will need full urological investigating to rule out cancer, while patients with NVH with no symptoms will need their investigations tailored.

As general guide, all patients with VH and symptomatic NVH will need urine dipstick with and without urine cultures, upper tract ultrasound, and a flexible cystoscopy, with patients >40 years of age requiring contrast computed tomography (CT) scans. Asymptomatic patients with NVH will need urine dipstick with and without urine cultures, upper tract ultrasound, and a flexible cystoscopy; if those come back clear, there is no need for further investigations.

Patients with persistent NVH do not need repeated investigations; however, if estimated glomerular filtration rate (eGFR) is <60 ml/min−1, protein-to-creatinine ratio <50 (or proteinuria), or blood pressure >180 mm Hg, a nephrology review is warranted. IgA nephropathy is the most common cause of NVH in patients <40 years of age.

### 21.1.4.1 Urine Cytology

Urine for cytology must be fixed in formalin; otherwise, cytology makes interpretation difficult. The cytological features of malignancy include increased nuclear-to-cytoplasm ratio or clumps of multinucleate cells. False-positive findings occur with urothelial injury (e.g. by a stone). Nuclear enlargement is better assessed by flow cytometry [24]. Improved sensitivity of cytology is achieved if three separate specimens on three consecutive days are analysed. The sensitivity is reported to be 9% in grade 1 (G1) tumours, 32% in grade 2 (G2) and in high-grade lesions sensitivity is up to 90% and specificity...
98–100% [25, 26]. However, false-positives occur due to infection, inflammation, stones, instrumentation and catheterization, intravesicular instillations, and in patients who had previous radiotherapy.

21.1.4.2 Urinary Biomarkers
Specific bladder cancer urinary markers have recently been shown to increase the detection rates of bladder cancer using noninvasive methods. Enzyme-linked immunosorbent assay (ELISA) tests for bladder tumour antigen or nuclear matric protein 22 increase the sensitivity for detecting transitional cell cancer (TCC). ImmunoCyt has a high sensitivity for low-grade cancers, fluorescence in situ hybridization (FISH) (urovysion) detects chromosome nine mutations, leading to increased detections. Despite the progress made in urinary biomarkers, they still remain costly and do not replace cystoscopy. Therefore, direct visualisation of the bladder tumour remains the gold standard.

21.1.4.3 Imaging
21.1.4.3.1 Ultrasound
Ultrasound assessment of the kidneys and bladder has largely been replaced with CT urography. As sensitivity of ultrasound for detection of ureteric and pelvic tumours is low, most patients require a CT urogram [27].

21.1.4.3.2 Intravenous Urogram
Traditional intravenous urograms (IVUs) have almost entirely been replaced with CT urography. Standard IVU may show filling defects in the upper urinary tract and bladder as well as ureteric obstruction which usually signifies invasion of the muscle [27].

21.1.4.3.3 CT
A CT, besides assessing the local stage, may show enlarged pelvic lymph nodes and other metastases [28].

21.1.4.3.4 Magnetic Resonance Imaging
The main advantage of magnetic resonance imaging (MRI) in staging bladder tumours over CT is its ability to distinguish between oedema and infiltrating cancer [29].

21.1.4.3.5 Bone Scan
Bone scan is not routinely performed in bladder cancer. If a patient is symptomatic or liver function tests are abnormal, specifically the alkaline phosphatase, a bone scan can be performed to rule out metastasis.

21.1.4.4 Cystoscopy
Unless a tumour is clearly demonstrated on ultrasound or CT urogram, the next investigation for haematuria or suspected bladder cancer is a cystoscopy.

21.1.4.4.1 Flexible Cystoscopy
Flexible cystoscopy has revolutionised outpatient assessment of the lower urinary tract under local anaesthesia. Flexible cystoscopes can be classified as fibrescopes because they contain fibre-optic bundles within a flexible shaft that illuminate the viewing area and transmit images to the eye piece. In these cystoscopes tip deflection is up to 210°.

Digital flexible cystoscopes use a video chip instead of fibres. Focusing is not necessary as video chip delivers a uniform-focused picture with a high optical resolution. The tip of these is only 9.8 F and hence easier to insert.

21.1.4.4.2 Rigid Diagnostic Cystoscopy
Technological advances in optical diagnosis of bladder cancer have exploited the physical properties of light and biochemical principles to enhance diagnostic yield of the procedure.

Narrow band imaging (NBI) involves filtration of white light into two distinct bands: blue (415 nm) and green (540 nm) with different penetration depths. The blue band enhances the superficial capillary network, whereas the green component enhances the visibility of deeper vessels. As tumours are vascular, the contrast between the tumours and the normal bladder is enhanced by NBI [30, 31].

NBI-assisted resection of the bladder tumours improves complete surgical removal of the bladder tumours compared to resection with white light cystoscopy (WLC) [32].

Photodynamic diagnostic cystoscopy (PDD) involves administration of 5-aminolevulinic acid (5-ALA), which bypasses the rate limiting step in the biosynthesis of heme. It induces high levels of proto-porphyrin IX (PpIX) in mitochondria of neoplastic or highly proliferating cells. PpIX is an effective photo-sensitizer. Lipophilic derivative of 5-ALA, hex aminolevulinic acid (HAL) has better penetration of cell membranes and interstitial spaces producing twice as good fluorescence in half long dwell time compared at a concentration that is 45 times lower [33].

Fluorescence is caused by interaction of light (photons) with the outer electrons of fluorochromes. Fluorochromes absorb light with higher energy per photon and re-emit light with lower energy per (secondary photon). This produces a shift in colour between excitation and fluorescent light. A special endoscope system which has a xenon lamp and is equipped with blue filter illuminates the bladder cavity. A gel cable is used for light transmission as light intensity is higher. Scope and camera head are fitted with additional filters to increase contrast and sharpness of the images. Pp IX + blue light (high energy 400 nm) = red fluorescence (low energy 640nm.).

PDD is more sensitive in detecting additional tumours (by 20%) than WLC (Figure 21.1). This is particularly the case in patients with carcinoma in situ (by 23%). PDD-assisted tumour resection achieves better clearance of
the tumours, and hence, reduced the risk of residual tumours (WLC = 1:2 vs PDD = 1:7). This translates into longer recurrence-free survival [34]. However, the higher diagnostic sensitivity with PDD does not translate into improved recurrence-free survivals [35].

21.1.5 Transurethral Resection

Transurethral resection of bladder tumour (TURBT) is the most common oncological operation in urological surgery, usually performed under general anaesthesia (GA) with full muscle relaxation. In patients unfit for GA, the procedure can be carried out under spinal anaesthesia. Bimanual examination should be performed before and after resection routinely, to assess palpable masses that can give an indication of the stage (no palpable mass post-TURBT: T2 disease; palpable mass: T3l fixed mass: T4).

This procedure has three clear objectives [36]:

1) Removal of all the visible tumours
2) Establishing type of the tumour and grade
3) Accurate pathological staging

There is a tendency in many units to delegate the procedure to junior team members without any supervision, resulting in need for repeat resections due to the higher rate of residual tumours left and variable rates of recurrence at three months (single tumours 0–36% and multiple tumours 7–75%) [37]. Recurrences detected at the first follow-up cystoscopy may represent residual tumour rather than recurrence. Hence, recurrence at the first check cystoscopy is regarded as one of the surrogate markers of quality of resection. This is also an important prognostic marker for subsequent recurrences and progression in higher grade and T1 disease [38, 39].

Small tumours may be removed with a single stroke of the resectoscope loop (Figure 21.2). In resecting a larger bladder tumour, one should keep to a regular plan [40].

The first step is to find the edge of the stalk by trimming away the overhanging papillary bush at one side (Figure 21.3). Once the edge has been found, the base of the stalk is coagulated with the roly-ball electrode to seal the vessels in the stalk; the rest of the resection then becomes relatively bloodless.

The resection is continued by following the edge of the stalk all round carrying the strokes of the resectoscope from the periphery towards the centre, to keep the margin of the stalk cleanly cut and prevent the bush from overhanging. Eventually, the entire bush will have been removed. The chips are now evacuated and sent to the laboratory in formalin labelled ‘bladder tumour’.

A second deliberate resection is then performed of the base of the stalk to sample the deeper layers of muscle. This tissue is sent separately labelled as ‘deep tumour base’ to help the pathologist stage the tumour (Figure 21.4). The base is thoroughly coagulated with the roly-ball to seal off blood vessels and destroy any malignant cells that may have been left behind. Haemostasis must be complete.

If the tumours are situated on the lateral wall of the bladder near the base, there is a risk of obturator nerve stimulation, which in turn can cause perforation or bleeding due to the sudden jerking movement as the thigh muscles are stimulated (obturators supplies the adductors of the thigh). Risk can be reduced by anticipating potential obturator stimulation, low intensity short bursts of the current, avoiding overfilling the
and even leaving it slightly underfilled, and using muscle relaxation to paralyse the patient. After removal of a small tumour, a catheter is not always necessary, but for larger tumours it is wise to leave an irrigating catheter in place for 24 hours.

### 21.1.5.1 Complications

Complications of TURBT include:

1) Infection and bleeding

2) Small perforations of the detrusor are of little consequence; in fact, as a complete resection needs to include detrusor muscle, small perforations can be deemed as part of the procedure with an intent to cure. A minor extravasation of the irrigant will soon be reabsorbed, so long as the catheter is draining freely.

3) Large perforations will need repair, especially if into peritoneal cavity; laparotomy will be required for closure of the hole in the bladder and to detect and repair any potential diathermy injury to the adjacent bowel (Figure 21.5). If the perforation is extraperitoneal, a leaving urinary catheter in situ for 10–21 days will be sufficient.

4) Transurethral syndrome: fluid overload can occur with large tumours

5) Urethral strictures if the resectoscope was forcibly entered causing urethral trauma.

### 21.1.5.1.1 Very Large Papillary Tumours

Papillary tumours may fill the whole bladder. In these unusual situations, it is best to plan a staged resection (Figures 21.6 and 21.7). If the tumour proves to be of
Figure 21.5 (a and b) A moderate sized bladder tumour on computed tomography (CT); (c–e) CT cystogram showing preformation post-transurethral resection of bladder tumour (TURBT) with contrast leaking outside the bladder. Source: Photographs courtesy of Dr Neil Collins Southmead Hospital.
lower grade and noninvasive then one should proceed to clear the residual tumour. On the contrary, if the tumour is of higher grade or invasive radical cystectomy would be the treatment of choice [41, 42].

21.1.5.1.2 Large Solid Tumours
There is little point in attempting to resect a large solid tumour completely because some permutation of radiation, chemotherapy, or cystectomy is going to be needed. A few deep bites should be taken from the rolled edge of the tumour for the purpose of staging and grading (Figures 21.6 and 21.7).

21.1.5.1.3 Tumours in the Divertica
On performing a cystoscopy for haematuria in a bladder with diverticula, it is important to get a good look inside each of them. Cancer inside a diverticulum may cause erythema and also oedema of the edge of the opening causing complete closure. Imaging (MRI/CT) is advisable in suspected tumours within diverticula with a narrow neck [43].

21.1.5.1.4 Re-resection in High-Risk NMIBC
Repeat transurethral resection two to six weeks after initial resection can increase recurrence-free and progression-free survival by completely clearing any residual

\[\text{Figure 21.6 Very large bladder tumour occupying the majority of the bladder. Source: Photographs courtesy of Dr Neil Collins Southmead Hospital.}\]
21.2 Field Biopsies

These are not recommended as a routine, but should be obtained in the following situations;

a) Positive urine cytology in the absence of a visible tumour.
b) Nonpapillary exophytic tumour.
c) Abnormal appearance of urothelium.

Prostatic urethral biopsies are indicated if

a) Positive cytology but no visible tumour in the bladder.
b) Multifocal tumours in the bladder or bladder neck.
c) Carcinoma in situ (CIS) at the bladder neck or trigone.
d) Visible abnormalities in the urethra.
e) Patient who is a potential candidate for orthotopic bladder substitution.

These biopsies should be sent in separate containers for pathologic assessment. The biopsy sites should be coagulated to stop bleeding.

21.3 Pathology

21.3.1 Benign Lesions of the Bladder

Many benign lesions of the bladder pose diagnostic challenge on endoscopic examination. The definitive diagnosis relies on histology (Table 21.1).

21.4 Malignant Tumours of the Bladder

Malignant tumours can be classified into primary and secondary. The primary can be further divided into urothelial and nonurothelial tumours. The majority of primary bladder cancer (>95%) arises from the epithelium.

21.4.1 Primary Tumours

21.4.1.1 Urothelial Neoplasm

For classification of the urothelial tumours and its variants (Table 21.2) [59].

21.4.1.2 Urothelial Dysplasia

Urothelial dysplasia may represent an early phase in the sequence of evolution to malignant change in the bladder. It is characterised by cell crowding and loss of cell polarity. The changes within cell structure include enlargement and variation in the shape of the nuclei, whereas the nucleoli remain small. Additional features include coarsening of the chromatin and hyperchromasia and absence of mitosis.

21.4.1.3 Carcinoma in Situ

CIS is a flat lesion featuring severe cellular atypia, which is a form of noninvasive urothelial carcinoma. The hallmark of CIS is loose cells, which easily slough off, thus making urine cytology a reliable test. CIS is primary when occurs in isolation, concurrent when it is associated with exophytic tumours, or secondary when occurring in patients with a history of previous tumour. At cystoscopy, CIS may appear entirely normal or at worse, slightly injected, resembling ordinary bacterial cystitis, and looks like velvety patch on cystoscopy [60].

21.4.1.4 Papillary and Solid Urothelial Carcinoma

Other tumours arising from urothelium are either papillary or solid. Some urothelial cancers are however
<table>
<thead>
<tr>
<th>Table 21.1 Benign lesions of the bladder.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postoperative spindle cell nodule</strong></td>
</tr>
<tr>
<td>a) Reactive spindle cell proliferation at the site of a previous surgical procedure, evident about 4 months after the procedure.</td>
</tr>
<tr>
<td>b) Friable nodule on cystoscopy</td>
</tr>
<tr>
<td>c) Microscopically – interlacing bundles of unremarkable spindle cells with background of inflammation, haemorrhage, oedema, neo-vacuolarisation, and myxoid change [44].</td>
</tr>
<tr>
<td><strong>Inflammatory pseudo-tumour</strong></td>
</tr>
<tr>
<td>a) Appears as a broad-based polyp.</td>
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<tr>
<td>b) Histologically similar to spindle cell nodule but may involve full thickness of the bladder.</td>
</tr>
<tr>
<td>c) No history of previous surgery in these patients</td>
</tr>
<tr>
<td>d) Differential diagnosis includes leiomyosarcoma and sarcomatoid carcinoma [45].</td>
</tr>
<tr>
<td><strong>Urothelial hyperplasia</strong></td>
</tr>
<tr>
<td>a) Flat or papillary.</td>
</tr>
<tr>
<td>b) Papillary hyperplasia – mucosa is thrown into folds but without secondary branching of papillary structures. These are lined by benign papillary epithelium with increased thickness of more than seven layers [46].</td>
</tr>
<tr>
<td><strong>Nephrogenic metaplasia</strong></td>
</tr>
<tr>
<td>a) Reactive mucosal lesion associated with trauma, stones, infection, or a recent surgical procedure.</td>
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<tr>
<td>b) Single or multiple sessile or papillary lesions ranging 1–4 cm</td>
</tr>
<tr>
<td>c) Differential diagnosis – mucin producing adenocarcinoma or papillary urothelial carcinoma.</td>
</tr>
<tr>
<td>d) Histologically it may be cystic, papillary or polypoid. The cells lining the tubules and cysts are however uniform and benign showing no mitotic activity [47].</td>
</tr>
<tr>
<td><strong>Ectopic Prostate</strong></td>
</tr>
<tr>
<td>a) Cystoscopy – papillary or polypoid lesion either on trigone or bladder neck.</td>
</tr>
<tr>
<td>b) Histologically similar to the prostate gland covered by normal urothelium [48].</td>
</tr>
<tr>
<td><strong>Fibro-epithelial polyp</strong></td>
</tr>
<tr>
<td>Commonly a solitary polyp composed of a fibromuscular core with scanty inflammatory infiltrate covered by normal urothelium.</td>
</tr>
<tr>
<td><strong>Amyloidosis</strong></td>
</tr>
<tr>
<td>a) Primarily from the bladder without evidence of systemic amyloidosis.</td>
</tr>
<tr>
<td>b) Primary bladder amyloidosis – sessile or nodular lesion on cystoscopy.</td>
</tr>
<tr>
<td>c) Microscopically there is deposition of amyloid within the submucosal and muscle layers of the bladder.</td>
</tr>
<tr>
<td>d) Systemic disease – amyloid deposition is mainly in the blood vessels and lamina propria [49].</td>
</tr>
<tr>
<td><strong>Endometriosis</strong></td>
</tr>
<tr>
<td>a) Found in 1% of patients with pelvic disease.</td>
</tr>
<tr>
<td>b) Most patients are asymptomatic.</td>
</tr>
<tr>
<td>c) Symptomatic patients – increased urinary frequency, dysuria, and haematuria. Almost 50% of patients have a lower abdominal mass on examination.</td>
</tr>
<tr>
<td>d) Cystoscopy – blue, red, black, or brown cysts.</td>
</tr>
<tr>
<td>e) Microscopically lesion consists of glandular spaces lined by endometrial epithelium surrounded by a variable amount of endometrial stroma [50].</td>
</tr>
<tr>
<td><strong>Endocervicosis</strong></td>
</tr>
<tr>
<td>a) Müllarian lesion involving the bladder after a Caesarean section.</td>
</tr>
<tr>
<td>b) Storage symptoms, lower abdominal pain, or haematuria.</td>
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<tr>
<td>c) Cystoscopy – mucosal nodules</td>
</tr>
<tr>
<td>d) Microscopically consist of mucin containing glandular structure involving the detrusor muscle lined by a single layer of cuboidal or columnar epithelium [51].</td>
</tr>
<tr>
<td><strong>Villous adenoma</strong></td>
</tr>
<tr>
<td>a) Exophytic papillary tumour which usually has a mucinous surface.</td>
</tr>
<tr>
<td>b) Microscopically it is composed of papillary structures lined by atypical columnar epithelium mixed with goblet cells.</td>
</tr>
<tr>
<td>c) Once removed, they do not tend to recur [52].</td>
</tr>
<tr>
<td><strong>Papilloma</strong></td>
</tr>
<tr>
<td>As per WHO Criteria, for a lesion to be qualified as papilloma, it should have the following five features:</td>
</tr>
<tr>
<td>i) Size &lt;2 cm in greatest dimension</td>
</tr>
<tr>
<td>ii) Number: Usually solitary with one or more fine fibromuscular cores</td>
</tr>
<tr>
<td>iii) Lining: architecturally and cytologically normal urothelium</td>
</tr>
<tr>
<td>iv) Intact umbrella cell layer and no mitotic figures</td>
</tr>
<tr>
<td>v) Patients younger than 50 years</td>
</tr>
<tr>
<td>Bladder papilloma accounts for less than 3% of the papillary lesions It has a single layer of cells, with no malignant cytological features, and an intact basement membrane [53].</td>
</tr>
</tbody>
</table>
non-papillary and classified as (i) a papillary growth, (ii) a solid nodule, or (iii) an ulcer. In general, the less differentiated the tumour, the more solid and ulcerated it becomes. Bladder tumours may be single (60%) or multiple (40%) and sometimes are associated with urothelial tumours of the kidney pelvis and ureter. The rare variants of the urothelial tumours include:

- Nested
- Microcystic
- Inverted growth pattern
- Giant Cell
- Lymphoepithelioma-like
- Lymphoma like
- Sarcomatoid

21.4.1.5 Nonurothelial Tumours
Most of the tumours arising from urothelium are TCCs. Neoplastic transformation in metaplastic transitional epithelium leads to squamous cell and adenocarcinoma. Primary nonurothelial tumours account for less than 5% of all bladder malignancies in the Western world. These tumours include:

- **Squamous cell carcinoma**: This arises in areas of urothelium that have undergone metaplasia due to chronic irritation such as is usual in bilharziasis, long-term catheters, bladder stones, or recurrent UTIs. It is preceded by keratinising squamous metaplasia (leucoplakia), also called ‘squamous pearls’ [61]. This needs to be distinguished from the ‘squamous metaplasia’ of the trigone, which is a normal finding in many women and is not pre-malignant [62]. Mutations in the p53 and retinoblastoma (RB) genes have also been implicated.

- **Adenocarcinoma**: Primary adenocarcinoma of the bladder may originate in the bladder or urachus. Nonurachal adenocarcinoma accounts for the majority of tumours (80%). The urachus is the foetal allantois, a continuation of the hindgut. It is usually lined by columnar epithelium and almost invariably gives rise to adenocarcinoma arising from the dome or outside the bladder invading into the dome (Figure 21.8). Elsewhere, adenocarcinoma arises in areas of urothelium that have undergone metaplasia through the intermediate stage of cystitis cystica and cystitis glandularis [63]. Adenocarcinoma is classified according to its cellular features into enteric, mucinous or colloid, signet ring, clear cell, mixed, and nonspecific subtypes. Presentation is either of haematuria, bloody discharge from the umbilicus, or as a subumbilical mass. Treatment is by a partial cystectomy with excision of the median umbilical ligaments and umbilicus.

- **Lymphoma**: Primary lymphomas of the bladder account for 0.2% of extranodal disease. The majority
Table 21.2 Classification of urothelial (transitional cell) neoplasms including variants of urothelial carcinoma.

I. Urothelial (transitional cell) neoplasia
   A. Benign
      i. Transitional papilloma (WHO [2002]/ISUP; WHO, 1973, grade 0)
      ii. Inverted papilloma
   B. Papillary urothelial neoplasm of low malignant potential (WHO [2002]/ISUP; WHO, 1973, grade I)
   C. Malignant
      i. Papillary
         a. Typical (low grade or high grade, WHO [2002]/ISUP; WHO 1973, grade I, II and III)
            1. Variant
               (a) With squamous or glandular differentiation
            b. Micropapillary
      ii. Nonpapillary
         a. Carcinoma in situ
         b. Microinvasive carcinoma
         c. Frankly invasive carcinoma
            1. Variants containing or exhibiting
               (a) Squamous differentiation
               (b) Glandular differentiation
               (c) Deceptively benign features
                  • Nested pattern
                  • Small tubular or glandular pattern
                  • Microcystic pattern
                  • Inverted pattern
               (d) Micropapillary histology
               (e) Sarcomatoid foci ('sarcomatoid carcinoma')
               (f) Urothelial carcinoma with unusual cytoplasmic features
                  • Clear cell (Glycogen rich)
                  • Plasmacytoid
                  • Rhabdoid
                  • Lipoid rich
               (g) Urothelial carcinoma with trophoblastic differentiation
               (h) Unusual stromal reactions
                  • Pseudosarcomatous stroma
                  • Stromal osseous or cartilaginous metaplasia
                  • Osteoclast-type giant cells
                  • With prominent lymphoid infiltrate
      (i) Urothelial carcinoma with multiple patterns of divergent differentiation
   II. Undifferentiated Carcinoma
      i. Small-cell carcinoma
      ii. Large-cell neuroendocrine carcinoma
      iii. Lymphoepithelioma-like carcinoma
      iv. Osteoclast-rich carcinoma
      v. Giant cell carcinoma
      vi. Not otherwise specified
of the patients are women in sixth or seventh decades of life presenting with haematuria or storage symptoms. Bladder involvement may be diffuse or appear as polypoid lesion. Immunohistochemistry helps in clinching the diagnosis and classification of the type of lymphoma. The variants include mucosa-associated lymphoid tissue (MALT), diffuse large cell, small cell, and rarely, Hodgkin lymphoma [64]. Involvement of the bladder can be secondary to the systemic disease.

d) Plasmacytoma: This may be part of the multiple myeloma or primarily a bladder lesion called ‘plasmacytoma’. It appears as sessile or pedunculated mural nodule with intact overlying mucosa. On histology, it appears as sheets of atypical cells. Solitary plasmacytoma is radiosensitive lesion with low risk of recurrence. Almost 25% patients with terminal leukaemia have bladder involvement [65].

e) Melanoma of the bladder can be primary or secondary, usually presenting with haematuria. Lesions vary in size and appear as polypoid fungating lesions usually with dark pigmentation. They are composed of polygonal or spindle-shaped cells with some pigment, and diagnosis is supported if immunostaining for s-100 protein and HMB45 is positive [66, 67].

f) Paraganglioma (Pheochromocytoma): This lesion usually affects adolescents or young adults. There is no sex predilection. About 50% patients may experience symptoms caused by catecholamine release on bladder filling or voiding (i.e. paroxysmal hypertension during micturition). The manifestations include tachycardia, headache, and dizziness or fainting. On cystoscopy, the lesion is intramural and varies in size. If suspected, TURBT should be avoided because the procedure can lead to a hypertensive crisis. Paragangliomas are usually lobulated, well circumscribed, yellow-brown or pink, and composed of nests of cells (zellballen) with nuclei, which may be round or oval but bland. The cells contain abundant cytoplasm. Up to 15% of these paragangliomas are malignant [68, 69]. Treatment is by a partial cystectomy.

g) Rhabdomyosarcoma: This presents with painful frequency in children and until recently was almost uniformly fatal. It is important to be aware of its existence and make sure the child is referred to a specialist paediatric urological centre, where today a survival rate of 55% may be obtained by a combination of systemic chemotherapy and radiation; the bladder can be preserved in more than half of these cases.

### 21.4.2 Secondary Bladder Tumours

Secondary bladder involvement from neoplasms of the other organs either by direct spread or metastases accounts for 13% of the bladder lesions. Of these almost 75% are direct extension from surrounding organs such as colon, rectum, prostate, ovary, or uterine cervix. Nearly 17% are metastases from distant sites or infiltration by haematological malignancies (11%). Metastases accounts for slightly more than 2% tumours, and the most common sites include stomach, breast, kidney, and lung.

Figure 21.8 Urachal adenocarcinoma arising from the dome of the bladder along the route of the foetal allantois to the anterio-abdominal wall. Source: Photographs courtesy of Dr Neil Collins Southmead Hospital.
These lesions are generally asymptomatic but rarely may be the first manifestation of a systemic disease.

### 21.5 Grading of Transitional Cell Carcinoma

Bladder cancers are classified into three grades G1, G2, and G3 [70]. Flow cytometry gives a more objective measure of ploidy [71, 72]. The following Table 21.3 compares the histological characteristics of the different grades.

#### 21.5.1 Grading ISUP/WHO2004

Grading of tumors is according to the WHO/ISUP 2004 classification:

1. Urothelial papilloma
2. Papillary urothelial neoplasm of low malignant potential (PUNLMP)
3. Low-grade papillary urothelial carcinoma
4. High-grade papillary urothelial carcinoma

### 21.6 Staging of Bladder Tumours

TCC is staged using tumour, node, and metastasis (TNM) classification, the details are provided in Table 21.4 and (Figure 21.9).

### 21.7 Risk Stratification after Transurethral Resection of Bladder Tumour

The risk of recurrence and progression of non-invasive–muscle bladder cancer (NMIBC) is dependent on many variables; therefore, risk stratification is helpful in rationalising management. A multivariate analysis of the European Organisation for Research and Treatment of Cancer (EORTC) trials led to the development of a scoring system to calculate the short- and long-term risks of recurrence and progression based on available clinical and pathological data (Tables 21.5 and 21.6) [73]. Main prognostic factors are the size and number of the tumours, recurrence history, histological type, and grade, stage, and presence of flat lesions (CIS). Recurrent tumours, high-grade T1 tumours, and recurrence at the three-month cystoscopy are significant independent predictors of muscle-invasive disease [74].

The pitfalls of this nomogram include:

1. This table was based on a combined analysis of individual patient data with superficial bladder cancer included in seven EORTC trials.
2. Most of their patients were treated with chemotherapy, and in the 171 treated with bacillus Calmette-Guérin (BCG) therapy, no maintenance was administered.
3. The tables overestimate the risk of recurrence and progression in patients treated with BCG (for the reason cited previously).
4. Very few cases of were CIS included; hence not accurate in assessing risk of recurrence and progression in CIS

### 21.8 Treatment of Transitional Cell Carcinoma

#### 21.8.1 Non-Muscle–Invasive Bladder Cancer

This group constitutes more than 75% of the bladder tumours. Of these 60% are Ta, 30% are T1m, and 10% are CIS. Following even an adequate TURBT of NMIBC, risk of recurrence is in the range of 15–80% (Table 21.7). Most of the recurrences occur within 6–12 months after initial resection. Recurrences are generally of the same stage, but 10–15% of these tumours can progress to a

<table>
<thead>
<tr>
<th>Features</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orderliness</td>
<td>Intact</td>
<td>Slight variation</td>
<td>Complete loss</td>
</tr>
<tr>
<td>Architecture</td>
<td>Minimal change</td>
<td>Variable change</td>
<td>Loss of normal architecture</td>
</tr>
<tr>
<td>Nuclei</td>
<td>Uniform, normal spacing</td>
<td>Moderate nuclear crowding,</td>
<td>Pleomorphic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>variation of polarity</td>
<td></td>
</tr>
<tr>
<td>Chromatin</td>
<td>Finely granular</td>
<td>Hyperchromasia</td>
<td>Variable</td>
</tr>
<tr>
<td>Urothelium</td>
<td>Normal maturation, polarity and cohesiveness</td>
<td>Variable</td>
<td>Loss of polarity and cohesiveness</td>
</tr>
<tr>
<td>Nucleolus</td>
<td>No enlargement</td>
<td>Mild enlargement</td>
<td>Abundant enlargement</td>
</tr>
<tr>
<td>Cellular Polarity</td>
<td>Normal</td>
<td>Mild loss of polarity</td>
<td>Loss of polarity</td>
</tr>
<tr>
<td>Mitosis</td>
<td>Rare</td>
<td>Present</td>
<td>Abundant</td>
</tr>
</tbody>
</table>
Table 21.4: TNM staging of bladder cancer.

<table>
<thead>
<tr>
<th>T (Primary Tumour)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: ‘flat tumour’</td>
</tr>
<tr>
<td>Ta</td>
<td>Noninvasive papillary carcinoma</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades muscle (muscularis propria)</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour invades superficial muscle (inner half)</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour invades deep muscle (outer half)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades beyond muscularis propria</td>
</tr>
<tr>
<td>T3a</td>
<td>into perivesical fat</td>
</tr>
<tr>
<td>T3b</td>
<td>Microscopic invasion</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades other adjacent structures</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades any of: prostate, uterus, vagina, bowel</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades pelvic wall or abdominal wall</td>
</tr>
<tr>
<td>N (Regional lymph nodes)</td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single lymph node in the true pelvis (below the common iliac bifurcation) (hypogastric, obturator, external iliac, or presacral)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in multiple lymph nodes in the true pelvis (below the common iliac bifurcation) (hypogastric, obturator, external iliac, or presacral)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in common iliac lymph node(s)</td>
</tr>
<tr>
<td>M (Distant metastasis)</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

TNM, tumor, node metastasis.

higher grade or stage and even metastasise [75]. Thus transurethral resection of the tumour as monotherapy is an inadequate treatment. To reduce the risk of recurrence and progression, adjuvant therapies are required in the form of intravesical chemotherapy or immunotherapy. Checking cystoscopy in three months’ time is essential because it can demonstrate either incomplete resection or recurrence. If clear, then future recurrence is <30%.

21.8.2 Intravesical Chemotherapy (Mitomycin)

Instillation of a single dose of Mitomycin immediately following TURBT in patients thought to have NMIBC eliminates residual tumour cells and prevents reimplantation of tumour cells in other areas of urothelium [76]. Mitomycin C (MMC) is an antibiotic agent that inhibits DNA synthesis. It is produced by Streptomyces caesipitosus or laven-dula bacterium. The standard dose is 40 mg in 50 ml of saline instilled for about an hour after TURBT. This has to be administered in the 24 hours after the initial resection.

A single instillation reduced the overall recurrence by 35% and reduced 5-year recurrence rate from 58.8 to 44.8%. This benefit was not observed in patients with >1 recurrence in a year or EORTC recurrence score ≥5. The single instillation does not prolong either time to progression or death from bladder cancer. Hence, it is not advisable to administer intravesical agents to patients at high risk of recurrence because of its lack of efficacy in this subgroup [76].

Although a single instillation is considered sufficient in low-risk disease, it is inadequate for patients with higher-risk NMIBC [77]. MMC is beneficial in reducing the risk of recurrence but does not decrease risk of progression [78–80]. A six-week course of MMC can be offered to patients with newly diagnosed intermediate risk.

The efficacy of chemotherapeutic agent can be enhanced by reducing the urine output with preinstillation restriction of fluid intake and dissolving the drug in a buffered solution at optimal pH [81].

21.8.2.1 Contraindications: Bleeding or Bladder Perforation

Bladder irritation as a side effect is seen in nearly 15% of patients, presenting with suprapubic or back pain, dysuria, frequency, urgency (similar symptoms to cystitis, which it normally gets confused with and is treated with antibiotics; however, symptoms settle with time, ergo presuming an infection was treated). With rashes and itching where the chemicals came in contact with skin. Flulike symptoms can occur. Systemic toxicity is rare but leads to significant consequences of bone marrow suppression: neutropenia, thrombocytopenia, and anaemia.

21.8.2.2 Adjuvant Therapy with Bacillus Calmette-Guérin

Calmette and Guérin developed BCG as a live attenuated vaccine for tuberculosis originally. In 1929, Pearl noted fewer numbers of malignancies at autopsy studies in patients dying of tuberculosis. The landmark publication by Morales in 1976 on intravesical BCG in the treatment of bladder cancer changed the landscape of managing high-risk NMIBC including CIS [82]. Although there are still gaps in understanding of the anti-cancer mechanism of BCG, it is attributed to interplay of direct cytotoxic effects of BCG on the host immune response, leading to stimulation, activation, and upregulating of the immunity. A summary of key steps is presented in Table 21.8 [83].
BCG is more efficacious in reducing risk of recurrence compared to intravesical chemotherapy. BCG may delay or prevent progression in high risk tumours by 27% and reduces recurrence by 31%. This risk reduction is observed in a spectrum of high-risk G3, T1, and CIS.

BCG therapy involves a period of induction, generally once weekly for six weeks followed by maintenance therapy. BCG (80 mg in 50 ml saline) is instilled into the bladder for one hour, at least two weeks after TURBT. There is no consensus on the optimal maintenance schedule. At least one year of maintenance BCG is required to

---

**Table 21.5** Variables and assigned scores in European Organisation for the Research and Treatment of Cancer (EORTC) nomogram.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recurrence score</th>
<th>Progression score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2–7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td><strong>Tumour size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥3 cm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Prior recurrence rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≤1 per year</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1 per year</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>T classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ta</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Carcinoma in situ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Grade (1973 WHO)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>0–17</td>
<td>0–23</td>
</tr>
</tbody>
</table>

**Table 21.6** Risks of recurrence and progression.

<table>
<thead>
<tr>
<th>Total score</th>
<th>At 1 year (%)</th>
<th>At 5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15 (10–19)</td>
<td>0</td>
</tr>
<tr>
<td>1–4</td>
<td>24 (21–26)</td>
<td>1–4</td>
</tr>
<tr>
<td>5–9</td>
<td>38 (35–41)</td>
<td>5–9</td>
</tr>
<tr>
<td>10–17</td>
<td>61 (55–67)</td>
<td>10–17</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.2 (0–0.7)</td>
<td>0</td>
</tr>
<tr>
<td>2–6</td>
<td>1.0 (0.4–1.6)</td>
<td>2–6</td>
</tr>
<tr>
<td>7–13</td>
<td>5 (4–7)</td>
<td>7–13</td>
</tr>
<tr>
<td>14–23</td>
<td>17 (10–24)</td>
<td>14–23</td>
</tr>
</tbody>
</table>
demonstrate its superiority over Mitomycin in preventing recurrence as well as progression [84]. The reduction in stage progression is only seen in patients who receive induction and maintenance BCG (for at least 27 treatments over three years) (Tables 21.9 and 21.10) [85].

Nearly 60–70% of patients will have a complete response to BCG treatment, with two-thirds of non-responders and about 20% of initial responders maybe progressing to MIBC and requiring a radical cystectomy; however, they have a cure rate of >90%.

**Table 21.7** Risk stratification of bladder cancer and recommended treatment options.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Components</th>
<th>Risk of recurrence</th>
<th>Risk of progression</th>
<th>Recommended treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>G1pTa</td>
<td>15–30%</td>
<td>0–15%</td>
<td>TURBT Single MMC instillation within 24 hours (better within 1 hour of TURBT)</td>
</tr>
<tr>
<td></td>
<td>G2pTa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-grade tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PUNLMP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;3 cm in size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solitary tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>Recurrent tumours within 12 months</td>
<td>&gt;70%</td>
<td>10–15%</td>
<td>TURBT Course of MMC installations (six doses, once weekly)</td>
</tr>
<tr>
<td></td>
<td>High-grade tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;3 cm in size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>G3</td>
<td>&gt;80%</td>
<td>&gt;40%</td>
<td>TURBT Re-Resection TURBT Course of BCG (total 27 doses) or Cystectomy</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nest or micropapillary subtypes (highly aggressive)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCG, Bacillus Calmette-Guerin; MMC, Mitomycin C; TURBT, transurethral resection of bladder tumour.

**Table 21.8** Summary of mode of action of intravesical Bacillus Calmette-Guerin (BCG).

<table>
<thead>
<tr>
<th>Steps in BCG activity</th>
<th>Mediated by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Infection of urothelial or bladder cancer cells</td>
<td>Fibronectin</td>
</tr>
<tr>
<td>2) Induction of immune reaction</td>
<td>Cell types: granulocytes, T-helper cells, dendritic cells and macrophages. Immune molecules: MHC class I, CD4+, various cytokines including IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, IL17, TNF-α, and IFN-γ.</td>
</tr>
<tr>
<td>3) Induction of anti-tumour effects</td>
<td>Th1 cells (acquired immunity) via CD4+ cells and CD8+ cytotoxic T lymphocytes (driven by IL-2, TNF-α, IL-12 and IFN-γ) Th2-cells (innate immunity) through NK cells (driven by IL-4, IL-5, IL-6 and IL-10) Neutrophil recruitment (via IL-17 release) and macrophages</td>
</tr>
</tbody>
</table>

II.; interleukin, MHC; major histocompatibility complex, NK; natural killer, TNFα; tumour necrosis factor-alpha, IFNγ; interferon gamma.

**21.8.2.2.1 BCG Side Effects**

About half of patients are able to complete the induction course of BCG with only one in six completing the full three years (27 doses) course [85].

BCG can cause either local irritation with cystitis symptoms in nearly all patients (95%). It can also be associated with a fever lasting a couple of days. Systemic side effects occur in nearly 25% of patients with flulike symptoms and myalgia. Treatment is with paracetamol and anticholinergics. Rarely, hospitalisation is required.

BCGosis, or BCG sepsis is rare (<5%), but it has devastating side effects. Patients develop a high-grade fever, rigours, and progress to shock. In severe cases multiorgan failure may occur leading to death. Treatment is with anti-tuberculous drugs for six months (i.e. isoniazid, rifampicin, ethambutol, and pyridoxine).

The risk of systemic toxicity is due to systemic absorption if BCG is administered within two weeks of transurethral resection of tumour, if patient is having active bleeding, or if BCG is administered after traumatic catheterisation. During six weeks of BCG instillations, immune stimulation peaks at six weeks, and during maintenance, at three weeks. The dose response is bell-shaped and suggests that excess BCG may actually reduce the anti-tumour activity [86, 87].

**21.8.2.2 Other**

Allergic reactions with arthralgia and conjunctivitis requiring antihistamine and stopping BCG if persists over seven days.

Granulomatous prostatitis or epididymitis, requires anti-tuberculous treatment.
BCG is contraindicated in patients who are immunosuppressed or immunocompromised, pregnant, or breastfeeding, who have had a traumatic catheterisation, or a haematological malignancy.

The combination of intravesical BCG and intravesical electromotive drug administration (EMDA) MMC intravesical therapy has shown superior results to BCG alone; however, it is still being studied [88].

21.8.2.2.3 BCG Failure

- BCG-refractory: Recurrence or persistence of cancer after BCG induction treatment or presence of MIBC at first check cystoscopy.
- BCG-resistance: persistence of cancer at first check cystoscopy.

These patients will either need a radical nephrectomy or second-line chemotherapy.

21.8.2.4 BCG-Resistant CIS

The options for patients with CIS who will have recurrence subsequent to BCG therapy are:

1) Radical cystectomy
2) Thermo-chemotherapy, 50–80%
3) Intravesical gemcitabine, 50%
4) Photodynamic therapy (Photofrin 1.5 mg/Kg) + Red Laser (630 nm) 15 J/cm² - RR 75% (CIS)

Thermo-chemotherapy involves uniform heating of the bladder by radiofrequency (microwave) radiation (Figure 21.10). The temperature will be monitored by thermocouples. Cooled Mitomycin is circulated into and out of the bladder.

Adverse effects of thermo-chemotherapy include local pain, haematuria, dysuria, and bladder contracture.

21.8.3 Photodynamic Therapy

It relies on photosensitization of cancerous cells with subsequent administration of light of a specific wavelength in the presence of oxygen. These interactions lead to generation of free radicals causing cell death through apoptosis. Additionally, acute inflammatory response enhances cytotoxicity of this therapy similar to BCG therapy [89].

21.8.4 Adjuvant Intravesical Chemotherapy

The anatomical design of bladder renders it most suitable for treatment with intravesical administration of anti-tumour agents and subsequent monitoring of the response with follow-up cystoscopies. This is essentially a topical therapy which minimises the systemic toxicity of these agents due to limited absorption. Table 21.11 shows the list of drugs used.

21.8.5 Follow-up of NMIBC

Because majority of the bladder tumours are NMIBC (Ta or T1), they can be managed by endoscopic treatment, but in view of the tendency to recur, they need careful follow-up. A graphic record of the tumour site, grade, and T stage of each recurrence and number of recurrences should be maintained for continuity of care. Follow-up regimes are based on the risk stratification of each patient (Table 21.12) [90]:

Any recurrent tumours are biopsied and resected or coagulated with laser or diathermy. Very-low-risk tumours in high-risk patients may be managed with
Muscle-Invasive Bladder Cancer

When tumours recur often, and in large numbers one should have high index of suspicion of seeding from the upper tract. This should be assessed with appropriate imaging (CT urography). Blue light cystoscopy (BLC) is helpful in achieving complete clearance. Once all visible tumours have been removed, adjuvant intravesical therapy may help in reducing the recurrences. The high rate of tumour recurrence in patients with NMIBC mandates lifetime surveillance and leads to high healthcare-related costs despite the use of adjuvant intravesical therapy.

Table 21.11 Follow-up of non-invasive–muscle bladder cancer (NMIBC).

<table>
<thead>
<tr>
<th>Recurrence or progression risk</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Low risk                      | - Check cystoscopy at 3 months  
- If negative, the following cystoscopy at 9 months  
- Consideration for either yearly check cystoscopies thereafter or discharge |
| Intermediate risk             | - Patients should have an intermediate follow-up scheme (low & high risk) adapted according to individual factors  
- Check cystoscopy at 3 months  
- If negative, the following cystoscopies at 9 and 18 months  
- If negative, yearly cystoscopy checks for 5 years  
- Consideration for either yearly check cystoscopies thereafter or discharge |
| High risk                     | - Cystoscopy at 3 months.  
- If negative, flexibly cystoscopy 3 monthly for 2 yrs.  
- 6 monthly for 2 yrs.  
- Yearly thereafter  
- A yearly assessment of the upper tract is recommended |

Figure 21.10 A diagram of circuit of bladder thermos-chemotherapy.

21.9 Muscle-Invasive Bladder Cancer

Almost a third of patients have MIBC at presentation. Patients with NMIBC may also progress to MIBC. Prognosis of patients varies with the stage of the disease and status of the pelvic nodes. MIBC confined to the bladder muscle (T2) without evidence of the lymph node metastases and absence of lymphovascular invasion has an almost 90% disease-free survival at five years. On the contrary, this is reduced to 40–50% in patients with locally advanced disease (PT3-T4) and 15–35% in those with lymph node metastases [91].

Despite advancement of surgical technique, little progress has been made in improving the outcome of MIBC. The majority of patients succumb to systemic disease (22%) despite excellent local control with surgery (7% recurrence) [92]. This suggests that a significant number
of patients have micrometastatic disease at diagnosis. Hence, research is focusing on methods of eradicating occult micrometastasis with perioperative chemotherapy in MIBC.

### 21.9.1 Spread of Bladder Tumours

#### 21.9.1.1 Direct Spread
Bladder cancer spreads directly through the perivesical fat into adjacent bowel, uterus, and bone. It also spreads across the wall of the bladder probably by direct implantation – ’kiss cancer’ [93].

#### 21.9.1.2 Urine-Borne Spread
Tumours may be carried down the urethra and implanted onto abrasions caused by the passage of urethral instruments and are often implanted near the air-bubble presumably because particles of tumour are carried there at the time of transurethral resection [93].

#### 21.9.1.3 Lymphatic Permeation
Spread by lymphatic permeation, embolism carries the tumour to the regional nodes along the branches of the internal iliac artery, and from there, along the para-aortic nodes.

#### 21.9.1.4 Haematogenous Spread
Blood-borne spread by veins is a late event in bladder cancer, but occasionally it is seen even in well-differentiated and apparently superficial tumours which unexpectedly give rise to pulmonary or other distant metastases.

#### 21.9.1.5 Prostatic Route
Once a bladder cancer has invaded the prostate, it can spread by lymphatics and veins directly into the bone marrow of the pelvis, femora, and lumbar vertebrae.

### 21.9.2 Investigations in MIBC

After the initial investigations for investigation of bladder cancer, in patients established to have MIBC, a CT of the chest, abdomen, and pelvis or MRI is required to stage the disease. Bone scan is not routinely performed, but it can be useful in patients with suspected bone metastasis. These scans should be performed during the preceding six weeks prior to considering cystectomy because rate of disease progression can be fluid.

### 21.9.3 Management of Localised Muscle-Invasive Bladder Cancer (MIBC) (T2 disease +− T3a)

Radical cystectomy with appropriate urinary diversion remains the mainstay of surgical treatment for MIBC. In those who are unfit or unwilling for surgery, external beam radiotherapy (EBRT) may be of use. Radical cystectomy has traditionally been performed through the open approach, but in recent years, minimally invasive surgical (MIS) approaches for cystectomy (laparoscopic or robotic) has been increasingly adopted worldwide in an attempt to reduce the morbidity of the procedure and improve postoperative recovery.

Parra et al. reported the first cystectomy performed laparoscopically in 1992 [94]. Since then, the operation has been widely adopted in many urological centres. Improved dexterity has aided pelvic lymph node dissection and suturing in laparoscopy. With the advent of da Vinci (Intuitive) robotic systems, which utilises a master–slave concept and three-dimensional visual planes, Menon et al. [95] carried out the first robot-assisted radical cystectomy (RARC) in 2002.

The technique of robotic-assisted cystectomy is to mimic movements of the surgeon through the arms of the ‘slave’ robot in the abdomen and pelvis. In this technique,
the bladder is dissected and pelvic lymph node dissection is performed. The urinary diversion was initially performed extracorporeally, but the improvement in surgical skills has also enabled intracorporeal urinary diversions. However, robotic systems are expensive and are often inaccessible for many centres.

Lymphadenectomy is the integral component of radical cystectomy. Interestingly, there are considerable variations in outcomes with well-defined templates of lymphadenectomy. This is due to lack of standardisation of pathologic assessment of the tissue removed, variation in the number of regional lymph nodes in individual patients, and the quality of dissection amongst surgeons despite defined templates [96].

There is a therapeutic benefit of extended lymphadenectomy in patients with locally advanced disease (pT3), with 30% improvement of five-year disease-free survival regardless of the nodal status [97].

The surgical technique of a radical cystectomy begins with a long midline incision, then adhesions are separated. The peritoneum is divided to mobilise the caecum and mesentery (Figure 21.11). The bowel is packed away from the pelvis. The incision in the peritoneum is continued anteriorly to separate the bladder from the symphysis and allow the bladder to be retracted medially. If not already done, a bilateral node dissection is performed, taking the lymph nodes medial to the common and external iliac artery (Figure 21.12). The internal iliac artery is cleaned on one side and all its medial branches are ligated and divided one after the other (Figures 21.13 and 21.14). The ureters are divided and marked with stay sutures. The same procedure is repeated on the other side.

Retracting the bladder upwards, the fat is carefully cleaned from the puboprostatic ligaments to define the retropubic veins which are meticulously taken up by suture ligature and divided (Figure 21.15). If one plans to retain the urethra, the neurovascular bundles may be pushed down and laterally, without compromising the dissection and may preserve penile erection in men (Figure 21.16). Lifting the bladder upwards and depressing the rectum, the plane of cleavage between the layers of Denonvilliers fascia is opened, and the dissection carried down behind the prostate and seminal vesicles, keeping clear of the rectum (Figure 21.17).
If the urethra is to be removed, a second midline incision is made in the perineum (Figure 21.18). The corpus spongiosum is separated from the corpora cavernosa piecemeal, until the entire corpus spongiosum has been removed by turning the penis inside out (Figure 21.19). The dissection of the membranous urethra is easiest from the perineum. In front, the bulbar arteries can be seen and ligated before being divided (Figure 21.20), as are the two dorsal arteries of the penis on either side of its dorsal vein. Once this has been done, each side of the membranous urethra is freed by dividing the tough fascial bands on each side. Finally, the urethra is pulled upwards, while one finger either side of the midline depresses the rectum, and throws into prominence the rectoprostatic ligament which is divided close to the prostate (Figure 21.21). The membranous urethra is now free and is drawn up into the pelvis, allowing the prostate to be separated from the rectum under vision.

The specimen is now free. The rest of the operation is determined by the choice of urinary diversion to be employed in the particular case.

### 21.9.4 Perioperative Chemotherapy

#### 21.9.4.1 Neoadjuvant Chemotherapy

Patients with MIBC who have a good performance status and glomerular filtration rate (GFR) > 60 ml min\(^{-1}\) can receive neoadjuvant chemotherapy to downgrade the cancer as part of perioperative chemotherapy. The regimens used have only been of modest survival benefit in the range of 5–7%. A 10-year follow-up of MRC/EORTC trial of neoadjuvant CMV Phase 3 trial has demonstrated improved 10-year survival from 30 to 36%. The combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) therapy regimen has shown an improved survival of 77 months versus 46 months with surgery alone [98]. MVAC neoadjuvant chemotherapy is associated with significant toxicity such as leucopenia, mucositis, and drug-related mortality of 3–4% [99], but adding granulocyte colony-stimulating factor has significantly improved safety profile [100]. Alternative combination of gemcitabine and cisplatin (GC) therapy has gained popularity as a safer alternative after a study showing equivalent efficacy (GC = 49% and MVAC = 46%) but better safety profile [101]. However, there is no prospective study to date on comparative efficacy of this alternative regimen in the neoadjuvant setting. In an attempt to shorten the duration of therapy and improve the efficacy a dose-dense (DD) regimen of MVAC, involving administration every
Figure 21.16 To spare the neurovascular bundle to the penis, (a) the fascia is incised on either side of the dorsal veins. (b) The veins are ligated. (c) The neurovascular bundles are displaced laterally and posteriorly to reveal the urethra (d).

Figure 21.17 The bladder is pulled up, and the plane between the layers of fascia of Denonvilliers is opened between the bladder and rectum.

Figure 21.18 Urethrectomy. A midline incision is made in the perineum.
two weeks instead of four weeks with growth factor support have been tried in the treatment of metastatic bladder cancer. Similar protocols have been used in neoadjuvant setting and reported to be well tolerated [102].

Currently three different drug regimens are used in the context of neoadjuvant setting for treatment of MIBC including: (MVAC), accelerated DD MVAC, or GC have similar efficacy with response rates of 40–60%. Patients with good performance status and no visceral disease, who account for 20% of patients with MIBC, are reported to achieve more durable remission rates [101, 103, 104].

Although evidence is in support of effectiveness of neoadjuvant chemotherapy in improving survival in patients with operable bladder cancer and negative lymph node based on radiological assessment (T2–T4aN0M0) [105, 106], multi-institutional studies revealed underutilization of neoadjuvant chemotherapy; with only around 15% of patients receiving it [107].

Patients are not suitable candidates for neoadjuvant chemotherapy if they have impaired renal function, have bilateral obstruction of the upper urinary tract, or have intractable haematuria, severe lower urinary tract symptoms, or a poor performance status. Finally, patients may refuse to receive neoadjuvant chemotherapy and patient choice should always be considered.

### 21.9.4.2 Adjuvant Chemotherapy

Approximately half of patients undergoing curative cystectomy develop metastasis within two years [108]. Underutilization of neoadjuvant chemotherapy has prompted encouragement of adjuvant chemotherapy in patients who have not received neoadjuvant chemotherapy to improve outcomes. A meta-analysis of cisplatin,
Muscle-invasive Bladder Cancer has shown reduction of mortality by 23% with adjuvant chemotherapy. Similarly, Tjokrowidjaja et al. showed 25% risk reduction in mortality with adjuvant chemotherapy [106, 109]. The greatest effect of adjuvant chemotherapy is in extravesical extension (pT3a-T4a) or patients with positive lymph node diagnosis [110]. One trial of MVAC has suggested a similar long-term outcome between neoadjuvant and adjuvant chemotherapy [111].

Studies for patients with pT3a or pT4a with or without lymph node positivity randomised 327 patients to cisplatin and methotrexate (CM) against M-VAC. The five-year overall survival and tumour progression were not significantly different, although patients on the M-AC arm had a higher rate of leucopenia [112]. A phase III trial by the Association of Urogenital Oncology of adjuvant gemcitabine compared to usage after disease progression failed to show significant difference in three-year overall survival [113].

Currently, no evidence is available to support usefulness of non-cisplatin–based chemotherapy regimens in adjuvant setting. There is also lack of evidence to support the effectiveness of disease progression triggered adjuvant chemotherapy [114]. The International Consultation on Bladder Cancer in 2012, based on the available data, recommends that patients with pT3/4 or

Figure 21.20 The dorsal arteries and vein (a), and the bulbar arteries (b) are divided.

Figure 21.21 The rectum is pushed down with two fingers to display the rectoprostatic ligament which is divided.
lymph node-positive post-cystectomy who have not received neoadjuvant chemotherapy could be considered for cisplatin-based adjuvant chemotherapy if they are medically fit [105].

21.9.4.2.1 Bladder Preservation
Not all patients are fit for radical surgery or prefer such a life-changing operation. The alternative to radical surgery is EBRT. The five-year overall survival rates of concomitant radiation and chemotherapy in addition to TURBT demonstrates a median overall survival of 57% as compared to 52% in patients having a radical cystectomy [115].

21.9.4.2.2 Urethrectomy
The risk of urethral recurrence is <10%. In men, urethrectomy is considered if there is prostatic urethral involvement or positive distal urethral surgical margin of the specimen. Alternatively, a frozen section of the distal urethral margin can be done, proceeding to a urethrectomy if positive. In women, urethrectomy is considered standard practice.

21.9.4.2.3 Radiotherapy
There is no role for radiation as a monotherapy or in the neoadjuvant setting. Radiotherapy is currently used as component of multimodal treatment of MIBC in bladder-sparing strategy or for palliation of bladder cancer symptoms. The dose is 60–66 Gy to the bladder with 1.5–2 cm margin and also limited pelvic lymph nodes. EBRT is given once or twice daily in a course limited to six to seven weeks. A further booster dose to the bladder can also be given [116, 117].

Complications occur in the majority of patients (>70%); however it is self-limiting in 95% of cases. These are radiation cystitis, radiation proctitis, urethral stricture, and haematuria. Rarely, haematuria due to radiation cystitis will require intravesical treatments with transurethral resection diathermy; however, it is invariably futile. Other measure includes intravesical alum, hyperbaric oxygen, segmental artery, or even iliac embolisation, or ongoing palliative cystectomy.

Radiotherapy is not recommended in the following situations:

- Squamous cell bladder cancer.
- CIS involving large areas of the bladder.
- No response to initial chemotherapy.
- Obstructed ureters.
- Significant storage symptoms.
- Upper tract obstruction [118].

Palliative radiotherapy at a lower dose of 30–50 Gy is effective for metastatic disease-related symptoms such as bone pain and bleeding and with management of spinal cord compression.

21.9.4.2.4 Partial Cystectomy
Partial cystectomy (PC) has been categorised as a bladder-sparing modality for MIBC. It is usually reserved for tumours in the dome or in anterior bladder wall and is particularly suited for patients with relatively small urothelial tumours (Figure 21.8). PC includes full-thickness excision of the tumour with pelvic lymph node dissection. It has been reported to have 39–67%, five-year recurrence-free survival [119]. However, these patients remain at risk of intravesical recurrence and therefore need close surveillance [120].

21.9.4.2.5 Brachytherapy
Brachytherapy has been used in selected group of patients with tumours less than 5 cm and distant from the bladder neck. A 5-year and 10-year overall survival of patient with T1–3 disease is around 62% and 45%, respectively [121]. Cancer-specific survival 5 and 10 years after brachytherapy is 71 and 57%, respectively, compared to cystectomy with 76 and 64%, respectively [122]. However, these findings are limited due to the retrospective nature of the studies and variable patient population which drew up these figures. Therefore, it is difficult to draw any firm conclusions. However, in the future, brachytherapy may have potential for incorporation into a mainstay for bladder preservation.

21.9.4.2.6 Enhanced Recovery after Surgery for Cystectomy
Enhanced recovery after surgery (ERASC) is a multimodal approach to reduce postoperative complications and expedite recovery from surgery. There are four principles of enhanced recovery: preoperative planning and preparation, reducing stress of surgery, postoperative care, and early mobilisation [123].

21.9.4.2.7 Palliative Cystectomy
Management of locally advanced bladder cancer is a huge challenge. Locally advanced bladder cancer can be associated with debilitating symptoms such as bleeding, pain, severe voiding symptoms, and ureteric obstruction. The majority of patients are not eligible for radical surgery because operative management carries substantial morbidity [124].

Some studies have suggested that radical cystectomy can be offered in selected patients with reasonable general health [125–127]. Primary cystectomy in T4 bladder cancer is technically possible [128]; palliative cystectomy should only be offered when it is the only option available [129]. The alternatives are repeated transurethral resection or palliative radiotherapy or chemotherapy;
palliation and nephrostomy insertion can also be offered to relieve urinary obstruction [130].

21.10 Recurrence and Follow-up of MIBC

After cystectomy, patients remain at risk of cancer recurrence and are also prone to complications from urinary diversion. Therefore, they need adequate follow-up after cystectomy. Knowledge of the patterns of recurrence is paramount to having an efficient monitoring strategy from a cost perspective and also to maximise detection of recurrences. A recurrence rate of 48.6% has been reported after radical cystectomy over an extended 20-year follow-up [131].

Most recurrences occur in the first two years after cystectomy. Recurrence can occur either locally in the pelvis, upper part of the urinary tract, urethra, or at distant anatomical locations [132]. The most common sites of distant metastases are lung, liver, and bone [133]. As expected, recurrence is dependent on the pathological stage of the disease [132], with risk being higher in locally advanced tumours and in case with a positive lymph node involvement [134].

Recurrence can be detected either on routine follow-up tests or by symptoms such as flank pain and visible haematuria. There is a slight survival benefit for recurrences detected on routine follow-up compared to recurrences identified as a result of symptoms. This justifies the need for routine cross-sectional imaging [135]. Table 21.13 details the follow-up schedule [136].

Upper urinary tract recurrence is in the range of 2–9% at median 24–41 months after cystectomy [137–141]. The risk factors for recurrence of urothelial cancer in the upper urinary tract are history of CIS, history of recurrent bladder tumours before cystectomy, and involvement of distal ureter in cystectomy histopathology. Fifteen-year recurrence rate was 0.8% in the upper tract in patients without any risk factors, whilst rate of recurrence was found to be 8.4 and 13.5% for one to two risk factors and three to four risk factors, respectively. This risk was non-existent for non-TCCs of the bladder [142]. Therefore, the routine follow-up should be based on risk factor stratification.

Suspicious findings on cross-sectional imaging can be further investigated by ureterorenoscopy to obtain a histologic diagnosis. However, it has limitations in acquiring adequate amount of tissue to determine accurate extent of the tumour. In cases of invasive upper tract recurrence, radical nephroureterectomy can provide prolonged survival in patients [139].

Local recurrence rate is 5–16.5% over five years [143, 144]. About 50% of tumours metastasise without local recurrence. However, 70% of local recurrences are associated with distant metastasis. The prognosis from local recurrence is very poor; survival from diagnosis is four to eight months. Approximately 80% of patients die of disease within one year, and only 3.5% experience five-year survival [145].

Recurrence rate in urethra at median 14–24-months is 3.7–8.1%. Patients at high risk of urethral recurrences are those with positive urethral margins at cystectomy [146], bladder neck tumours, and tumours involving the vagina in females [147]. Routine follow-up has not been shown to increase chance of earlier diagnosis in urethral recurrences. Urethral bleeding, mass, or pain should prompt thorough assessment by urethral washing and ureteroscopy. When recurrence occurs, the treatment option can be either fulguration for CIS and noninvasive tumours; or urethrectomy for invasive tumours [148, 149].

21.11 Management of Locally Advanced MIBC (T3b/T4) and Metastatic Disease (N1 or M1)

The natural history of metastatic bladder cancer has a median survival of four to six months. Survival is better in metastasis to lymph nodes, lung, and soft tissue compared to bone and liver [99, 150].

Poor prognostic indicators include Karnofsky performance status (<80), weight loss, elevated serum alkaline phosphatase or lactate dehydrogenase (LDH) levels, and non-transitional cell histology [108, 150, 151]. Unfavourable outcomes are also associated with visceral metastasis [152] and multiple metastatic sites [103]. However, age alone has a negligible impact on response or toxicity to chemotherapy [153–159]. This led to introduction of combination regimens (MVAC) which achieved 36% complete response [160]. In a randomised trial, MVAC was compared with cisplatin alone and a superior response rate of 39 vs 12%, respectively, was achieved [99]. Combination of gemcitabine with cisplatin (GC), has however been shown to have improved response by 25–40% and are better tolerated than MVAC. GC combination is quickly becoming the standard chemotherapy regimen, with <1% toxic death rate as opposed to 3% with MVAC, mainly from neutropenic sepsis. Carboplatin can be used if cisplatin is contraindication such as those with poor performance status or eGFR <60 ml min⁻¹. Taxanes, such as paclitaxel and docetaxel,
### Table 21.13  Recommended follow-up for bladder cancer after radical treatment (cystectomy or radiotherapy).

<table>
<thead>
<tr>
<th>Cancer stage</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>History, physical examination, laboratory testing, upper tract ultrasound</td>
<td>History, physical examination, laboratory testing, upper tract ultrasound</td>
<td>History, physical examination, laboratory testing, upper tract ultrasound</td>
<td>History, physical examination, laboratory testing, upper tract ultrasound</td>
<td>History, physical examination, laboratory testing, upper tract ultrasound</td>
</tr>
<tr>
<td>T2</td>
<td>6 monthly: history and physical examination Laboratory testing Chest/abdo/pelvic CT scan bone scan if symptomatic</td>
<td>6 monthly: history and physical examination Laboratory testing Chest/abdo/pelvic CT scan bone scan if symptomatic</td>
<td>6 monthly: history and physical examination Laboratory testing Chest/abdo/pelvic CT scan bone scan if symptomatic</td>
<td>Annual: history and physical examination Laboratory testing Chest/abdo/pelvic CT scan bone scan if symptomatic</td>
<td>Annual: history and physical examination Laboratory testing Chest/abdo/pelvic CT scan bone scan if symptomatic</td>
</tr>
<tr>
<td>T3</td>
<td>History and physical examination, laboratory study at 3 months, repeat 6 monthly; CT at 6 and 12 months, upper tract imaging at 12 months</td>
<td>6 monthly: history and physical examination laboratory study CT at 24 months bone scan if symptomatic</td>
<td>6 monthly: history and physical examination laboratory study Chest/abdo/pelvic CT scan loopogram bone scan if symptomatic</td>
<td>Annual: history and physical examination laboratory study Chest/abdo/pelvic CT scan loopogram bone scan if symptomatic</td>
<td>Annual: history and physical examination laboratory study Chest/abdo/pelvic CT scan loopogram bone scan if symptomatic</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Similar Follow up as for high-risk NMIBC History and physical examination, laboratory study Chest/abdo/pelvic CT scan at 6 and 12 months</td>
<td>Similar Follow up as for high-risk NMIBC History and physical examination, laboratory study Chest/abdo/pelvic CT scan</td>
<td>Similar Follow up as for high-risk NMIBC History and physical examination, laboratory study Chest/abdo/pelvic CT scan</td>
<td>Similar Follow up as for high-risk NMIBC History and physical examination, laboratory study Chest/abdo/pelvic CT scan</td>
<td>Similar Follow up as for high-risk NMIBC History and physical examination, laboratory study Chest/abdo/pelvic CT scan</td>
</tr>
<tr>
<td>T4, metastatic SCC, adenocarcinoma</td>
<td>Symptomatic control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory study: renal function, FBC, liver function test, vitamin B₁₂.  
CT: to include chest, abdomen, and pelvis.  
Bone scan is not a routine follow-up study, it can only be performed in patients suspected of having bone metastasis.  
FDG-PET whole body is indicated for suspected or nodal metastasis.  
CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; NMIBC, non-invasive–muscle bladder cancer; SCC, squamous cell carcinoma.
are microtubule disassembly inhibitors and are used as second-line agents, with responses ranging between 25 and 80% when used with cisplatin.

21.12 Bladder Cancer Variants

21.12.1 Squamous Cell Carcinoma

Squamous cell cancer is almost never diagnosed before it has invaded deeply into the wall of the bladder. The squamous cell cancer that occurs as a sequela of chronic bilharziasis is said to be unresponsive to radiation treatment. Treatment by radical total cystectomy has excellent results. Bilharziasis is endemic in countries where the standard of living is poor, and few patients can afford urostomy appliances even if they would stick on in conditions of heat and moisture. This should be taken into consideration for the type of urinary diversion to be fashioned. Where squamous cancer is not associated with bilharziasis, it is also somewhat radioresistant, and total cystectomy is advised for cases with muscle invasion. The diagnosis of squamous cell cancer is usually obvious at cystoscopy; there is a thick dead white crust of keratin, and the urine has a characteristic and unforgettable stink.

21.12.2 Carcinoma of the Urachus

This rare carcinoma presents with haematuria (Figure 21.8). On cystoscopy, a cherry-red swelling is seen in the vault near the air-bubble. Bimanual palpation always shows a much larger mass outside the bladder than the lump seen on cystoscopy (Figure 21.22).

Through a midline incision, the skin and anterior rectus sheath are separated (Figure 21.23), and then a wedge-shaped en bloc excision is performed of all the tissues from the umbilicus downwards and outwards to the obliterated hypogastric arteries (Figure 21.24). This broad wedge of tissue is taken down to the
trigone, leaving only a rim, perhaps 1-cm wide, well clear of the dome of the bladder (Figure 21.25). This is closed over a catheter. It was shown more than 90 years ago that the bladder will regenerate to a normal capacity from this rim of trigone within a few weeks. There is no need to perform a total cysto-prostatectomy or to enlarge the bladder with ileum or colon.

### 21.12.3 Cancer in a Diverticulum

The wall of a diverticulum is so thin that a tumour has only to penetrate the lamina propria, and it has gone through its wall (Figure 21.26). For this reason, tumours in diverticula have a sinister reputation, and even a small and apparently superficial one calls for wide partial cystectomy.

Through an adequate midline incision, the superior vesical artery on the side of the diverticulum is divided between ligatures to allow the lateral wall of the bladder to be rolled forwards. The bladder is opened and ureteric catheters are placed in both ureters to protect them. A wide cuff of bladder is removed including the orifice of the diverticulum (Figure 21.27). The diverticulum itself is removed together with all its surrounding fat and the internal iliac and obturator lymph nodes. The bladder is closed with drainage.
In addition to smoking and occupational carcinogens, other factors may play a role in causing the urothelial cancer. As there is a long latency period between exposure to the carcinogens and development of cancer, there might be other additional culprits in development of bladder cancer, particularly in younger people with no history of smoking or occupational exposure.

In patients presenting with painless haematuria, symptoms must be thoroughly investigated with appropriate imaging and cystoscopy. Various developments in cystoscopy techniques in the form of narrow-band imaging (NBI) and photodynamic diagnosis (PDD), also known as blue light cystoscopy (BLC), increase the diagnostic accuracy. Obtaining imaging before transurethral resection is most appropriate because accurate staging after becomes difficult due to distortion caused by the resection. Complete resection of the tumour and obtaining detrusor muscle in the first resection is important for reliable staging and avoiding the need for repeat resections. Presence of an experienced supervisor is essential in the case of resection being performed by a trainee. A single dose of intravesical Mitomycin-C within 24 hours is the current standard of care if the tumour on cystoscopy does not appear to be solid.

Mapping of the size, number, and location of tumours in a diagram assists in guiding subsequent management. Risk stratification using appropriate tables (e.g. EORTC risk tables) is useful in rationalisation of management and prognostication. The high rates of tumour recurrence and risk of progression in high-grade tumours may be reduced with adjuvant intravesical immunotherapy or chemotherapy. Combination therapy has been used with excellent results in a select group of patients. Discovery of an accurate biomarker to detect early recurrence remains elusive, and hence, cystoscopy continues to be the diagnostic tool of choice for follow up of patients.

Perioperative chemotherapy has been used to downstage tumours and treat any occult micrometastasis in muscle-invasive cancers before radical cystectomy. A survival benefit of 5–8% has been reported. However, there are no markers to predict the sensitivity of the tumours to the chemotherapy, and hence, some non-responders receive toxic chemotherapy with no benefit.

Radical cystectomy is currently the mainstay of treatment for muscle-invasive bladder cancer. This procedure is associated with significant morbidity and mortality and is a life-changing operation due to the need for urinary diversion. Bladder-preservation strategies using a combination of chemotherapy and EBRT are an option in highly select group of patients with equivalent oncological outcomes. Immunotherapy is under evaluation for treatment of patients with metastatic disease unresponsive to standard chemotherapy regimens.
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Urinary Diversion

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Abstract

Urinary Diversions

Urinary diversion involves rerouting of urinary drainage to outside of the body. These procedures can be performed either as a temporising measure or a permanent solution. The most common reason for a permanent urinary diversion is after ablative surgery for malignancy of the urinary bladder or other pelvic organs. However, it can be performed for functional and anatomical abnormalities of the urinary tract. Urinary diversions can be classified as percutaneous, continent, or incontinent.

The majority of diversions involve incorporating a segment of bowel in to the urinary tract to either create a conduit or a reservoir. An ideal diversion is one with low pressure, no reflux in to the upper tract, spontaneous and controlled emptying, maintains body image, and is of no functional consequences. However, at present an ideal urinary diversion does not exist. Choice of a urinary diversion depends mainly on the underlying pathology, patient’s compliance and dexterity, renal function, presence of bowel disease, previous bowel surgery, and patient’s preference.

All types of diversions have certain advantages and disadvantages. As most types of diversions include change in the body image and lifelong commitment to diversion care, patients need to be appropriately counselled prior to operations as to what the operation might entail. In addition, long-term monitoring of renal function and metabolic and nutritional status are required. In this chapter, we discuss common types of urinary diversion, indications, contraindications, and pros and cons of each.

Keywords urinary diversions; nephrostomy; cystostomy; continent or incontinent urinary diversions; ileal conduit; Mitrofanoff; Bricker; Wallace; Mainz II; Studer pouch; orthotopic bladder substitution

Key Points

Types of urinary diversion:
- Percutaneous
  - Nephrostomy
  - Cystostomy
- Incontinent diversion
  - Cutaneous ureterostomy
  - Intestinal conduit
- Continent diversion
  - Orthotopic substitution
  - Continent pouches and bladder augmentation
  - Natural evacuation urinary diversion (ureterosigmoidostomy)
  - Orthotopic bladder substitution-neobladder
22.1 Urinary Diversions

22.1.1 History

The long history of urinary diversion begins, it is said, with Franco, who created an artificial urinary fistula in 1556 [1]. Later Petit (1770) made a nephrostomy for calcified pyonephrosis [1]. Any kind of external fistula requires either an indwelling tube or a suitable external collecting appliance, and none were really suitable until the invention of the adhesive bag in 1950. The most extreme example of an external fistula was exstrophy, for which life with collecting devices was so miserable that it led Simon to attempt the first ureterosigmoidostomy; he was led to this bold step by the consideration that: ‘patients whose bladder, after the operation of lithotomy, opens into the rectum, acquire a certain control over the fluid contents of that bowel, by means of both sphincters ani’ [2]. Using special catheters armed with sharp stylets, he passed seton sutures from ureters into the rectum and tied them tightly. His patient became dry, but within a year both ureters became ‘choked with calculous concretions’ [3] and he died. Shortly afterwards, in 1851, Lloyd attempted the same procedure, but perforated the peritoneum and the patient died 10 days later [4]. These two complications were to bedevil urinary diversion for another century.

22.1.2 Nephrostomy

Nephrostomy is one of the most common procedures employed by interventional radiologists, especially in emergency obstructive uropathy scenarios. Inserted under local anaesthetic percutaneously, nephrostomies can be temporary, or in certain cases, permanent, requiring regular changes.

Nephrostomy can allow for antegrade studies to be carried out as well as procedures such as ureteric dilation or stent insertion. If a percutaneous nephrolitholapaxy is to be carried out for a large renal stone, the nephrostomy can be used as the tract site for dilation intraoperatively.

Complications include infection, bleeding, and pain most commonly. Inadvertent renal vessel cannulation, atrioventricular (AV) fistulation, and ureteric or renal pelvic perforation are more severe but rare.

22.1.3 Suprapubic Cystostomy

The simplest and most useful temporary diversion is the suprapubic percutaneous cystoscopy better known as suprapubic catheterisation (SPC). SPC is commonly used in retention of urine where a urethral catheter is difficult to pass. The technique is simple (Figure 22.1). Local anaesthetic is given with a large-bore needle. A small 1- to 1.5-cm incision is made about two fingerbreadths above the symphysis pubis. A long needle is directed into the bladder. A rigid guidewire inserted and needle removed. A dilator is railroaded over the guidewire and a catheter is inserted through the dilator sheath.

SPC insertions can be done in an emergency scenario, or more commonly, electively. It can be carried out percutaneously with blind insertion, or using the aid of an ultrasound to ensure the bladder is cannulated. Alternatively, under flexible or rigid cystoscopic guidance.

22.1.3.1 Indications of SPC Insertion [5]

- Acute or chronic urinary retention
- Neurological disorders (i.e. multiple sclerosis or patients with spinal cord injuries)
- For patients requiring long-term catheterisation (i.e. patients who are frail or elderly)
- Urinary incontinence
- Postoperative
- Trauma settings

22.1.3.2 Contraindications of SPC Insertion [5]

- Bladder cancer
- Patients with bleeding diathesis or use of anticoagulation or antiplatelets
- Previous abdominal surgery, higher risk of bowel damage
- Previous vascular surgery where subcutaneous vascular graft is present

22.1.3.3 Complications [5]

- Bleeding
- Infection

<table>
<thead>
<tr>
<th>Table 22.1 Ideal characteristics of a urinary reservoir.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Low pressure system</td>
</tr>
<tr>
<td>Stores a functional amount of urine (approximately 500 ml)</td>
</tr>
<tr>
<td>Reliable, complete continence</td>
</tr>
<tr>
<td>No absorption of urinary waste products by the reservoir walls</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<tr>
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</tr>
<tr>
<td>No absorption of urinary waste products by the reservoir walls</td>
</tr>
</tbody>
</table>
Bladder discomfort or pain,
- Urine leakage from around the catheter
- Stone and debris formation which can block the catheter
- Injury to the bowel (see figure in Chapter 23)

In rare cases, an open cystostomy might be required, especially if the bladder cannot be palpated, or there is a high risk of bladder injury. Such cases are nearly always men who have undergone previous surgery when the peritoneum is apt to be stuck to the symphysis, and great care is needed in finding the bladder (Figure 22.2).

22.2 Bladder Urinary Diversion

Urinary diversions may be incontinent or continent. The ideal reservoir should have a low‐pressure system, store a functional amount of urine, and be reliable in maintaining continence either through natural orifices or through appliances with voluntary control of voiding and no absorption of urinary wastes. In Table 22.1, the characteristics of an ideal reservoir are shown. Unfortunately, such a reservoir does not exist, and the aim of fashion urinary diversion is to achieve as close as possible to these characteristics. Selection of any type of urinary diversion are determined by a number of factors which are presented in Table 22.2.

22.2.1 Incontinent Urinary Diversion

The incontinent urinary diversion options include cutaneous ureterostomy, or more commonly, intestinal conduit urinary diversion. Although technically less demanding, these entail application of an external appliance and hence cosmetically are less pleasing.

22.2.1.1 Cutaneous Ureterostomy

Ureterostomy is also a method of diversion, rarely used, and usually only as a last resort. Cutaneous ureterostomy involves direct drainage of urine from the ureters to an appliance over the abdominal wall. The most suitable patients for this kind of urinary diversion are:
- High‐risk patients with symptomatic bladder cancer combined with palliative cystectomy.
- Diversion in patients with urinary fistula.
- Salvage procedures.

This type of diversion should not be considered in patients with following clinical situations:
- Patients who are obsess.
- After radiotherapy.
- Short ureteric stumps.
- Poorly vascularized ureters.

Technique: when the ureter is wide it can be split, everted, and brought to the skin like an ileostomy (Figure 22.3). For ureters of more normal calibre, there is a tendency for the stoma to undergo stenosis, which a double‐Z plasty may partly avoid (Figure 22.4).

22.2.1.2 Intestinal Conduit

Originally described by Zaayer in 1911, intestinal conduit is now the most frequently performed diversion. It is a passive conduit for urine to drain into an appliance. Most commonly, a segment of ileum is used to construct the conduit, although a colonic segment may be used as alternative in cases of previous pelvic radiation.
Figure 22.2 Formal open cystostomy. After (a) separating the recti, the peritoneum is displaced upwards and (b) the bladder is opened between stay sutures. (c and d) The catheter lies in a long oblique tunnel, well away from the symphysis.

Table 22.2 Issues affecting urinary diversion selection.

<table>
<thead>
<tr>
<th>Cancer Control</th>
<th>General Health</th>
<th>Technical</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of local recurrence</td>
<td>Functional status</td>
<td>Functioning urethra</td>
<td>Compliance</td>
</tr>
<tr>
<td>Previous pelvic radiation</td>
<td>Previous surgeries</td>
<td>Tumour location</td>
<td>Sexual function</td>
</tr>
<tr>
<td>Need for adjuvant therapy</td>
<td>Renal or hepatic function</td>
<td>Ability to catheterize</td>
<td>Body image</td>
</tr>
<tr>
<td>Secondary malignancies</td>
<td>Medical comorbidities</td>
<td>Mesentery length</td>
<td>Urinary function</td>
</tr>
<tr>
<td>Urethral or bladder neck involvement</td>
<td>Status of gastrointestinal tract</td>
<td>Bowel condition</td>
<td>Family support</td>
</tr>
<tr>
<td></td>
<td>Body habitus</td>
<td>Operative time</td>
<td>Daily maintenance</td>
</tr>
</tbody>
</table>
The ileal conduit was developed in occupied France during World War II. The French surgeons were glad to explain their new techniques to the surgeons in the liberating forces. The technique did not gain wide acceptance until an effective adhesive appliance for ileostomy was introduced in 1950. The operation was first described in the English literature by Bricker [6] (sadly, without any acknowledgement of priority to the French). The ileal conduit soon replaced the now historic ureterosigmoidostomy.

There are a number of useful simplifications of the original French/Bricker method of making an ileal conduit, notably, the simple anastomosis of Wallace [7]. Using this technique, the ileal loop became the diversion of choice.

After bowel preparation, a length of ileum with a good blood supply, from an unirradiated area (Figure 22.5), is selected. Having isolated the loop, an end-to-end anastomosis is performed (the Wallace technique; Figure 22.6). The ureters are spatulated and anastomosed together to form a common stoma which is then sewn to the open end of the bowel (Figure 22.7). In the Bricker technique, each ureter is spatulated and anastomosed to the bowel separately. It saves anxiety if the ureters are stented for a few days and an intra-abdominal drain left in situ.

Early Complications [8, 9]:

- Ischemia
- Ileus
- Bowel anastomotic leak
- Urinary leak
- Bowel obstruction

Delayed Complications [8, 9]:

- Parastomal hernia
- Stomal retraction or stenosis
- Renal impairment (with up to 6% dying from end-stage renal failure)
- Urinary tract infection (UTI)
- Stomal stenosis
- Bowel complications
- Stomal bleeding
- Uretero-ileal obstruction or stenosis
- Redundant loop
- Stones
- Incisional hernia
- Metabolic disorders
- Psychological disorders

As much care should be given in choosing the right site for the appliance as is given to the operation itself. The site of the stoma is chosen after the patient has worn an appliance, filled with water, when sitting, lying down, and with his or her clothes on. Care must be taken to avoid placing the site of the stoma on a scar, skin crease, or where the belt is usually tightened.
From time to time it is convenient to make a conduit out of a suitable length of the large bowel (e.g. the sigmoid after pelvic exenteration); these are known as colonic conduits. Exactly the same principles are used. There are no special advantages or disadvantages in using large rather than small bowel. Urinary absorption and the risk of reflux is identical.

The follow-up of patients with either type of intestinal conduit should include regular monitoring of their electrolytes, especially when there is already some impairment of renal function. In addition, ultrasound or urography is necessary to detect dilatation of the loop or of the upper tracts. Stones are a frequent long-term complication of intestinal conduits. The indications and metabolic consequences of each part of the gastrointestinal tract are presented in Table 22.3.

### 22.2.2 Continent Urinary Diversions

Despite the safety of the ileal conduit, many patients disliked their urinary stoma, and however good the appliance, it was always likely to leak or come unstuck at the least convenient moment.

The options include:

- **a)** Orthotopic substitution
- **b)** Continent pouches and bladder augmentation
- **c)** Natural evacuation urinary diversion (ureterosigmoidostomy)

---

*Figure 22.5* (a) The mesentery is viewed with transmitted light. (b and c) The mesenteric vessels are ligated to isolate the loop.

*Figure 22.6* (a–d) The ends of the ileum are anastomosed together.
22.2 Bladder Urinary Diversion

22.2.2 Orthotopic Bladder Substitution (Neobladder)

Although there is no ideal urinary diversion, this option is closest to the native bladder because patients opting for this type may void spontaneously, be continent, and also maintain the body image. A variety of techniques have been described, but currently the most widely used is the Studer technique [10]. The techniques all essentially involve a reservoir fashioned from bowel and a neo-sphincter mechanism or catheterisable conduit. Contraindications of a continent urinary diversions are summarised in Table 22.4. In general, the continent urinary diversions be it neobladder or catheterisable pouches are associated with early and long-term complications; the complications and their rate are shown in Table 22.5 [11, 12].

22.2.2.1 Contraindications to Neobladder Formation

Poor mental capacity
Poor manual dexterity (unable to perform self-catheterisation)
Prostate or bladder neck cancer involvement
Estimated glomerular filtration rate (eGFR) <35 ml min⁻¹
Severe gastrointestinal disease (e.g. inflammatory bowel, history of bowel cancer, radiotherapy to the bowel)
Unmotivated poor compliant patient

Complications of bladder substitute include:
 ● Urinary incontinence and nocturnal enuresis
 ● Mucus production (could be more than 3–5 g daily requiring regular catheterisation or washouts)
 ● Urinary leakage and peritonitis
 ● Abscess
 ● Stones
 ● UTIs
 ● Late onset neobladder rupture

Table 22.3 Primary indications and metabolic consequences for use of bowel segments.

<table>
<thead>
<tr>
<th>Bowel Segment</th>
<th>Primary Indication</th>
<th>Metabolic Consequences</th>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>Children requiring diversion (exstrophy, pelvic radia</td>
<td>Metabolic alkalosis (↓ K and Cl, hypergastrinemia)</td>
<td>Haematuria-dysuria syndrome</td>
</tr>
<tr>
<td></td>
<td>tion)</td>
<td></td>
<td>Dehydration, lethargy, seizures, respiratory distress</td>
</tr>
<tr>
<td></td>
<td>Renal insufficiency</td>
<td></td>
<td>Dehydration, nausea/vomiting, weakness, lethargy, seizures</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Pelvic radiation</td>
<td>Metabolic acidosis (↓ Na and Cl, ↑ K, azotaemia)</td>
<td>Fatty acidosis, weight loss, diarrhoea, polydipsia</td>
</tr>
<tr>
<td></td>
<td>Deficient ureteral length</td>
<td></td>
<td>B₁₂ and fat soluble vitamin deficiency</td>
</tr>
<tr>
<td></td>
<td>Compromised viability of other small or large bowel</td>
<td></td>
<td>Diarrhoea, urinary calculi, cholelithiasis</td>
</tr>
<tr>
<td>Illeum or ileo-colic</td>
<td>Malignancies requiring removal of the bladder</td>
<td>Metabolic acidosis (↑ Cl, ↓ bicarbonate, azotaemia)</td>
<td>Fatigue, anorexia, weight loss, diarrhoea, polydipsia</td>
</tr>
<tr>
<td>reservoirs</td>
<td>Severe haemorrhagic cystitis</td>
<td></td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td></td>
<td>Incontinence</td>
<td></td>
<td>Adenocarcinoma at anastomotic site</td>
</tr>
<tr>
<td>Colon (ureterosigmo</td>
<td>Children requiring diversion (exstrophy, pelvic radia</td>
<td>Metabolic acidosis (↑ Cl, ↓ bicarbonate, azotaemia)</td>
<td>Fatigue, anorexia, weight loss, diarrhoea, polydipsia</td>
</tr>
<tr>
<td>idostomy)</td>
<td>tion)</td>
<td></td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td></td>
<td>No other bowel segment alternative</td>
<td></td>
<td>Adenocarcinoma at anastomotic site</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>Malignancies requiring removal of the bladder</td>
<td>Metabolic acidosis (↑ Cl, ↓ bicarbonate, azotaemia)</td>
<td>Fatigue, anorexia, weight loss, diarrhoea, polydipsia</td>
</tr>
<tr>
<td>conduit</td>
<td>Small bowel not practical</td>
<td></td>
<td>Pyelonephritis</td>
</tr>
</tbody>
</table>

Cl, chlorine; K, potassium; NA, sodium.

22.2.2.1 Orthotopic Bladder Substitution (Neobladder)

Although there is no ideal urinary diversion, this option is closest to the native bladder because patients opting for this type may void spontaneously, be continent, and also maintain the body image. A variety of techniques have been described, but currently the most widely used is the Studer technique [10]. The techniques all essentially involve a reservoir fashioned from bowel and a neo-sphincter mechanism or catheterisable conduit. Contraindications of a continent urinary diversions are summarised in Table 22.4. In general, the continent urinary diversions be it neobladder or catheterisable pouches are associated with early and long-term complications; the complications and their rate are shown in Table 22.5 [11, 12].

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Unmotivated poor compliant patient

Complications of bladder substitute include:
 ● Urinary incontinence and nocturnal enuresis
 ● Mucus production (could be more than 3–5 g daily requiring regular catheterisation or washouts)
 ● Urinary leakage and peritonitis
 ● Abscess
 ● Stones
 ● UTIs
 ● Late onset neobladder rupture

Table 22.4 Absolute and relative contraindications for continent cutaneous or orthotopic neobladder urinary diversions.

Absolute contraindications
Impaired renal function: serum creatinine values >2.0–2.5 mg dl⁻¹ or 1.5 µmol l⁻¹ or eGFR <40 ml min⁻¹/1.73 m²
Impaired hepatic function
Physical or mental impairment to perform self-catheterization
Positive apical urethral margin (for neobladder)
Unmotivated patient

Relative contraindications
Associated comorbid conditions
Advanced age
Need for adjuvant chemotherapy
Prior pelvic radiation
Bowel disease
Urethral pathology
Extensive local disease with soft tissue extension and high risk of local recurrence

eGFR, estimated glomerular filtration rate.
Figure 22.7 (a) The ends of the ureters are spatulated and sewn together and anastomosed to one end of the isolated ileal loop (b). The other end is brought out on the skin as an ileostomy (c and d).

Table 22.5 Early versus late complications of continent urinary diversions.

<table>
<thead>
<tr>
<th>Complication Type</th>
<th>Early (within 30 days)</th>
<th>%</th>
<th>Long Term (30 days to death)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reservoir-related</td>
<td>Urinary leak</td>
<td>1.8–10</td>
<td>Pyelonephritis</td>
<td>3–10</td>
</tr>
<tr>
<td></td>
<td>Pyelonephritis</td>
<td>0.9–13</td>
<td>Upper tract calculi</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pouch calculi</td>
<td>5–35</td>
</tr>
<tr>
<td>Anastomosis-related</td>
<td>Ureteral obstruction</td>
<td>0–6.3</td>
<td>Ureteral obstruction or stricture</td>
<td>2–30</td>
</tr>
<tr>
<td></td>
<td>Urethral or stomal stricture</td>
<td>2–14.3</td>
<td>Renal deterioration</td>
<td>0.4–10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ureteral reflux</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Bowel-related</td>
<td>Faecal leak</td>
<td>1–2</td>
<td>Metabolic abnormalities</td>
<td>15–50</td>
</tr>
<tr>
<td></td>
<td>Prolonged ileus</td>
<td>2–11</td>
<td>Bowel obstruction</td>
<td>4–8</td>
</tr>
<tr>
<td>Other</td>
<td>Wound infection</td>
<td>5</td>
<td>Incisional hernia</td>
<td>0–10</td>
</tr>
<tr>
<td></td>
<td>Wound dehiscence</td>
<td>5</td>
<td>Deep venous thrombosis</td>
<td>0–6.3</td>
</tr>
<tr>
<td></td>
<td>Deep venous thrombosis</td>
<td>2–2.7</td>
<td>Loss of continence mechanism</td>
<td>15–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypercontinence (male vs. female)</td>
<td>3–9 vs. 10–50</td>
</tr>
</tbody>
</table>
22.2.2.2 Continent Pouches and Bladder Augmentation
There were attempts by the turn of the century to use the bowel as a reservoir for urine. Bricker, Eiseman, Gilchrist, and Merricks [13–15] developed a technique that was claimed to give a capacious reservoir with a continent ileal stoma which could be emptied by periodic intermittent self-catheterization (Figure 22.8). Couvelaire was critical of the method ‘Elle n’a rien d’une vessie, ni la continence, ni la miction’ [16]. Nor was it free from the complications of acidosis, ascending infection, and calculus formation.

More recently, a continent pouch is fashioned from about 60 cm of detubularised ileum rather than colon but employs the same principles. The ureters are anastomosed to the pouch with an anti-reflux submucosal tunnel. A catheterisable stoma is brought out in the right iliac fossa.

In 1980 Mitrofanoff first described a continent supravesical catheterisable channel, using appendix on vascular pedicle [17]. In patients who have either lost an appendix at operation or do not have suitable lumen or length, alternatives have been used including small bowel [18, 19], ureter, Fallopian tube, colon, vas deferens, or even stomach [20–24].

The earliest attempts to enlarge the bladder with bowel were performed for bladders that had undergone contracture from tuberculosis or interstitial cystitis. Different segments of intestine were used, including colon, small intestine, and caecum (Figure 22.9).
Spontaneous contractions of the bowel, especially the caecum, would result in incontinence of urine especially at night, but a more serious consequence of these uninhibited contractions was that they generated such a high pressure that there would be ureteric reflux and obstructive nephropathy. These could be avoided if the bowel were ‘detubularised’ (i.e. opened out and sewn into the bladder as a flat patch). The uncoordinated bowel contractions would not generate any pressure; indeed, such a patch could be used in ‘clam cystoplasty’ to overcome deliberately raised bladder pressure in patients with vesical detrusor instability (Figure 22.10) [25–28].

As a result of this discovery, it became possible to devise a new kind of pouch or bladder enlargement with a very low pressure – so low indeed that it would not take much pressure on the outlet to maintain continence (Figure 22.11). Continence was usually at the expense of needing self-catheterization and occasional spontaneous rupture [29].

Although Kock had first developed this pouch as a faecal reservoir for patients undergoing colectomy for

Figure 22.10 Clam cystoplasty. (a) The bladder is opened in the coronal plane and a length of ileum is isolated. (b) The ileum is opened and sewn into the bladder (c) to give extra volume and lower the pressure.
ulcerative colitis, the idea was quickly adapted as a urinary reservoir. At first, the stoma was led out on the skin, later, it was anastomosed to the urethra as a true substitute for the bladder [30]. Because only a very low pressure was needed to keep in the urine, one could make use of an artificial sphincter, a loop of ileum, plicated ileum, or the appendix.

The ingenuity of its enthusiasts knew no bounds, and every conceivable permutation and combination of every part of the gastrointestinal tract was used to provide low-pressure continent substitutes for the bladder (Figure 22.12) [31–34]. The multiplicity of these techniques and their innumerable modifications shows that none of them are yet perfect. Preoperative radiation to the bowel rules them out.

The two problems that remain a challenge are how to prevent reflux up the ureters and how to maintain continence. In the Kock pouch, reflux from the reservoir to the ureters is prevented by an ileal intussusceptum which forms a long nipple-like valve. Continence of urine is achieved by a second intussusceptum valve on the efferent limb of ileum.

In a Camey technique, reflux is prevented by a submucosal tunnel similar to the classical Leadbetter valve in ureterocolic anastomosis (Figure 22.13) [35]. Mitrofanoff [34, 36] uses the appendix, where present, as a long narrow stoma, joining it to the skin or the urethra. At the umbilicus, it is invisible [37]. Others use plicated ileum to provide continence [38].

Complications of continent pouches [39–41] include:

- Mortality
- Small bowel obstruction
- Ischaemic necrosis of channel
- Peristomal abscess
- Stones
- Renal impairment
- Catheterisation difficulties
- Revision rate
- Stenosis
- Prolapse
- Reservoir rupture
- UTIs
- Metabolic disorders
- Malignancy

As mentioned previously, the choice of continent or conduit urinary diversions is based on a number of factors, but there are a number of studies which have reported the rate of complications of either type in the early postoperative period or in the long term. The studies with their number of patients, duration of follow up, and rate complications are tabulated in Table 22.6.

---

**Figure 22.11** Kock’s pouch. (a) A 45-cm length of ileum is isolated, and (b) the middle 20 cm opened out. (c–e) The ileum at each end is intussuscepted to form an anti-reflux nipple, which is secured with staples. (f) One end forms the stoma, and the other is anastomosed to the ureters. The middle portion is formed into a reservoir.
22.2.2.3 Natural Evacuation Urinary Diversion

22.2.2.3.1 Ureterosigmoidostomy

The first type of urinary diversion applied in 1852 by Simon had significant morbidities and mortality due to obstruction and sepsis. Innumerable techniques were devised for performing the ureterosigmoidostomy, but it was not until a direct elliptical mucosal anastomosis was combined with an anti-reflux tunnel that the ascending infection complication was reduced, but remained significant. However, metabolic complications were significant. Physiologists had long been aware that if enough urine was absorbed by the intestine, it could eventually lead to renal tubular damage [42, 43], but the complication was thought to be very rare [44, 45]. Then, in 1950 Ferris and Odel published their long-term follow-up of 124 patients and found that no fewer than 62% had developed severe acidosis [46].

The biochemical changes were due to two factors: first and foremost was absorption of urine. Since normal

![Diagram of the Mainz pouch](image)
urine is acidotic to the plasma by one-third too much chloride, this absorption at a milliequivalent for miliequivalent rate can cause hypochloraemia, and the real problem is how much absorption occurs [47]. The second factor was renal function. If renal tubular function was perfect, it could cope with the acidosis. But when continued absorption of urine or damage from ascending infection and obstruction began to impair tubular function, acidosis would appear. This explained why it took so long for acidosis to develop in patients who started off with good kidneys [48].

Once the hazards of acidosis were appreciated, surgeons welcomed other alternatives to ureterosigmoidostomy. Nevertheless, the method still has a place (e.g. when the patient has a good anal control, good renal function, and a relatively short life expectancy) [49]. The Leadbetter tunnelled anti-reflux technique reduced infection rates; however, high intrarectal pressures led to persistent infection as well as incontinence (Figure 22.14). The Mansoura and Mainz II techniques were devised to reduce intrarectal pressures.

### 22.2.3.2 The Mansoura Diversion

In Egypt as well as many countries where the poor and low socioeconomic uneducated class are prevalent, incontinence means social ostracism, and adhesive appliances are expensive and unreliable in the hot climate. Ghoneim, working with Kock, devised an ingenious modification of a historical urinary diversion technique the Mauclaire’s operation, which offers the patient a capacious urinary reservoir, prevents reflux of urine even in ureters that have been damaged by bilharziasis, and employs an intussusception valve which keeps the urine in the rectum and out of the rest of the colon (so it limits the absorvent surface area; Figure 22.15). The sigmoid colon is intussuscepted to prevent reflux and Kock ureteric anastomosis fashioned, an ileal augmentation of the sigmoid reduces intraluminal pressures.

### Table 22.6 Comparison of complications: ileal conduits versus continent diversions.

<table>
<thead>
<tr>
<th>Type of Diversion</th>
<th>Year</th>
<th>Series</th>
<th>No. of Patients</th>
<th>Time From Surgery (months)</th>
<th>% Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal conduit</td>
<td>2000</td>
<td>Parekh, et al.</td>
<td>81</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>Gburek, et al.</td>
<td>66</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>Studer, et al.</td>
<td>131</td>
<td>98</td>
<td>66</td>
</tr>
<tr>
<td>Continent diversion</td>
<td>2000</td>
<td>Parekh, et al.</td>
<td>117</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>Gburek, et al.</td>
<td>66</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>Shimogaki, et al.</td>
<td>8</td>
<td>59.9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>Mills, et al.</td>
<td>15</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>Ali-el-dein, et al.</td>
<td>60</td>
<td>20.2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>Hautmann, et al.</td>
<td>363</td>
<td>57</td>
<td>15.4–23.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>Steven, et al.</td>
<td>166</td>
<td>32</td>
<td>23.5–37.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>1997</td>
<td>Studer, et al.</td>
<td>200</td>
<td>30–134</td>
<td>12–22&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Early (within 90 days) vs. late (>90 days) complications.
Figure 22.14 Leadbetter technique of ureterosigmoidostomy. (a) The ureter is brought between the layers of the mesosigmoid. (b) A tunnel is made for the ureter through the muscle of the colon. (c) An elliptical anastomosis is made between the spatulated ureter and colonic mucosa. The muscle is closed over the ureter; to prevent closing it too tightly, a catheter is placed alongside the ureter while the stitches are tied.

Figure 22.15 The Mansoura diversion. (a) The sigmoid is intussuscepted to form a nonreturn valve. (b) The ureters are led down between the layers of the intussuscepted bowel to prevent reflux. (c) An isolated patch of ileum is added to the rectosigmoid to give extra capacity.
22.2.2.3.3 Mainz II Diversion
It is a type of continent urinary diversion in which a pouch is created from rectosigmoid. A length of 15–20 cm of the sigmoid is opened on the antimesentric side and closed side to side to form a pouch. The ureters are then implanted in a 3.5-cm submucosal tunnel to act as an anti-reflux mechanism. A well-functioning anal sphincter is essential for patients selected for this procedure. In patients requiring urethrectomy, or those live in hot climates or developing countries where acquiring and maintaining external appliance might be difficult, it is the diversion of choice.

Contraindications for a Mainz II diversion include poor anal sphincter function, pelvic radiotherapy, and diverticulosis.

Complications of a Mainz II diversion are:
Early:
- Urinary or bowel leak
- Bowel obstruction
Late:
- Metabolic disturbances
- Incontinence
- Renal function deterioration
- UTIs
- Diarrhoea
- Ureterosigmoid cancer

22.3 Functional Follow-Up

Resection of a part of subterminal ileum for construction of ileal conduit predisposes patients to vitamin B_{12} deficiency. The body has a large reserve of vitamin B_{12}; therefore, levels may decrease after three years. These patients will be at risk of megaloblastic anaemia and subacute combined degeneration of spinal cord. Once a diagnosis of vitamin B_{12} deficiency is made, supplementation is indicated. Monitoring of vitamin B_{12} levels should be checked at follow-up every 6–12 months [50].

Metabolic hyperchloreaemic acidosis can occur in up to 15% patients after a radical cystectomy and ileal conduit and up to 50% of patients with continent diversions [51]. It is less likely in patients with normal renal function (eGFR >60 ml min^{-1} as can compensate). These patients require regular monitoring for metabolic abnormalities every 6–12 months and generous supplementation with sodium bicarbonate if found to have metabolic acidosis. Metabolic follow-up should continue up to 15 years after cystectomy [52]. If left uncorrected can lead to bone demineralization and osteomalacia.

Adenocarcinoma may develop in the ileal conduit or neobladder in the long term (15–20 years) in 5% of patients. This is due to the carcinogenic bacterial metabolism of urinary nitrosamines; there is a risk of cancer in the long term. It took 20 years of experience with ureterosigmoidostomy before the risk of colonic cancer came to light [53]. Therefore, annual cystoscopy is recommended on a long-term basis.

22.4 Quality of Life Urinary Diversion after Cystectomy

It is obvious that radical cystectomy is a major surgery and also involves structural changes. With treatments aiming to prolong life in bladder cancer, there has also been increasing interest in the quality of life (QoL) after cystectomy [54]. There have been questions regarding the social aspects of life, sexual function, adaptation to the new body image, and new appliances. Efforts have been made to produce relevant validated tools for evaluation of QoL that reflects QoL in patients with bladder cancer [55, 56].

To date, there are no randomised controlled studies to support superiority of QoL in continent diversions in comparison with conduit diversions and studies show varying outcomes. Some studies have shown that global QoL is better with orthotopic neobladder compared to ileal conduit [57], whilst others have failed to report a better QoL in continent, incontinent, or orthotopic neobladders [58–60]. Orthotopic neobladder is associated with a marginally better QoL [54].

However, improvement in surgical techniques has been shown to affect the aspects of QoL, especially in nerve-sparing surgery. Impaired sexual function, altered bowel function, and urinary function have been found to be causes of concern with continent neobladders [61]. In nerve-sparing surgeries, erectile function was improved, but better outcomes are seen in patients who are younger [62–65]. Similarly, sexual function is affected in females after cystectomy, and nerve-sparing cystectomy in females has also been shown to have superior sexual function recovery [66, 67].

Despite the approach of surgery, appropriate preoperative counselling about the type of the urinary diversions and its impact on the functional status and body image remains important [68]. The operation, the side effects, and outcomes have to be appropriately explained to patients, and patients should also be counselled before the operation about the operation might entail.
Expert Opinion

Urinary diversion is a life-changing procedure, usually becoming unavoidable in the treatment of muscle-invasive and high-risk non-muscle-invasive bladder cancer. It not only results in permanent change of body image but also requires lifelong care and follow-up. The simpler forms of urinary diversions (non-continent) are cosmetically less attractive but require less labour-intensive maintenance and have limited metabolic implications. On the contrary, more complex (continent) urinary diversions are challenging to construct because of potential metabolic problems but have superior cosmetic appeal. Various factors, such as the nature of the underlying disease, renal function, dexterity, and mental suitability, are determinants in choosing the right type of procedure for a patient.

Currently there is no ideal urinary diversion to mimic exactly the natural bladder. There have been no randomised trials to show clear superiority of one type of urinary diversion over another. Because the procedure is associated with a number of sequelae, it is essential to counsel patients appropriately to help patients select an appropriate type of urinary diversion. Some patients need time to accept the idea of living with a urinary diversion, but they must be made aware of the risks of undue delay in cancer treatment. Patients should be given the freedom to choose an appropriate diversion best suited to their physical, mental, social, and oncologic factors.

References


23

Bladder Disorder of Function

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³ Department of Urology, Erasmus MC, Rotterdam, The Netherlands

Abstract

Normal bladder function is divided into storage and voiding. We consider disorders of function, which for ease of explanation will also be divided into storage, voiding, and some other secondary disease processes. However, this is a purely academic division because symptoms overlap to a large degree in clinical practice. All female, functional, and neurological urology will be covered here with the single exception of bladder outflow obstruction (BOO) secondary to benign prostatic enlargement. We discuss primary storage dysfunction (i.e. overactive bladder syndrome, urinary incontinence [UI], painful bladder syndrome, nocturia or nocturnal polyuria), primary voiding dysfunction (i.e. detrusor failure, functional obstruction, urethral disorders) and bladder disorders secondary to other disease processes (e.g. neurogenic bladder dysfunction, including detrusor sphincter dyssynergia and genitourinary prolapse). We incorporate the advice from current National Institute for Health and Care Excellence (NICE) and European Association of Urology (EAU) guidelines.

Keywords overactive bladder syndrome; stress urinary incontinence; urgency urinary incontinence; painful bladder syndrome; nocturia; functional bladder obstruction; detrusor failure; neurogenic bladder dysfunction; urethral disorders; genitourinary prolapse

Key Points

● Female urinary dysfunction includes mainly urinary incontinence (UI) and overactive bladder syndrome (OAB) and can be associated with pelvic organ prolapse (POP).
● Lower urinary tract (LUT) dysfunction in men can be more complex, and although causes may vary, OAB and UI are still prevalent, along with the more familiar bladder outflow obstruction (BOO).
● Sufficient knowledge of the pelvic floor anatomy is critical for understanding the symptoms of urinary dysfunction in men and women.
● Evaluation should consist of history, physical examination, bladder diaries, urinalysis with and without microscopy and culture, postvoid residual assessment, and urodynamics (where appropriate).
● Flexible cystoscopy and urine cytology are indicated in selected patients.
● UI is classified as stress UI, urgency UI, mixed UI, nocturnal UI, and continuous UI.
● Symptomatic urethral diverticula require surgical repair.

23.1 Introduction

The urinary bladder is a quintessential organic ‘machine’ – once trained, it usually goes about its business with very little fuss. A ‘normal’ bladder will come to its owner’s attention for little more than one or two minutes a day. In fact, it could be said that abnormal bladder function is quite simply any situation that causes an excessive awareness or consciousness of what the bladder is doing. Some would call this a gross oversimplification, but the current debates on the nature of urgency, subjective versus objective evaluation of function, the proliferation of receptors...
and subepithelial pathways, and surgical materials and techniques seem to suggest that overcomplication has not really helped us either.

This is not to say that we have not come a long way in our understanding of the pathophysiology of lower urinary tract (LUT) dysfunction. Improvements in imaging modalities, biophysical assessment tools, and biochemical analysis have all made an impact on our diagnostic ability. A consequence of these tools and algorithms is the classification and categorisation of patients into groups. Although useful in planning treatment strategies, we must be careful to remember that sometimes bladder dysfunction is as individual as the patients themselves.

23.1.1 Physio-Anatomy

The main purpose of the urinary bladder is to receive urine from the kidneys and act as a compliant pouch to store that urine, until such time as it is socially appropriate and convenient to void. Structurally it is made up of interwoven fibres of detrusor muscle that make up the body of the bladder and specialised smooth muscle fibres within the detrusor that arise from a distinct embryological source. The muscle layers are lined internally by an inner urothelium that acts as a protective layer. The bladder urothelium is distensible along with the bladder muscle and forms an effective blood–bladder barrier to prevent uraemia. Deep to the urothelium, the interstitial cells are found, responsible for the ‘pace-making’ activity in the bladder. Two types of interstitial cells have been identified – the suburothelial interstitial cells (or myofibroblasts) and the intradetrusor interstitial cells. These cells differ in molecular constitution and neurotransmitter content, but M2 and M3 muscarinic receptor activity of suburothelial interstitial cells have been found to correlate with urgency scores in humans, and their position makes them ideally situated to modify feedback mechanisms of adenosine triphosphate (ATP) and acetylcholine (Ach) between the urothelium and nerve endings. The intradetrusor interstitial cells can be spontaneously active and so possibly have the pacemaker role, and they also demonstrate cyclic guanosine monophosphate (cGMP) activity.

Bladder dysfunction can therefore be broadly divided into storage dysfunction and voiding dysfunction. We will consider each of the major recognised patterns of dysfunction in turn, but first let us take a look at the relevant definitions related to LUT dysfunction.

23.1.2 Definitions

Terminology and definitions are a source of constant debate in the functional and reconstructive urology community. The reasons for this are varied, but the consequences are important because they guide research and development in the field. Tables 23.1–23.3 list the current International Continence Society (ICS) terminology.

<table>
<thead>
<tr>
<th>Storage symptoms</th>
<th>International Continence Society (ICS) terminology [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased daytime frequency</td>
<td>is the complaint by the patient who considers that he/she voids too often by day.</td>
</tr>
<tr>
<td>Nocturia</td>
<td>is the complaint that the individual has to wake at night one or more times to void.</td>
</tr>
<tr>
<td>Urgency</td>
<td>is the complaint of a sudden compelling desire to pass urine, which is difficult to defer.</td>
</tr>
<tr>
<td>Urinary incontinence (UI)</td>
<td>is the complaint of any involuntary leakage of urine.</td>
</tr>
<tr>
<td>Stress urinary incontinence (SUI)</td>
<td>is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.</td>
</tr>
<tr>
<td>Urge urinary incontinence (UUI)</td>
<td>is the complaint of involuntary leakage accompanied by or immediately preceded by urgency.</td>
</tr>
<tr>
<td>Mixed urinary incontinence (MUI)</td>
<td>is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.</td>
</tr>
<tr>
<td>Enuresis</td>
<td>means any involuntary loss of urine.</td>
</tr>
<tr>
<td>Nocturnal enuresis</td>
<td>is the complaint of loss of urine occurring during sleep.</td>
</tr>
<tr>
<td>Continuous urinary incontinence</td>
<td>is the complaint of continuous leakage.</td>
</tr>
<tr>
<td>Other types of urinary incontinence</td>
<td>may be situational, for example the report of incontinence during sexual intercourse, or giggle incontinence.</td>
</tr>
<tr>
<td>Bladder sensation</td>
<td>can be defined, during history taking, by five categories: Normal: the individual is aware of bladder filling and increasing sensation up to a strong desire to void. Increased: the individual feels an early and persistent desire to void. Reduced: the individual is aware of bladder filling but does not feel a definite desire to void. Absent: the individual reports no sensation of bladder filling or desire to void. Non-specific: the individual reports no specific bladder sensation, but may perceive bladder filling as abdominal fullness, vegetative symptoms, or spasticity.</td>
</tr>
</tbody>
</table>
for lower urinary tract symptoms (LUTS). Tables 23.4 and 23.5 list the current ICS terminology for some symptom syndromes and objective measurements. These apply to both male and female patients.

### Table 23.2 Voiding symptom definitions.

<table>
<thead>
<tr>
<th>Voiding symptoms</th>
<th>International Continence Society (ICS) terminology [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow stream</td>
<td>is reported by the individual as his or her perception of reduced urine flow, usually compared to previous performance or in comparison to others.</td>
</tr>
<tr>
<td>Splitting or spraying of the urine stream may be reported.</td>
<td></td>
</tr>
<tr>
<td>Intermittent stream (Intermittency)</td>
<td>is the term used when the individual describes urine flow, which stops and starts, on one or more occasions, during micturition.</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>is the term used when an individual describes difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine.</td>
</tr>
<tr>
<td>Straining to void</td>
<td>describes the muscular effort used to either initiate, maintain, or improve the urinary stream.</td>
</tr>
<tr>
<td>Terminal dribble</td>
<td>is the term used when an individual describes a prolonged final part of micturition, when the flow has slowed to a trickle or dribble.</td>
</tr>
</tbody>
</table>

### Table 23.3 Postmicturition symptom definition.

<table>
<thead>
<tr>
<th>Postmicturition symptoms</th>
<th>International Continence Society (ICS) terminology [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling of incomplete emptying</td>
<td>Is a self-explanatory term for a feeling experienced by the individual after passing urine.</td>
</tr>
<tr>
<td>Postmicturition dribble</td>
<td>Is the term used when an individual describes the involuntary loss of urine immediately after he or she has finished passing urine, usually after leaving the toilet in men, or after rising from the toilet in women.</td>
</tr>
</tbody>
</table>

### Table 23.4 Symptom syndrome definition.

<table>
<thead>
<tr>
<th>Some symptom syndromes</th>
<th>International Continence Society (ICS) terminology [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful bladder syndrome (PBS)</td>
<td>Is the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime or nighttime frequency in the absence of proven urinary tract infection or other obvious pathology. It is chronic in its nature with pain being the major complaint.</td>
</tr>
<tr>
<td>Urethral pain syndrome</td>
<td>Is the occurrence of recurrent episodic urethral pain usually on voiding, with daytime frequency and nocturia, in the absence of proven infection or other obvious pathology. It is chronic in its nature with pain being the major complaint.</td>
</tr>
<tr>
<td>Overactive bladder syndrome (OAB)</td>
<td>Urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as the overactive bladder syndrome, urge syndrome or urgency-frequency syndrome.</td>
</tr>
<tr>
<td>Dysfunctional voiding</td>
<td>Is characterised by an intermittent or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated muscle during voiding in neurologically normal individuals</td>
</tr>
</tbody>
</table>

### Table 23.5 Objective measurements.

<table>
<thead>
<tr>
<th>Some objective measurements</th>
<th>International Continence Society (ICS) terminology [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia</td>
<td>Is the number of voids recorded during a night’s sleep; each void is preceded and followed by sleep.</td>
</tr>
<tr>
<td>Polyuria</td>
<td>Is defined as the measured production of more than 2.8 l of urine in 24 hours in adults.</td>
</tr>
<tr>
<td>Nocturnal polyuria</td>
<td>Is present when an increased proportion of the 24-hour output occurs at night (normally during the 8 hours whilst the patient is in bed). The nighttime urine output excludes the last void before sleep but includes the first void of the morning.</td>
</tr>
<tr>
<td>Maximum voided volume</td>
<td>Is the largest volume of urine voided during a single micturition and is determined either from the frequency or volume chart or bladder diary.</td>
</tr>
</tbody>
</table>

### 23.1.3 History Taking and Physical Examination

A complete medical history is essential in the workup of any patient with LUTS, as it is with any medical patient. It is important in a patient with LUTS, however, to try and quantify their symptoms. A three-day voiding diary is a validated tool to do this and should be completed by all patients at baseline. Validated questionnaire such as the International Consultation on Incontinence Modular questionnaire (ICIQ) can also be used.

It is also important to discuss the individual’s personal circumstances and what their expectations are of treatment. Managing expectations is a key component of therapy for any LUT disorder but especially so for overactive bladder (OAB) and urinary incontinence (UI). Each individual’s definition of what it is like to be ‘dry’
can vary, sometimes subtly, but subtle variations can be the difference between success and failure from the patient’s point of view, even though it may make no difference to an objective outcome measure.
A full medical examination is warranted in all patients.

23.2 Investigating Bladder Function

23.2.1 Initial Investigations

1) Frequency volume charts: these record the volume and frequency of urine passed over a period of time, along with documentation of any urgency or incontinence episodes.
2) Bladder diaries: these are recorded over a three-day or five-day period and record the fluid intake, the frequency and volume of urine voided, number of incontinence episodes, number of daily pads used, and urgency perceived.
3) Urine dipstick: if suggestive of infection urine is sent for urinalysis and microscopy for culture and sensitives.
4) Imaging and flexible cystoscopic examination to identify organic pathology.

23.2.1.1 Specialised Investigations

23.2.1.1.1 Urodynamics

The term ‘urodynamics’ encompasses all tests of function, assessment of pressure or flow in the LUT, including uroflowmetry, measurement of postvoid residual (PVR) urine, pad tests, filling cystometry, pressure or flow cystometry, video cystometry, and ambulatory urodynamics.

Urodynamic studies provide a snapshot in time. The observations are specific to the individual patient and relevant to the duration of the test. This is borne out in studies that have shown results of urodynamic tests to be variable even in the same individual at different time points [2]. The results of urodynamics do not appear to influence the outcome of treatment for stress UI [2].

Urodynamics, as the name suggests, is a dynamic test, and therefore, interpretation of results is dependent on the interpreter being present for the duration of the test. Review of traces ‘after the fact’ can be misleading, unless the events and occurrences during the test are described in detail in the report. Figure 23.1 depicts the various traces for the corresponding complaints.

The use of urodynamics is largely a matter of preference, expertise, and availability. It is a urologist’s tool,
Figure 23.1 (Continued)
Figure 23.1 (Continued)
Figure 23.1 (Continued)
Figure 23.1 (Continued)
and when used appropriately, can help inform management decisions. Equally, when used inappropriately or without the required expertise, it may at best put the patient at unnecessary risk and embarrassment, and at worst, cause significant harm.

### 23.2.1.1.2 Urine Flow Rate

The rate of urine flow depends upon the expulsive force developed by the detrusor and the outflow resistance during micturition. Both factors can be affected by psychological factors and flow rate measurements on a voided volume of less than about 150 ml may not be reliable. A uroflow measurement will usually give a graphic read out which presents the pattern of flow, its maximum (Qmax) and average (Qave) rate, as well as the total volume of urine passed (Vcomp) (Figure 23.2). A single flow measurement should be treated with caution, but most normal men should be able to produce a maximum peak flow of 15 ml s\(^{-1}\) or more. A maximum flow of less than 10 ml s\(^{-1}\) is usually taken as abnormal. A normal flow rises to a peak which is sustained for most of the void. Infravesical obstruction produces a flattened curve (Figure 23.3), which classically has a box shape when the obstruction is caused by urethral stricture. Obstructed voiding due to failure of sphincter relaxation typically gives a pattern of intermittent flow (Figure 23.4). This picture is seen in the detrusor–sphincter dyssynergia of neurological disease as well as the rather less well-explained failure of voluntary relaxation of the external sphincter which afflicts some men, especially when they attempt to void in public places.

The urine flow rate is normally greater in women who may be able to generate maximum rates in excess of 25 ml s\(^{-1}\) if 50 years of age or younger and >18 ml s\(^{-1}\) if 50 years of age or older.

### 23.2.1.1.3 Filling Cystometry

Compliance is the change in intravesical pressure which occurs with a given change in volume (ml/cm H\(_2\)O). There is very little increase in the pressure within the normal bladder as it fills (i.e. compliance is very high). There is a cessation of detrusor activity possibly mediated in part by the sympathetic nervous system. At some point, which partly depends upon the filling rate, the subject becomes aware of a sensation from the bladder. This first sensation is succeeded by an urge to void which can be suppressed even though it is associated with a transient rise in intravesical pressure. Further bladder filling is usually uncomfortable.

The technique of filling cystometry varies, but the principle is simple. Starting with an empty bladder, a catheter is used to fill the bladder while intravesical pressure is measured by means of a second catheter. A pressure line in the rectum measures variations in intra-abdominal pressure which are electronically subtracted from the intravesical pressure to give a graphic read out of the calculated detrusor pressure (Figure 23.5).

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**Figure 23.2** Normal uroflow measurement.

**Figure 23.3** The flattened curve of infravesical obstruction (a) with prostatic hyperplasia (b) with a urethral stricture.
During the filling study, the patient is asked to report sensations from the bladder. The volumes at which first sensation is felt and when there is an urge to void are taken as important measures of bladder sensation. The pressure trace is scanned to detect rises in pressure which reflect abnormal detrusor contractions. The onset of these contractions may be affected by the rate of filling and the temperature of the filling fluid, and patients may be asked to perform other manoeuvres (e.g. to cough or to change position) to provoke them. If they occur, the patient is asked to attempt to suppress them, and a note is made as to whether this is possible.

**Abnormalities of the Filling Cystometrogram**  

**Sensory Frequency or Urgency** Even if patients are carefully selected for filling cystometrography because they have unexplained urgency and frequency with or without incontinence, the detrusor pressure trace is often normal, with an end filling pressure of less than 15 cm H₂O and no abnormal detrusor contractions. A proportion of these patients report their first sensation and urge to void at a smaller filling volume than would be expected; they are labelled as suffering from 'sensory urgency.' Because this may be the result of intravesical pathology, a cystoscopy is always indicated. If there is no bladder lesion, the term might be taken to imply a hypersensitivity of the bladder,
but no adequate explanation of the pathophysiology of this condition has ever been offered.

**Detrusor Overactivity** Uninhibited detrusor contractions during filling that cannot be suppressed and give rise to detrusor pressures of more than 15 cm H$_2$O (Figure 23.6) are characteristic of ‘idiopathic detrusor overactivity’ in patients without neurological disease. In the presence of neurological disease, this is termed ‘neuropgenic detrusor overactivity’. The urethral sphincter can withstand high intravesical pressures up to a point, but beyond that threshold (which will vary from individual to individual and is usually higher in men than in women) leakage will occur. If detrusor overactivity leads to intravesical pressures that overcome sphincteric resistance that leads to leakage, this is termed ‘urge urinary incontinence’ (UUI).

**Poor Detrusor Compliance** Sometimes the detrusor pressure shows a steady rise during filling to reach an end filling pressure greater than 15 cm H$_2$O (Figure 23.7). This may be due to ‘small bladder syndrome’ from fibrosis after radiotherapy or extensive bladder surgery. Alternately, it is seen against a background of neurological disease, especially of the lower segments of the spinal cord. It may also be seen sporadically in neurologically intact individuals and is then difficult to explain, but is thought to be due to failure of the neurally mediated normal bladder compliance mechanism.

![Figure 23.6 Filling cystometrogram. (a) Normal: spikes of intra-abdominal pressure occur during coughing. (b) Uninhibited detrusor contractions cause a rise in detrusor pressure which cannot be suppressed.](image)

![Figure 23.7 Filling cystometrogram: poorly compliant detrusor.](image)

**23.2.1.4 Voiding Pressure Studies**
In some patients, it is impossible to tell whether they have BOO just from a measurement of flow rate and postmicturition residual volume, and in these patients, it may be useful to measure the detrusor pressure as the patient voids. In men, the upper limit of normal voiding pressure is about 60 cm H$_2$O and in women 40 cm H$_2$O. In those with outflow obstruction, the voiding pressure may be significantly higher and may or may not be associated with a low flow. There is a
tendency for the urethral pressure line to be expelled during voiding, and to get a true measurement, it may be necessary to insert a line through a suprapubic needle. As the bladder outlet obstructs, the pressure-flow dynamics are generally thought to follow a pattern of going from ‘normal pressure, normal flow’ to ‘high pressure, normal flow’ to ‘high pressure, low flow’ and finally ‘low pressure, low flow’ as the obstruction gets steadily worse. The perceived wisdom is that once the stage of ‘low pressure, low flow’ is reached then the success rate of interventions such as a transurethral resection of prostate (TURP) is generally poorer.

23.2.1.5 Videocystometry

If X-ray fluoroscopic equipment is available, important anatomical information can be obtained by using watersoluble X-ray contrast medium to fill the bladder. This will demonstrate the saccules, the thickened bladder wall, and the ‘fir tree’ appearance of the high-pressure neuropathic bladder. In stress incontinence, weakness of the supportive tissues around the bladder neck may become evident with descent of the pelvic floor during coughing and at the same time contrast may enter the urethra to give the appearance of ‘beaking’ (Figure 23.8) or be seen to leak all the way through in frank incontinence. Urethral hypermobility during coughing or valsalva is an important screening observation and should be noted during video cystometry for stress incontinence. Another advantage of video screening is the ability to assess for vesi-coureteric reflux, although the value of this observation in adults with normal renal function is limited.

Uroflow, filling and voiding cystometry, with or without video, along with measurement of the postmiction residual urine volume are the elements of a standard urodynamics study. Other investigations including urethral pressure profilometry and the fluid bridge test for stress incontinence are research tools which are insufficiently standardised for general use.

23.3 Disorders of Function

The function of the bladder is to provide a low-pressure storage reservoir for urine until such time as it is socially appropriate and convenient to void and to then expel the urine as efficiently as possible. LUT dysfunction can therefore occur during the storage phase, the voiding phase, or both.

23.3.1 Primary Storage Dysfunction

The key properties of the bladder that allow it to function as a storage unit are stability, compliance, and a competent outlet. However, no organ functions in isolation, and as such the bladder is also dependant on a properly functioning upper urinary tract, nervous, vascular, lymphatic, and lower gastrointestinal systems. The true nature of the roles of these other systems in bladder function are still under investigation, but we will briefly discuss the major patterns of bladder dysfunction as we understand them today. These patterns include OAB, UI, painful bladder syndrome (PBS), nocturia or nocturnal polyuria, and disorders of bladder sensation.

23.3.1.1 Overactive Bladder Syndrome

23.3.1.1.1 Definition and Incidence

OAB is defined as urgency, with or without urgency incontinence, usually associated with frequency and nocturia. OAB has been described as a ‘syndrome’ due to the multitude of commonly associated symptoms, but the hallmark symptom classically described is urgency (Table 23.1).

Two types of OAB are distinguished in the literature: OAB dry and OAB wet (i.e. associated without or with UI).

The prevalence of OAB ranges between 8 and 30%, depending on the definitions used and age of patients [3, 4]. Risk factors associated with OAB are increasing age (nearly 20% of >40s will suffer OAB symptoms), high body mass index (BMI), cognitive impairment, depression, and diabetes [3, 5, 6].

23.3.1.1.2 Aetiology

Urgency and OAB symptoms are manifestations of bladder smooth muscle contraction during the filling phase of the bladder. What causes these contraction is yet to be determined. The probable cause of dysfunction is in the afferent sensory nervous pathways from the bladder. This is an area of ongoing study, as is the role of different sensory receptors. The classical muscarinic receptors have been targets for therapy for a number of years, but more recently, the beta-receptors (specifically beta-3) have been a source of great interest.

23.3.1.1.3 History, Physical Examination, and Important Differential Diagnoses

Important points in the history (applicable to OAB and UI) are:

- Duration and severity, such as number of pads or change of clothes per day.
- Circumstances around the incontinence – whether associated with any particular activity, change of
position or exercise; 'key-in-the-door syndrome'; associated urgency.
- Bowel function, such as faecal incontinence, constipation/diarrhoea, digitation.
- Red flag symptoms (pain, haematuria, recurrent UTI, incomplete emptying, lack of sensation and neurological symptoms) – presence of any of these symptoms requires urgent specialist referral.
- Past medical history, including diabetes, cardiac failure, or glaucoma.
- History of previous pelvic radiotherapy or surgery.
- Drug history, particularly use of anticholinergics, antidepressants, diuretics, oestrogens, laxatives, over-the-counter, and illicit drugs.
- Obstetric history, including episiotomy and any other assisted delivery.
- Mobility.
- Dexterity.

It is important to examine all patients to rule out other significant associated features such as neurological disease, stigmata of chronic kidney dysfunction, vaginal dryness and atrophy in women, vaginal prolapse, chronic retention (more commonly in men), rectal examination of the prostate in men, etc.

Other pathologic conditions, like bladder stones and UTIs, must have been excluded to diagnose OAB. The combination of urgency, frequency, and nocturia is suggestive of detrusor overactivity (DO). However, DO is a urodynamic finding and not a clinical one [7], and not all patients with symptoms of OAB will have demonstrable DO on urodynamic investigation.

Frequency can be both an initial symptom and a coping strategy in patients with urgency. In fact, urgency is often more troublesome than established UUI. A patient who is OAB dry may live in fear of leakage all day every day, whereas a patient who is OAB wet patient might just wear some containment device, and their life will no longer be ruled by the distance from the nearest toilet.

The following alternative diagnoses need to be considered and excluded to diagnose idiopathic OAB:
- Intravesical pathology (e.g. stones, bladder cancer, carcinoma in situ, or UTI).
- Neurogenic bladder dysfunction.
- BOO (e.g. benign prostatic enlargement [BPE] or urethral strictures).

DO can be triggered by certain events, such as key-in-the-door syndrome, or exertion. The latter is likely to complicate the diagnostic process because it is different from true stress UI.

However, the absence of DO during a urodynamic study does not exclude DO in the patient, rather one can only conclude that DO could not be demonstrated at the time of the study. It is crucial to note whether the patient’s symptoms were reproduced during the study and what was seen at that time. Any urodynamic study that failed to reproduce the patient’s symptoms is of little value. Equally, the absence of DO on urodynamics should not preclude pharmacological therapy for OAB if clinically indicated.

23.3.1.5 Treatment

1) Conservative treatment or lifestyle modification

General advice includes regular exercise and to stop smoking.

In patients who are overweight or obese, it is useful to start with weight loss to improve the symptoms of UI and OAB. It has been shown that losing weight can also be preventative in developing UI, especially in patients suffering from diabetes [8, 9]. Several studies have shown a correlation between constipation and UI and OAB, although no causal relationship has been established. If constipation is apparent, it should be addressed [1, 10, 11].

A number of patients report very high (>3 l) or very low (<1 l) fluid intake in their bladder diaries. Adaptation of fluid intake may result in an improvement of symptoms. Patients who are constipated might resolve their constipation by increasing their fluid intake [12].

Some patients have a high caffeine intake associated with OAB. A reduction in caffeine intake may improve OAB symptoms in some patients, especially symptoms of urgency and frequency [13].

In patients with UUI, MUI and OAB, bladder training can be an effective initial therapeutic strategy. However, there is a general lack of understanding as to what constitutes ‘bladder training’. It is sometimes used interchangeably with timed voiding, behavioural changes, scheduled voiding, bladder drill, etc. A fairly comprehensive definition is: ‘A program of patient education along with a scheduled voiding regimen with gradually adjusted voiding intervals. Specific goals are to correct faulty habit patterns of frequent urination, improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes and restore patient confidence in controlling bladder function’. The optimal duration remains unclear, but it is suggested to be a minimum of six weeks [14].

2) Medical treatment

Before considering the different classes of drugs available to treat OAB symptoms, it is important to distinguish the real-world difference in treating urgency and treating incontinence. Too often these objectives are confused, and the evidence from drug trials is heavily weighted
towards the treatment of urgency and frequency. When evaluating the literature for studies on anticholinergics or beta-3 agonists, it is therefore important to note the primary outcome measure used because this will guide the reader to determine whether the study was aimed at evaluating treatment of urgency or frequency or urge incontinence.

The use of anti-muscarinic drugs has been proven to be an effective treatment for OAB and UUI in 50–75% of patients. The muscarinic receptor blockade leads to a decreased ability of the detrusor muscle to contract and a decreased sensation of urgency. It also leads to increased bladder capacity and increased mean volume voided, all of which lead to reduction in symptoms. A wide range of anti-muscarinic drugs are available, such as oxybutynin, tolterodine, solifenacin, darifenacin, trospium chloride, and fesoterodine [3], but none of these specific drugs has been proven to be more effective than others in the treatment of OAB [15].

Optimal efficacy of anti-muscarinic drugs may take up to four weeks. When no satisfactory improvement can be established after four weeks, an increase in dose or change in drug may be indicated [14].

Anti-muscarinic drugs are commonly known to have a high incidence of adverse events due the wide presence of muscarinic receptors throughout the body (Table 23.6). Side effects include dry mouth, blurred vision and constipation. Cognitive impairment, particularly in the elderly, has become a recent focus of attention [16]. Side effects can cause discontinuation rates of up to 86% after 12 months of treatment [17].

Oxybutynin, trospium chloride, and tolterodine are nonselective muscarinic blockers. Solifenacin is selective M2 and M3, and darifenacin is selective for M3.

Myasthenia Gravis, narrow angle glaucoma, significant BOO, active ulcerative colitis, toxic megacolon, and gastrointestinal obstruction are contraindications of anticholinergics.

Oxybutynin and tolterodine are currently off-patent and therefore standard formularies would recommend them as first-line treatment, with other anticholinergics available as second-line in treatment failures or in case of intolerable side effects. There is evidence that Oxybutynin may worsen cognitive function in the elderly, and in these patients, fesoterodine, solifenacin, or darifenacin may be better alternatives [2].

The use of adrenergic drugs, such as the beta-3 adrenoceptor agonist mirabegron, for OAB and UUI has been introduced in recent years. It promotes receptive relaxation during the storage phase by binding to and activating the beta-3 adrenergic receptor (Chapter 17) [18]. Mirabegron has been shown to be better than placebo for the treatment of urgency or frequency symptoms, but the evidence for cure of incontinence is weak. Head-to-head studies comparing it to standard anti-muscarinics are currently lacking. However, it is interesting to note with mirabegron that most of the randomised studies were conducted on participants who had failed on anti-muscarinic therapy; hence, it may be underrepresenting its real-world effectiveness in treatment-naive patients.

National Institute for Health and Clinical Excellence (NICE) currently states, ‘Mirabegron is recommended as an option for treating the symptoms of overactive bladder only for people in whom anti-muscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects’ (NICE TA290).

Comparison of adverse events seems to favour mirabegron [19], but a recent safety update has been issued, warning against its use in patients with uncontrolled hypertension.

3) Botulinum toxin A (BoNT-A)

Botulinum toxin A (BoNT-A) is a neurotoxin produced by the gram-positive Clostridium botulinum bacteria. There are eight distinct serotypes, but only types A and B are licenced for therapeutic purposes. Botulinum toxin A has five subtypes, the most commonly used being onabotulinum toxin A (e.g. BOTOX™) and Abobotulinum toxin A (e.g. DYSPORT™). Botulinum toxin acts by binding to the synaptic vesicle protein (SV2) on the presynaptic nerve terminal. Once in the cells, it causes proteolysis of the synaptosomal associated protein, SNAP-25, one of the SNARE proteins (an acronym derived from ‘SNAP [Soluble NSF Attachment Protein] REceptor’) which are

<table>
<thead>
<tr>
<th>Muscarinic receptor subtype</th>
<th>Body part</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Brain</td>
<td>Impaired memory and cognition</td>
</tr>
<tr>
<td>M2</td>
<td>Heart and bladder</td>
<td>Prolongation of the QT interval, which can result in tachycardia and cardiac arrhythmias</td>
</tr>
<tr>
<td>M3</td>
<td>Eyes, skin, gastrointestinal tract, and bladder</td>
<td>Dry eyes, dry skin and rash with transdermal patches, dry mouth, constipation</td>
</tr>
<tr>
<td>M4</td>
<td>Brain</td>
<td>Impaired cognition</td>
</tr>
</tbody>
</table>
Disorders of Function

23.3 Disorders of Function

responsible for vesicle fusion with the cell membrane (i.e. endocytosis). It thus inhibits the release of Ach at the neuromuscular junction of cholinergic neurons, and hence, induces a flaccid paralysis of the detrusor muscle. In addition it reduces the expression of neuronal receptors such as the transient receptor potential cation channel subfamily V member 1 (TrpV1) (vanilloid receptor 1) and the purinoreceptor P2X3 on sensory nerves, leading to reduced sensation [20].

Injections with BoNT-A in the bladder can be performed in an outpatient setting under local anaesthesia, or in the operating theatre under sedation or general anaesthesia. The starting dose of 100 U for idiopathic OAB with or without UUI is optimal, but doses up to 200 U or, in rare cases, 300 U may be used. For neurogenic DO, a dose of 300 U is commonly required. The recommendation from the manufacturer of BOTOX™ is to dilute the required dose in 10 ml of saline and inject the solution in 0.5 ml aliquots to 20 sites in the submucosa of the bladder wall avoiding the dome (risk of extravescical injection) and trigone (theoretical risk of ureteric paralysis and reflux, although this has not been demonstrated in clinical trials).

The effects are noticeable by the first week and last between three and nine months. BoNT-A appears to have a much higher rate of cure of UUI compared to anti-muscarinics, with patients reporting on average 50% reduction in UUI episodes a day and 23% of patients reporting being completely dry [21].

Repeat injections are necessary because of the mean effectiveness of three to nine months, and there is no evidence so far that repeat injections have reduced efficacy. About 5–10% of the patients with OAB develop significant PVR (>150 ml) and sometimes urinary retention after intravesical BoNT-A injections, and this is more common in the elderly. Therefore, as a precaution, all patients should be instructed how to perform clean intermittent catheterization (CIC) before the first BoNT-A injections, or at least should be made aware that this may become necessary, and they must be willing to learn the technique if required. Haematuria is a common procedural complication. Also, UTIs are common [22, 23] with rates of up to 25%. Rarely systemic side effects occur such as generalised muscular weakness, difficulty in taking a deep breath or swallowing, or blurred vision due to intraocular muscle weakness. These are usually self-limiting, resolving within a few weeks.

Patients with Myasthenia gravis or Eaton-Lambert syndrome are contraindicated for Botulinum toxin injections due to the risk of increasing muscular weakness or paralysis. Aminoglycosides enhance the effects of the toxin and should be avoided.

4) Posterior tibial nerve stimulation (PTNS)

The posterior tibial nerve is stimulated using an electrode inserted above the ankle near the medial malleolus. This can be done percutaneously (P-PTNS) or transcatheterously (T-PTNS). Thirty-minute treatment is delivered on a weekly basis for 12 weeks. It is indicated in patients suffering from OAB who have not benefitted from antimuscarinic therapy and is minimally invasive. P-PTNS gives rise to an improvement of >50% in symptoms [2, 24]. In addition, compared to anticholinergic treatment, it showed similar satisfactory results [25]. Note that results with anti-muscarinics, in real-world practice, are extremely variable, and so with PTNS also.

5) Neuromodulation with sacral nerve stimulation (SNS)

An invasive treatment that can be considered to treat refractory OAB symptoms. The third sacral nerve is electrically stimulated and during a test phase with a temporary percutaneous lead electrode the effectiveness of the stimulation is evaluated. The percutaneous nerve evaluation (PNE) lasts one week and patients who show an improvement of more than 50% in their symptoms and mean voided volume are eligible for placement of a permanent electrode and a pulse generator in the buttock of the patient. This requires major surgery under anaesthetic; therefore, careful patient selection and optimisation is essential. It is also worth noting that this surgery requires prone positioning, and therefore, is not suitable for patients with a high BMI due to the risk of respiratory compromise.

The pulse generator is programmed with stimulation activated just above the threshold of a sensation in the urogenital area. Patients can choose between different programmes [26]. The average life span of the Interstim II battery is 4.5 years. This treatment modality has shown satisfactory results in up to 60% of the patients during long-term follow-up [27]. Complications involve occasional wound infections and surgical revision of the generator or tined lead [23].

6) Augmentation cystoplasty

Much less commonly performed for OAB these days, augmentation of the bladder may be performed in patients who are non-responsive to or who are not eligible for sacral neuromodulation and BoNT-A. An ileal intestinal segment is most commonly used, but any segment of the bowel may be adapted. The isolated segment is detubularised before placement in the bladder wall. The bladder wall is incised, either sagitally or transversely, after which the bowel segment is sutured in the gap to ‘augment’ the capacity of the bladder. The aim is to create a low-pressure bladder with increased capacity and improved continence. Long-term results indicate a success rate of 50%. Augmentation has been associated with high complication rates, ranging from stones to metabolic complications, fistulae, and changing bowel habits [28]. CIC is often needed after augmentation due
to impaired bladder emptying, mucus production, and high PVR [3].

7) Urinary diversion may also be performed in the most severe of cases.

23.3.1.2 Urinary Incontinence (UI)

23.3.1.2.1 Definition and Incidence

Urinary incontinence is defined as any involuntary leakage of urine. This definition is problematic in its simplicity; there is no mention of how often or how much involuntary leakage needs to occur before a patient is deemed ‘incontinent’ of urine.

Prevalence rates range between 30 and 60% [3, 29], while treatment is sought by approximately 35% of patients [29–31], and this is significant because it shows that the majority of patients either do not seek treatment because they are not bothered or do not know that treatment is available.

23.3.1.2.2 Aetiology

There are a number of theories proposed for the mechanisms behind stress UI, the most widely stated being the integral theory, urethral hypermobility, and intrinsic sphincter deficiency.

The integral theory states that vaginal laxity, either due to altered collagen or elastin in the vaginal connective tissue or in its ligamentous supports, causes not just loss of urethral support and therefore stress UI, but also activation of bladder base and proximal urethral stretch receptors, therefore, precipitating urgency or frequency and UUI. The urethra is sometimes described as resting in its vaginal ‘hammock’, and the laxer the hammock, the higher the likelihood of incontinence. Urethral hypermobility due to factors aside from vaginal laxity may also play a role, and intrinsic sphincter deficiency can cause a loss of outlet resistance, resulting in leakage from smaller rises in bladder pressure. Mechanically, continence is dependent on bladder pressure and outlet resistance; anything that causes the former to exceed the latter may result in leakage (i.e. abnormal rises in bladder pressure or loss of outlet resistance). Therefore, the evaluation of the patient should be aimed at identifying what is causing the imbalance and understanding how best to correct it with the tools and techniques available.

The biggest risk factor to develop UI seems to be increasing age. Other associated risk factors include pregnancy, vaginal deliveries, high BMI, constipation, UTIs, and previous pelvic surgery, or radiotherapy. Other risk factors are for patients with neurological disorders such as multiple sclerosis, spina bifida, or spinal cord injury.

23.3.1.2.3 History, Examination, and Differential Diagnoses

UI is classically subdivided into stress UI (SUI), urgency UI (UUI), and mixed UI (MUI) [7].

- SUI (50%) is defined as the complaint of involuntary leakage of urine on effort or exertion or on sneezing or coughing.
- UUI (10–20%) is defined as the complaint of involuntary leakage of urine accompanied by or immediately preceded by urgency.
- MUI (30–40%) is defined as the complaint of involuntary leakage of urine associated with urgency and also with exertion, effort, sneezing, or coughing.

Women younger than 50 years of age more often suffer from SUI, whereas UUI and MUI show an increase in prevalence in women older than 50 years of age [32].

A thorough history is important in the evaluation of the incontinent patient. A provisional classification of SUI, UUI, or MUI can often be made based on history alone. Important points in the history are as stated for OAB. Often the history will be the only clue suggesting UUI. SUI, on the other hand, is usually demonstrable on physical examination.

Physical examination should include assessment of BMI, abdominal palpation (masses, enlarged bladder), and inspection and digital exam of the external genitalia [33]. During inspection in women, assess the extent of vulvovaginal atrophy, visibility of any pelvic organ prolapse (POP), and perform a cough stress test to assess SUI. The digital exam is used to determine the contraction strength of the pelvic floor and severity of any POP using the POP-Q scale.

Primary SUI is much less common in men due to the more substantial external sphincter. However, men who have had bladder outlet surgery (such as TURP, bladder neck incision [BNI], or radical prostatectomy) and who are therefore more likely to have sphincter dysfunction, are at increased risk of SUI. This is now usually classified as a separate subtype of SUI.

UUI by definition is part of the OAB symptom complex, and therefore patients with pure UUI should be assessed and managed as per the algorithm set out in the OAB section.

Aside from the three classically described forms of UI, other types are also recognised: nocturnal enuresis, continuous UI, inappropriate urethral relaxation incontinence, post-TURP incontinence, and postprostatectomy incontinence, as well as incontinence in special situations, such as incontinence during sexual intercourse or giggle incontinence.

Nocturnal enuresis. Nocturnal enuresis is the complaint of loss of urine occurring during sleep. This is most commonly encountered in the paediatric setting and is discussed in Chapter 10. The main reason for new nocturnal enuresis during adulthood is chronic retention, usually due to BOO, but it can be due to poor detrusor contractility or both. If new nocturnal enuresis is present, it should always prompt a full LUTS history, PVR measurement, and (in men) a flow test.
Continuous urinary incontinence. The presence of continuous urinary incontinence should always prompt careful examination and investigation for possible fistulae and urethral diverticula. However, in the absence of any fistulae, continuous incontinence can result from particularly poor sphincter function, as can occur in occasional female patients after long-term urethral catheters use for many years or from particularly frequent SUI or UUI, such that individual episodes are not distinguished.

The treatment of urethral fistulae should be conducted by specialists experienced in such surgery. The most commonly performed procedure for fistula repair is the Martius fat pad interposition [34].

Inappropriate urethral relaxation incontinence. Inappropriate urethral relaxation incontinence is a term given to incontinence occurring due to sphincter relaxation with no measurable detrusor contraction. It is extremely rare and only occurs in women. However, detrusor pressure often shows no measurable rise in healthy women during normal micturition. As such, inappropriate urethral relaxation incontinence may represent an unconsciously activated micturition reflex. Treatment is usually the same as for SUI.

Post-TURP incontinence. Post-TURP incontinence is perhaps more common than previously thought and can be caused by: (i) un-masked UUI (not previously apparent due to the prostatic obstruction) or (ii) sphincter injury during the operation causing SUI. A careful history may help distinguish one or the other, but video urodynamics may be necessary to confirm. Patients should always be carefully counselled regarding the risk of incontinence post TURP, particularly those who complain of significant storage LUTS and urgency preoperatively. Treatment is as for primary UUI or SUI. It is important to note that in a man with mixed LUTS, often it is more pragmatic to treat the obstruction first before considering invasive treatment (such as botulinum toxin injections) for OAB and UUI because of the risk of urinary retention with these treatments. Also there is significant reduction in storage symptoms post-TURP without any other therapy.

Postradical prostatectomy incontinence. Postradical prostatectomy incontinence is common irrespective of the surgical modality (i.e. open, laparoscopic, or robot-assisted), and men should be counselled accordingly. Pelvic floor exercises and physiotherapy help in restoring continence postoperatively, and many men will achieve acceptable levels of continence in 12–18 months postoperatively. However, nearly 5% of men will require treatment, and this is usually in the form of a male sling or an artificial urinary sphincter. Evaluation of persistent postradical prostatectomy incontinence before considering surgical treatment should consist of a flexible cystoscopy to exclude bladder neck stenosis and video urodynamics to assess the nature and degree of incontinence. The general consensus is that mild to moderate degrees of incontinence could be treated with a male sling, and more severe incontinence will require insertion of an artificial urinary sphincter [2].

Incontinence during sexual intercourse. This can be a symptom of both SUI and UUI. It is important to rule out other causes, such as UTI, and to take a gynaecological history for other associated symptoms.

Giggle incontinence. Isolated giggle incontinence sometimes occurs in young girls, but it is rarely a problem persisting into adulthood. If it persists, investigation, and management would be as for an adult presenting with UI.

23.3.1.2.4 Investigations

Outpatient investigations: three-day bladder diary, urine dipstick, PVR, and uroflowmetry.

Uroflowmetry can suggest dysfunctional voiding but should be interpreted with caution. A reasonable voided volume is required (at least 100–150ml) and although arbitrary Qmax figures of 10mls⁻¹ have been suggested as a cut-off for clinically significant obstruction, a single reading is probably of minimal diagnostic value.

Questionnaires can be used to evaluate the impact of the urinary dysfunction. Several scales are available, measuring general urinary dysfunction and also specific UUI, pelvic floor dysfunction (PFD), and sexual dysfunction. These questionnaires can also be used to report on the effectiveness of certain treatments [33]. The International Consultation on Incontinence has recommended to use, amongst others, the following symptom specific short questionnaires: UID-6 and IQ-7 for UI, PFQ-20 and PFIQ-7 for PFD, and FIQL and FISI for faecal incontinence [35].

Patients who prove to be refractory to conservative or pharmacological treatment, or those with complicated UI, may benefit from further investigations, such as cystometrography (CMG or video CMG). CMG can objectively demonstrate SUI and DO, although the absence of demonstrable SUI or DO during a test does not preclude the diagnosis. Some studies have suggested that surgical treatment of SUI also relieves DO and symptoms of OAB in up to 30% of cases, although this figure varies widely.

The Valsalva leak point pressure (VLPP) can be helpful to determine the severity of SUI. Stress leakage at a pressure of <60cm H₂O suggests intrinsic sphincter deficiency, while pressures >90 cm H₂O indicate urethral hypermobility [36]. The implication of this in terms of choice of treatment remains unclear in women. However, in men with postprostatectomy incontinence, there is a general trend to treat men with moderate decrease in VLPP with a male sling and those with severe decrease in VLPP with an artificial urinary sphincter (AUS).
Detrusor hypocontractility or detrusor underactivity can be defined as a bladder contraction of reduced strength, which prolongs urination and may lead to significant PVR or urinary retention. The significance of detrusor underactivity may be particularly important in men with voiding symptoms, as surgical treatment of presumed BOO may not improve their symptoms. Urodynamic demonstration of detrusor underactivity may therefore be an important factor when counselling men for consideration of bladder outlet surgery.

23.3.1.2.5 Treatment of UI
The treatment algorithm for UUI is as stated for OAB. However, it must be noted that patients with significant UUI are less likely to be cured of their incontinence by medical therapy and are more likely to require invasive treatments.

1) Conservative treatment or lifestyle modification
A wide variety of treatment options is available for UI and OAB. Choice of treatment is dependent on the severity and duration of symptoms, comorbidities, and local expertise. It is recommended to start with conservative treatment before proceeding to more invasive treatment [23]. For patients with MUI, the most bothersome symptom should be treated first.

Overall, conservative treatment modalities are similar to those stated for OAB: regular exercise, smoking and caffeine cessation, weight loss, adequate hydration, and treating constipation.

Pelvic floor muscle training (PFMT). PFMT is aimed to improve control over the pelvic floor muscles. PFMT has not been standardised and can include pelvic floor muscle exercises, biofeedback and electrical or magnetic stimulation [33, 37]. Supervised PFMT should be carried out for at least three months with at least eight contractions three times a day [33]. It has been shown to be beneficial in improving symptoms and quality of life (QoL) in SUI, and to a lesser degree for MUI and anterior POP [14, 38, 39].

2) Medical treatment of UUI
Antidepressants. Duloxetine can be used as a second-line treatment for SUI in patients who are not eligible for surgical interventions or do not wish to have surgical intervention. It is a serotonin and noradrenaline reuptake inhibitor and increases sphincteric muscle activity by increasing the pudendal nerve and Onuf’s nucleus stimulation. A significant reduction of symptoms by >50% is seen during the use of duloxetine, but adverse events may lead to discontinuation in some cases. It is important to counsel patients that they must not discontinue duloxetine abruptly and should wean off it gradually. It should be used only in select patients and rarely effects cure. The effects are also limited to while the patient stays on the drug.

3) Surgical treatment of SUI
a) Midurethral slings or tapes
Currently the gold-standard surgical treatment for SUI. It is a minimally invasive procedure in which a synthetic sling is placed under the middle urethra to provide support and reduce urethral mobility during stress. The synthetic tapes are type I ( pores are >75 μm) monofilament polypropylene meshes. Others include type II ( pores are <10 μm), type III (macro-multifilament), and type IV (sub-micron pores). Continencc rates higher than 80% have been described with the standard retropubic and transobturator approach, equivalent to Burch colposuspension but with considerably less associated morbidity. The advantages of this procedure include short operation times, minimal blood loss, and short hospital stay [40].

In the transobturator procedure, the tape is inserted with two trocars through a vaginal incision beneath the mid-urethra, anchored to the obturator foramina on either side. Both outside-in and inside-out approaches have been described [41].

The originally described retropubic tension-free vaginal tape (TVT) procedure involves two needles, which are blindly passed through the retropubic space. No fixation sutures are necessary in the TVT approaches. The transobturator approach has been shown to result in less complications like bladder perforation and urinary retention, but postoperative pain (groin or thigh pain) is more common compared to the retropubic route. Other complications include de novo bladder overactivity, urethral infection or erosion, and rarely, bowel or blood vessel injury.

The inside-out insertion has less postoperative complications compared to the outside-in insertion and might be the preferred route [23]. Satisfaction declines over time, but the urinary continence rates remain high [42]. The use of single-incision slings does not appear to have satisfactory long-term results compared to standard midurethral slings but can be performed under local anaesthesia and may be effective in experienced hands [43].

b) Colposuspension
This procedure can be performed open (Burch) or laparoscopic with or without robotic assistance. The general principles do not differ between the different approaches. The anterior vaginal wall is attached by paravaginal sutures on both sides to the ileopectineal ligaments. The anchor site, types of sutures, and extraperitoneal and abdominal approach may vary.

Studies have shown that although the colposuspension is more invasive, continence outcomes are similar to midurethral sling procedures. The open approach has proven to be effective in the long-term with continence rates of about 80% after five years. An increased risk of POP is reported following colposuspension compared to other surgical techniques [44].
c) Autologous fascial sling
The autologous fascial sling is a traditional suburethral sling, which uses the patient’s own tissue obtained from the rectus fascia or the tensor fascia lata. A combined vaginal and abdominal approach is used to place the suburethral sling. After mobilising fascial tissue, it is tunnelled under the urethra, and then fixed with sutures to the periurethral fascia or anchored to the rectus fascia using the sling-on-a-string technique, similar to insertion of a synthetic retropubic sling. This results in a mechanical compression of the urethra [45].

Long-term results are similar to colposuspension and midurethral slings for incontinence improvement rates, and a recent study has suggested improvement rates may in fact be more durable with autologous slings. However, postoperative voiding dysfunction is found more frequently compared to colposuspension and CIC might be needed. The autologous rectus fascia seems to be favourable over other biological materials [46].

d) Urethral bulking agents
Urethral bulking agents can be used as second-line treatment. The results are inferior to midurethral slings and colposuspension and have usually only short-term beneficial effects. However, bulking agents might be considered in patients who are not fit for more invasive surgery, or those who do not want to undertake the risks of other surgery. Hyaluronic acid, polyacrylamide hydrogel, polytetrafluoroethylene (PTFE), collagen, adipose tissue (autologous fat), and silicon agents have been injected submucosally into the proximal urethra until coaptation has been reached. Repeat injections are often needed to maintain a significant improvement of symptoms [47, 48].

e) Artificial urinary sphincter and adjustable continence therapy
Patients needing third-line treatment for SUI or complicated SUI have often already undergone conservative or second-line treatment. The management of complicated SUI should be provided in specialised centres, where enough expertise and experience are available. The AUS and adjustable continence therapy (ACT) have shown good results for this group of patients. AUS are indicated for patients with sphincter deficiency, usually seen in men after prostatectomy or transurethral surgery, or in patients who had pelvic radiotherapy or a pelvic fracture or failed other UI treatments. Nonetheless, if associated with OAB symptoms, the bladder needs to be treated first because this might alleviate the UI. Patients need to have good manual dexterity and cognitive function to understand the principle and be able to work the pump mechanism.

AUS is comprised of a pressure-regulating balloon, a pump, and a cuff. To void, the patient squeezes the pump, which deflates the fluid-filled cuff, transferring the fluid to the balloon. Over a three-minute period, the fluid slowly fills the cuff again. Depending on the site of cuff placement, the pressure can be 61–70 mm Hg for vulvar urethral placement or 71–80 mm Hg for bladder neck placement.

The AUS is inserted through an abdominal approach followed by cuff placement around the bladder neck between periurethral fascia and vagina [49]. A high number of patients reported improvement during long-term follow-up (85–86%). Complication rates range between 17 and 26% [50, 51]. The ACT is placed as follows: the bladder neck is identified with fluoroscopy. A trocar is introduced through incisions in the labia majora laterally of the urethra and balloons are placed paraurethrally just under the bladder neck. The ACT shows 66–78% improvement rates and significant improvement in QoL. Explantation or revision rates range between 19 and 31% [52].

Complications requiring revision include urethral atrophy or erosion, mechanical failure, and infections. Other complications include de novo bladder overactivity and urinary retention due to urethral strictures or bladder neck contracture.

23.3.1.3 Painful Bladder Syndrome
23.3.1.3.1 Definition and Incidence
Painful bladder syndrome (PBS) is the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime or nighttime frequency, in the absence of proven UTI or other obvious bladder pathology. It is chronic in its nature (>6 months) with pain being the major complaint. The diagnosis is one of exclusion. Other names for this condition are interstitial cystitis (largely historical) and bladder pain syndrome.

23.3.1.3.2 Aetiology
Prevalence within a population can be variable ranging from 0.06 to 30%, with a 10:1 female: male ratio, [53]. It has no easily identifiable aetiology; multiple triggers may manifest as a final common bladder response to different types of stimuli or insult. It can be considered a major part of the painful bladder disease complex that includes other painful bladder conditions with established aetiology such as radiation cystitis. Other disorders such as depression, irritable bowel syndrome, and fibromyalgia are more prevalent in patients with PBS.

Although the pathology is poorly understood, PBS usually affects the patient during the storage phase and appears to originate within the bladder. Possible or postulated causes include deficiencies in the glycosaminoglycan (GAG) layer, infiltration with mast cells, neurogenic inflammation, excessive sympathetic activity, stress, recurrent UTIs, autoimmunity, and allergy. Females are 10 times more likely to be affected than males. The natural history is one of remissions and exacerbations. Some patients ultimately develop a small fibrotic bladder.
23.3.1.3.3 Pathophysiology
Loss of bladder urothelium integrity secondary to an infective or inflammatory injury as well as enhanced mast cell activation and sensory nerve up regulation are thought to play a role [39]. The presence of antinuclear antibodies has suggested that an autoimmune process might be responsible. Nonetheless, the pathogenic processes lead to bladder neuropathy that produces pain and LUTS. Figure 23.9 demonstrates the hypothesis of aetiological bladder pain syndrome (BPS) cascade [54].

23.3.1.3.4 History, Examination, and Common or Important Differential Diagnoses
The diagnosis is difficult and is deemed a diagnosis of exclusion. Symptoms include pain, discomfort, or pressure localised to the bladder, accompanied by at least one other symptom such as urinary frequency or nocturia. Urine cultures are negative. Other pathologies must be excluded, and if indicated, by cystoscopy and biopsy.

Hydrodistension of the bladder under anaesthesia was used to assess for worsening pain (the patients grunt...
or vitals elevate in response to pain). Stimulated by small ulcerations of the mucosa as the bladder fills, this is followed by mucosal petechial haemorrhage because the water runs out of the bladder and the typical ‘cascade bleeding’ ensues.

Nonetheless, cystoscopically the appearance is similar to CIS, and biopsies should be taken. In both ulcer and nonulcer BPS cystoscopic and biopsy findings are consistent with defects in the urothelial GAG layer, which may expose submucosal nerve filaments to irritative urine components [55–58]. In severe BPS, there is elevated sulphated GAG levels and urinary urinate [59]. The underlying lamina propria is full of chronic inflammatory cells, amongst them mast cells, which are present in 30% of patients. Table 23.7 depicts the BPS classification.

Interstitial cystitis was originally described as bladder disease accompanied by severe inflammation of the bladder wall by Guy Leroy Hunner in 1915 and was described as an ‘ulcer’ [60]. However, the lesion described is not an ulcer but a vulnerable weak area of bladder wall that can ulcerate on distension. The term was later changed to ‘Hunner lesion’ [61]. Patients with Hunner lesions are considered to have a subtype of cystitis in the PBS spectrum.

Differential diagnoses to exclude bladder tumours, UTI, radiation cystitis, tuberculosis cystitis, cyclophosphamide cystitis, bladder calculi, lower ureteric calculi, OAB, urethral diverticulum, urethral cancer, vaginitis, gynaecological cancer, genital herpes, chronic prostatitis, and prostate cancer. If in doubt, some of these will need further investigations to be excluded.

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### Investigations

1) **Three-day bladder diary.** All patients need to complete a three-day bladder diary, including fluid intake, timing and volume of micturition, and timing of symptoms. This helps to determine the starting point in terms of symptoms.

2) **Urine dipstick and urine microscopy, culture, and sensitivity.** Urine dipstick and urine microscopy, culture, and sensitivity should be performed on all patients. If in doubt, special cultures should also be requested (e.g. tuberculosis culture). These investigations will exclude other diagnoses.

3) **Cytology** – bladder cancers, including CIS, can rarely present as pain.

4) **Filling cystometry.** Filling cystometry can be helpful in ruling out sensory urgency or DO, and may suggest painful bladder syndrome if there is reduced compliance, pain on filling, and a functional capacity of <400ml. However, most of these features can be assessed with simple flexible cystoscopy.

5) **Cystoscopy, cystodistension, and biopsy.** Cystoscopy, cystodistension, and biopsy are needed to rule out other intravesical pathology and is required to classify PBS (for diagnosis confirmation), but can also be a part of treatment. Cystodistension is done twice for one to two minutes at 80 cm H₂O.

Positive findings are glomerulations (pinpoint bleeding) and a Hunner ulcer (found in 10% of patients – a red area with small vessels radiating to the centre and oozing blood like a waterfall after distension). A positive biopsy shows inflammatory infiltrates or detrusor mastocytosis or granulation tissue or intrafascicular fibrosis. Patients might perceive pain during anaesthetic, and the anaesthetist needs to be informed to look for signs of pain (Table 23.7).

### Treatment

1) **Conservative treatment or lifestyle modification**

A key consideration is to build realistic expectations at the outset. A careful and frank counselling of the patient

### Table 23.7 The classification of painful bladder syndrome by the European society for the study of interstitial cystitis (ESSIC) [7].

<table>
<thead>
<tr>
<th>Cystoscopy and hydrodistension</th>
<th>Biopsy</th>
<th>Not Done</th>
<th>Normal</th>
<th>Glomerulations a</th>
<th>Hunner Lesion b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not done</td>
<td>XX</td>
<td>1X</td>
<td>2X</td>
<td>3X</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>XA</td>
<td>1A</td>
<td>2A</td>
<td>3A</td>
<td></td>
</tr>
<tr>
<td>Inconclusive</td>
<td>XB</td>
<td>1B</td>
<td>2B</td>
<td>3B</td>
<td></td>
</tr>
<tr>
<td>Positive c</td>
<td>XC</td>
<td>1C</td>
<td>2C</td>
<td>3C</td>
<td></td>
</tr>
</tbody>
</table>

a Cystoscopy: glomerulations grade 2–3.
b Lesion per Fall’s definition with and without glomerulation.
c Histology showing inflammatory infiltrates, detrusor mastocytosis, granulation tissue, or intrafascicular fibrosis.
is instrumental. The patient must understand that there is no definite cure, and the aim of treatment is to control symptoms. Joining a self-help or support group is recommended from the outset.

The patient should be asked to look for and avoid any triggers, which will vary from patient to patient. Some drugs, chilli, caffeine, alcohol, tomatoes, spices, chocolate, citrus beverages, high-acid foods, and artificial sweeteners may all contribute to bladder irritation and inflammation.

2) Medical treatment
All of the following oral medications can be tried alone or in combination: paracetamol, diclofenac, amitriptyline, pregabalin/gabapentin, cimetidine, hydroxyzine, and sodium pentosan polysulphate.

The following intravesical treatment may also be tried:
- Intravesical dimethyl sulphoxide (DMSO), 50 ml of 50% for 15 minutes, repeated after two to four weeks (50–80% response rate). DMSO is a chemical solvent that penetrates cell membranes. It has multimodal actions such as analgesic properties, anti-inflammatory, muscle relaxant, and collagen dissolution and effects histamine release.
- Intravesical local anaesthetic may provide short-term symptom relief.
- Intravesical pentosan polysulphate (Elmiron), response rate 15–30%.
- Intravesical hyaluronic acid, weekly, response rate 70%, aimed at repairing GAG layer defects.
- Intravesical chondroitin sulphate, for six weeks, then for four months, response rate 60%, aimed at repairing GAG layer defects.

All these treatments are hit and miss, and it is essential that patients understand this. Most patients will undergo trials with different agents and may or may not find one beneficial (trial and error).

If there is no improvement with medical or intravesical therapy, early referral to a pain clinic is advisable.

3) Surgical treatment
Hydrodistension under anaesthesia, one to two minutes at 80 cm H2O can be tried and is the only surgical option available to patients with PBS, short of cystectomy. If successful, it can be repeated as required.

Transurethral resection, laser coagulation, or dissection of Hunner ulcer is recommended for painful bladder syndrome type 3C only.

More complex surgery is reserved for resistant cases after careful counselling regarding side effects. Patients should have failed to respond to all medical treatment and failed to respond to any other options offered at the specialist pain clinic. The following procedures have been used for the treatment of PBS with varying successes:
- Botulinum toxin A injection can provide both symptomatic and urodynamic benefit by its anti-nociceptive effect on afferent pathways in the bladder. Efficacy is variable; studies have shown some short-term benefits and requires repeated treatments every few months. It is considered if intravesical instillations have failed.
- Neuromodulation studies of sacral and pudendal nerve stimulation have shown benefits, although implantation (28%) and reimplantation (50%) rates have been found to be high [58]. Pudendal nerve stimulation has shown to be superior compared to sacral nerve stimulation [59].
- In case of small fibrotic bladders:
  - Substitution cystoplasty with or without Mitrofanoff, especially for small capacity bladders
  - Urinary diversion via a conduit with or without a cystectomy (or cystourethrectomy) can be considered early on in the treatment if the bladder is small.

23.3.1.3.7 Other Treatment Options
Transcutaneous nerve stimulation (TENS) is an option with a response rate of 25%.

23.3.1.4 Nocturia or Nocturnal Polyuria
Nocturia is primarily a storage symptom and often difficult to treat.

23.3.1.4.1 Definitions and Incidence
Nocturia is the complaint that the individual has to wake at night one or more times to void (symptom). Nocturia is also the number of voids recorded during a night’s sleep: each void is preceded and followed by sleep. Polyuria is urinating >3l over a 24-hour period. Nocturnal polyuria (NP) is present when an increased proportion of the 24-hour output occurs at night (normally during the eight hours whilst the patient is in bed). The nighttime urine output excludes the last void before sleep but includes the first void of the morning. An ‘increased proportion’ is defined as >20% in patients younger than 65 and >33% in those 65 years of age or older.

A single episode of nocturia does not usually affect quality of life, but two or more voids per night may. Patients will vary in their assessment of this and should be counselled accordingly. Incidence of nocturia (two episodes or more) increases with age from the sixth decade of life onwards, with around 50% of the population affected by age 80. Comparative prevalence is greater in young females than young males, but greater in elderly males than elderly females.

23.3.1.4.2 Aetiology: LUT Related
Nocturia in elderly males is often believed to be secondary to BPE, but rates of improvement after treatment of BPE are variable. Nocturia is part of the OAB symptom
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complex and is also common in reduced bladder capacity due to any cause (e.g. BPS, neurogenic bladder dysfunction, LUT obstruction of any cause, LUT cancer, bladder calculi, detrusor failure, urogenital atrophy, and UTI).

23.3.1.4.3 Aetiology: Non LUT Related

Nocturia is more common in patients who are obese and very common in pregnancy. Exercise appears to protect against nocturia in some studies. Polydipsia causes polyuria, and depending on timing, may cause nocturia and nocturnal polyuria.

Medical conditions which may cause nocturia and should be excluded are diabetes, coronary heart disease, congestive cardiac failure, obstructive sleep apnoea (i.e. large negative intrathoracic pressure fluctuations can cause the heart muscle cells to secret atrial natriuretic peptide causing NP), and neurological diseases (e.g. multiple sclerosis, stroke, and Parkinson disease). Diuretic use should also be considered, and if possible, the timing of intake should be altered.

One must remember that nocturia could also occur if the person wakes for any other reason and decides to void before returning to sleep. As such, the potential list of causes could include any sleep disturbance such as insomnia, dementia, depression, anxiety, chronic pain, a baby crying in the house, or noisy neighbours!

Polyuria can be either solute or water diuresis. In patients who have undergone surgery, the more common causes are poorly controlled diabetes, diuresis seen in patients with high-pressure retention once obstruction is relieved, postoperative loading with saline, and primary polydipsia. A long list of medical causes is beyond the scope of this chapter.

23.3.1.4.4 History and Examination

Patients with nocturia need a detailed medical and surgical history, as well as examination of the abdomen, pelvic and rectal examination, and assessment of any ankle swelling. Further examination is guided by symptoms, such as possible neurological disease. It is important to ask whether the patient is bothered by their nocturia. It is often helpful to ask partners regarding snoring or interrupted breathing during sleep because the patient themselves may not know.

23.3.1.4.5 Investigations

Baseline investigations include BMI, forced vital capacity (FVC, including a marker for going to bed and for getting up), urine dipstick, flow rate, pelvic examination, and urea and electrolytes. Further urological investigations are only indicated if LUT pathology is suspected. In patients who are polyuric, urine osmolality to determine if solute (>250 mOsm/kg\(^{-1}\)) or water (<250 mOsm/kg\(^{-1}\)) diuresis.

23.3.1.4.6 Treatment

1) Conservative treatment or lifestyle modification and referrals

Simple measures to avoid nocturia are fluid advice, in particular avoiding fluid intake in the evening, encourage exercise, elevate legs to above heart level in the afternoon, changing diuretic doses to the morning or afternoon, and improving the sleep environment.

Depending on the results of history, examination and baseline investigations, it may be appropriate to refer the patient to other specialists for further assessment, such as the cardiologist, sleep specialist, neurologist, psychologist, or endocrinologist.

2) Medical and surgical treatment

Medical and surgical treatment of nocturia should be aimed at the underlying cause.

An afternoon dose of loop diuretic can be used for nocturnal polyuria.

In patients with nocturnal polyuria not responsive to other measures, desmopressin (a synthetic analogue of vasopressin antidiuretic hormone) therapy can be used, provided serum sodium is >135 mmol\(^{-1}\). Sodium levels should be monitored at three and seven days for hyponatraemia, detection of which is an indication to discontinue treatment.

23.3.1.4.7 Other Considerations

Nocturia raises the potential dangers of walking to the toilet in the dark, most notably causing falls, and in some cases, fractures in the elderly. Its impact should therefore not be underestimated.

23.3.1.5 Increased Bladder Sensation

23.3.1.5.1 Definition and Incidence

With increased bladder sensation, the individual feels an early and persistent desire to void, with actual voided volumes usually being small.

23.3.1.5.2 Aetiology

Increased bladder sensation can be caused by any inflammation of the bladder or urethra or could be idiopathic. This includes radiation cystitis, chemical cystitis, PBS, and urethral pain syndrome. The most common cause, however, is a UTI.

23.3.1.5.3 History, Examination, and Common or Important Differential Diagnoses

A careful history often reveals storage symptoms and may reveal dyspareunia or any relationship with the menstrual cycle or previous hysterectomy. Examination may be negative but may reveal a urethral caruncle (which is a mucosal prolapse) or bladder tenderness.
23.3.1.5.4 **Investigations**
Investigations usually include urinalysis, urine culture, voiding diary, abdominopelvic ultrasound, and pressure or flow cystometry. Further investigations may be required (e.g., cystoscopy with or without biopsy and urine culture). The aim is to exclude other causes, most notably UTI, bladder stones, OAB, or gynaecological disease.

23.3.1.5.5 **Treatment**
Treatment of increased bladder sensation is generally the same as for OAB or aimed at any identified underlying cause.

23.3.1.6 **Reduced or Absent Bladder Sensation**

23.3.1.6.1 **Definition and Incidence**
With reduced bladder sensation, the individual is aware of bladder filling but does not feel a definite desire to void. With absent bladder sensation, the individual reports no sensation of bladder filling or desire to void.

23.3.1.6.2 **Aetiology**
Reduced bladder sensation is either idiopathic, neurogenic (will be discussed in Section 23.4), or secondary to chronic retention. It often coexists with atonic bladder (Section 23.4).

23.3.1.6.3 **History, Examination, and Common or Important Differential Diagnoses**
Presenting symptoms may be infrequent bladder emptying and retention, straining to pass urine, or indeed frequency and urgency with small voided volumes and a feeling of incomplete emptying. Other symptoms can include straining to void, feeling of incomplete emptying, UI, recurrent UTIs, chronic retention of urine, known neurological injury, or disease. Examination should assess sacral dermatomes.

23.3.1.6.4 **Investigations**
All patients need a voiding diary, PVR, and pressure or flow cystometry; any further investigations are guided by the history. In idiopathic cases, there will simply be reduced sensation, but otherwise normal filling and voiding with a low PVR.

23.3.1.6.5 **Treatment**
Treatment of reduced bladder sensation consists of bladder retraining (voiding by the clock and double voiding), and if necessary CIC or a trial of α-blockers.

23.3.2 **Primary Voiding Dysfunction**
The vast majority of patients presenting with voiding dysfunction are men with BPE.

23.3.2.1 **Detrusor Underactivity and Detrusor Failure**

23.3.2.1.1 **Definition and Incidence**
Detrusor underactivity is defined as a contraction of reduced strength or duration, resulting in prolonged bladder emptying or a failure to achieve complete bladder emptying within a normal time span [7]. Detrusor failure or atonic bladder is the worst situation in this spectrum, whereby no detrusor activity can be demonstrated.

23.3.2.1.2 **Aetiology**
Detrusor underactivity or failure may be idiopathic or related to age, neurogenic bladder dysfunction, or associated with BOO and chronic retention.

A degree of detrusor underactivity can be reversible, and this is likely related to the length of time with the condition and the degree of overstretching of the bladder that has occurred. Complete detrusor failure is not reversible.

Detrusor underactivity is often associated with reduced bladder sensation and large voided volumes or large PVR.

23.3.2.1.3 **History, Examination, and Investigations**
Presenting symptoms may be infrequent bladder emptying and retention, straining to pass urine, or indeed frequency and urgency with small voided volumes and a feeling of incomplete emptying. Symptoms may not be evident to the patient until significant bother is caused by the symptoms or until retention occurs, seemingly suddenly. A poor urine flow rate may suggest detrusor underactivity, but normal flow does not exclude it. The diagnosis is confirmed during pressure or flow urodynamics because only then that specific information about the detrusor becomes available. The relative contribution of any type of BOO and detrusor underactivity can only be assessed during invasive urodynamics. Equally, the relative contribution to urine flow rate from detrusor pressure and abdominal straining are only distinguished during invasive urodynamics.

23.3.2.1.4 **Treatment**

1) **Conservative treatment or lifestyle modification**
The bladder must be allowed to drain without resistance, using CIC, urethral catheter, or suprapubic catheter. Any underlying pathology or causes of associated LUTS should be treated. The bladder can then be reassessed as to whether reasonable function has returned. This is done by measuring PVR over a period of time. Timed voiding (e.g., every two hours can be successful in idiopathic detrusor underactivity.

2) **Medical and surgical treatment**
There is currently no specific medical or surgical treatment for detrusor underactivity. Establishing bladder drainage by catheterisation of some variety (CIC, long-term catheterisation [LTC], or suprapubic catheterisation [SPC]) is usually the most effective strategy.
23.3.3 Functional Obstruction (Urinary Retention in Women)

Urinary retention in women is uncommon. Unless a positive diagnosis is made, the unfortunate sufferer is likely to be labelled as suffering from a hysterical conversion syndrome.

The anatomy of the female outflow tract is such that some women are able to void by relaxing the sphincter and pelvic floor musculature without a significant rise in detrusor pressure. Difficult or obstructed voiding is highly abnormal. Certain possible mechanisms should be considered:

1) Urethral stenosis may result from trauma during parturition or be associated with vulval atrophy in the elderly. They are rare.
2) Detrusor–sphincter dyssynergia (DSD) may cause urinary retention but clinical signs and symptoms of spinal cord disease will almost always be evident (e.g. signs in the lower limbs and detrusor hyperreflexia).
3) Loss of contractility of the detrusor muscle due to injury of the S3/S4 roots can result in bladder denervation, an atomic bladder, and urinary retention.
4) DSD (see Section 23.3) also causes functional obstruction.
5) The most common cause of retention in young women is dysfunctional voiding and Fowler syndrome.

23.3.3.1 Definition, Incidence, and Aetiology

Neither is fully understood, but rather they are descriptive terms.

*Dysfunctional voiding* is characterised by an intermittent or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated muscle during voiding in neurologically normal individuals. This is probably due to intermittent pelvic floor contractions. Dysfunctional voiding is most commonly found in children but can be present in some patients with pelvic pain syndromes.

*Fowler syndrome* is a rare condition characterised by impaired relaxation of the external sphincter during voiding. It occurs in premenopausal women, most commonly ages 20–40, and is often associated with polycystic ovary syndrome. Some patients have had lifelong voiding difficulties. Fowler syndrome can be associated with detrusor failure and can result in retention. The condition recovers spontaneously in some but continues for life in other patients.

23.3.3.2 History, Examination, and Common or Important Differential Diagnoses

The history and bladder diary are the most important tools pointing towards functional obstruction. Examination must be detailed to rule out any neurological dysfunction.

23.3.3.3 Investigations

Pelvic ultrasound is useful in ruling out any extrinsic compression by fibroids or other pelvic tumours. Pressure or flow cystometry will confirm high detrusor pressures during voiding. Urethral sphincter electromyography reveals abnormal myotonic-like activity (so-called complex repetitive discharges and decelerating bursts) which seem to impair relaxation of the sphincter. In uncertain cases, video urodynamics may help demonstrate the level of obstruction and also visualise any secondary changes (e.g. bladder trabeculation, diverticula, and vesicoureteric reflux).

23.3.3.4 Treatment

1) General treatment or lifestyle modification

   - General fluid advice and avoidance of bladder irritants is advocated but is unlikely to have any direct impact on functional obstruction. Where constipation coexists, increasing fluid intake and changing diet to resolve constipation can significantly improve LUTS. Advice to reduce psychological stress where possible may help. Regular voiding to manage symptoms may help.

2) Medical treatment

   - Often requires at least a period of CIC, which in some cases will be for life.

3) Surgical treatment

   - Sacral neuromodulation may be used in a few selected patients, at specialist centres only.

23.4 Urethral Disorders

These include urethral diverticulum, urethral pain syndrome, and urethral strictures and stenosis (this will be discussed in another chapter).

23.4.1 Urethral Diverticulum

23.4.1.1 Definition and Aetiology

A localised out-pouching of the urethra into the anterior vaginal wall. Distal and mid-third positions are most common, and shape can vary: simple pouching of the urethra, horseshoe shaped, or complete circumferential.

The exact origin of the urethral diverticulum is still unknown. The presence in children suggests a congenital nature. The walls of the diverticulum are lined with epithelium in these cases [62]. However, usually diverticula are thought to be acquired and to originate from an abscess in a paraurethral gland, iatrogenic trauma, or childbirth. Scar tissue is often found around these diverticula [63, 64].

23.4.1.2 Incidence

A urethral diverticulum might not be symptomatic. Delay in diagnosis is common and can be up to 5.2 years
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A prevalence in the general population of 0.6–6% has been reported [67, 68]. This increases up to 40% in women presenting with urinary dysfunction [69]. Women around the age of 40 are more prone to have a urethral diverticulum [64].

23.4.1.3 History and Examination
The classically described triad of symptoms are dysuria, postvoid dribbling, and dyspareunia. However, symptoms are not frequently this obvious. UI is present in 60% of the women. In addition, women suffer from UTIs 30% of the time. Concomitant stones in the diverticulum can be found in 10% of the patients. A less common find is carcinoma associated with the urethral diverticulum [70].

Palpation of the urethra during the physical examination is essential because the diverticulum is palpable in more than half of the patients. Pressure on the palpable mass can result in excretion of urine or pus and hard masses can be suggestive of stones or neoplasms [65].

23.4.1.4 Investigation
1) Bladder diary, mid-stream urine (MSU) catch, and urodynamics (give a biphasic recording),
2) Cystoscopy to exclude other pathology and possibly visualise the diverticulum.
3) Micturating cysto-urethrogram can delineate the diverticulum well (Figure 23.10)
4) Pelvic MRI delivers a sensitivity of 100%. MRI provides detail on the location and position of the diverticulum (Figure 23.11) [71]

23.4.1.5 Treatment
Surgical excision is the treatment of choice for a symptomatic urethral diverticulum. Several techniques have been described, but all follow the same principle of excising the diverticulum and its connection with the urethra followed by a three-layer closure.

A urethral catheter is placed and a flap is raised from the anterior vaginal wall. The entire diverticulum is excised. The urethra and vaginal flap are closed without overlapping sutures. If the diverticulum is located at the distal end of the urethra, marsupialization can be performed. A Martius flap may be used for large defects and to improve vascularization.

Complication rates range from 5 to 46% and include recurrence of diverticulum, urethrovaginal fistula, urethral stricture, UTIs, dyspareunia, and de novo SUI [64, 72]. SUI is postoperatively reported in 12–25% of patients [73, 74]. In women with pre-existing SUI, a concomitant placement of a sling can be considered [62, 75].

23.4.2 Urethral Pain Syndrome
23.4.2.1 Definition and Incidence
Urethral pain syndrome is the occurrence of recurrent episodic urethral pain usually on voiding, with daytime frequency and nocturia in the absence of proven infection or other obvious pathology. It is chronic in its nature (>6 months) with pain being the major complaint. The diagnosis is one of exclusion. It usually affects females.

23.4.2.2 Aetiology
The aetiology of urethral pain syndrome is unknown.

23.4.2.3 History, Examination, and Common or Important Differential Diagnoses
Condition to be excluded are UTI/urethritis, BPS, and urethral diverticulum.

23.4.2.4 Investigations
MSU, urethral swab, and endocervical swab will rule out infective causes. A three-day bladder diary is useful to confirm the starting point in terms of symptoms.

Depending on symptoms, cystoscopy and MRI may be required to rule out inflammation of the bladder and urethral diverticulum.

23.4.2.5 Treatment
Data on urethral pain syndrome is very sparse. Similar to BPS, the most important point is to build realistic expectations at the outset. The patient must understand that there is no cure, but the aim of treatment is to achieve symptomatic control. Joining a self-help or support group is recommended from the outset.

Figure 23.10 Micturating cystourethrogram showing the urethral diverticulum. Source: Photographs courtesy of Dr Neil Collins Southmead Hospital.
We recommend referral to a physiotherapist for evaluation of pelvic floor muscles and treatment of potential trigger points. In addition, assessment and treatment by a pain specialist is helpful.

23.4.3 Invasive Urodynamics in the Assessment of Male BOO

"Lower urinary tract symptoms suggestive of bladder out[flow] obstruction" is a term used when a man complains predominately of voiding symptoms in the absence of infection or obvious pathology other than possible causes of outlet obstruction’ [7].

‘BOO is the generic term for obstruction during voiding and is characterised by increased detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow rate and detrusor pressure’ (ICS 2002) [7].

23.4.3.1 Aetiology

BOO can be anatomical or functional. Anatomical causes include BPE, which is by far the most commonly encountered cause in clinical practice, bladder neck obstruction, urethral stricture, and extrinsic compression. Extrinsic compression can result from POP, tumours, or after surgery for UI. Functional obstruction includes dysfunctional voiding, Fowler syndrome, and DSD.

23.4.3.2 History, Examination, and Common or Important Differential Diagnoses

The hallmarks of BOO are predominantly voiding symptoms. Often, treatment in the male patient is initially directed at presumed BPE (modalities covered in detail in Chapter 10), but there is an increased awareness now amongst both clinicians and patients regarding the prevalence of OAB in men. The possibility of detrusor underactivity or failure also needs to be considered.

23.4.3.3 Investigations: The Role of Invasive Urodynamics

If medical treatment has failed to improve the patient’s LUTS (poor flow in particular), pressure or flow cystometry will help to distinguish outflow obstruction from detrusor failure and aids in preoperative counselling of the patient. The decision to carry out invasive...
urodynamics is still a clinical one and remains in the hands of the treating urologist.

‘Cystometry may be used when invasive treatment is being considered, or for equivocal or more complex cases. Recommendation: Consider offering multichannel cystometry to men with LUTS having specialist assessment if they are considering surgery’ (NICE 2010).

‘Cystometry can help inform decisions about future management, including possible surgery for bladder outlet obstruction or detrusor overactivity, and the management of men with neurological lower urinary tract dysfunction’ (NICE 2010).

‘Multichannel cystometry may also help to characterise bladder compliance, sensation and capacity. Performing an invasive procedure is a balance of the possible benefits vs. the possible risks and these must be explained to the patient during informed consent for the procedure and appropriate advice given should adverse events occur’ (NICE 2010).

Perhaps the most important aspect of the discussion is to recognise the possibility of detrusor underactivity or failure as a cause of the patients voiding symptoms, as opposed to the all too familiar, and outdated, diagnosis of ‘prostatism’. The role of invasive urodynamics is still unclear in terms of its impact on eventual outcomes after surgery; however, as a tool to aid proper counselling of the patient and managing expectations, it can be very useful. It should be considered, especially in men with a history of large residuals and symptoms out of proportion to rectal examination or cystoscopy findings, for BOO.

23.4.4 Bladder Disorders Secondary to Other Disease Processes

Here we discuss neurogenic bladder dysfunction and POP.

23.4.4.1 Neurogenic Bladder Dysfunction, Including DSD

23.4.4.1.1 Definition and Aetiology

Any central or peripheral neurological disorder can affect the lower urinary tract. These can be classified by describing the actions of the detrusor and sphincter separately as either overactive, underactive, or normo-active.

Neurological urology encompasses both static conditions, such as spinal cord injury and stroke, as well as progressive disorders, such as multiple sclerosis and Parkinson disease. It also includes congenital disorders, such as spina bifida.

23.4.4.1.2 History and Examination

Early and regular diagnostic evaluation and treatment are essential to prevent the ultimate endpoint of renal failure due to poor bladder compliance, the pressure rises progressively during filling phase leading to a high pressure system. Some situations are inherently ‘safe’ (e.g. bladder pressure always low throughout the micturition cycle), whilst others are not. These do not necessarily correlate with symptoms. The only symptom may be incontinence, yet almost any possible combination of detrusor and sphincter dysfunction can occur. Furthermore, as neurological conditions evolve, the situation with regard to the LUTS may change. Bladder dysfunction can be the presenting symptom of a neurological disorder.

The history needs to include details of any known neurological disorder, and if so, which part is affected (e.g. brain, spinal cord, systematic), disease progression, and prognosis. History of urinary function, bowel function, sexual function, and neurological function is also vital. Any pain, UTIs, or haematuria need to be considered carefully.

Examination can be divided into general, neurological, and urological. The neurological examination needs to determine detailed neurological function in the urogenital area, anal sphincter, bulbocavernosal reflex (absent in spinal cord injuries in the acute shock phase, and returns once shock phase over), and lower limb neurology. Assessment of overall mobility and hand function will be important to choose appropriate management options. History of any allergies, specifically latex allergy because there is a higher incidence in patients with neuropathy. Symptomatic consideration:

- Suprapontine lesions will cause DO and inappropriate voiding.
- Suprasacral lesions will cause DO, poor compliance, DSD, and autonomic dysreflexia.
- Sacral lesions: Detrusor underactivity or areflexia.

Autonomic dysreflexia is potentially life threatening and seen in patients with spinal lesions above the T6 spinal cord level. It is caused by overstimulation of the autonomic nervous system. Triggers are those that would normally cause a painful stimulus, such as bladder distention, catheterisation, or even cystoscopic, rectal, and vaginal examinations; other triggers include constipation, distal skin infections, or UTIs. It is characterised by sympathetic overactivity of the cord below the lesion leading to vasoconstriction and compensatory vasodilation of the normally innervated sympathetic areas above the spinal cord lesion. This manifests as significantly high blood pressure associated with headaches, profuse sweating, nasal congestion, flushing of the skin above the level of the lesion, with bradycardia. If left untreated, can lead to convulsions, intracranial bleeds, strokes, and death. Treatment is aimed to stop the triggering factor and reduce the blood pressure. Sublingual glyceryl trinitrate (GTN) spray, or captopril, nifedipine, or intravenous labetalol is recommended.
23.4.4.1.3 Investigations
A three-day bladder diary and uroflowmetry with PVR should be performed prior to mandatory video-urodynamic testing. Serum creatinine measurement and renal USS are also essential. During video urodynamics, the following information needs to be recorded and classical signs noted whether present:

- Type of bladder sensation (e.g. increased, decreased, absent, non-specific)
- Low compliance
- High capacity
- DO (‘neurogenic DO’)
- Incompetent sphincter
- Detrusor underactivity or failure
- DSD
- Ureteric reflux (grade)

DSD occurs when voiding from a detrusor contraction is interrupted by reflex closure of the urethral sphincter. Detrusor pressure rises and falls repeatedly with only minimal voiding and a large residual is left at the end of the contraction.

The patient should be re-evaluated routinely, usually after 6–12 months, but also after any change in treatment or any change in symptoms despite continuing the same treatment.

23.4.4.1.4 Treatment
The primary aim in treating neuro-urological patients is protection of the upper urinary tract from a high pressure poor compliant bladder. Considerations of continence and QoL are secondary aims.

- High-pressure bladder with intact sphincters: methods to lower bladder pressure, that is catheterisation techniques (e.g. intermittent self-catheterisation [ICS], LTC, and suprapubic catheterisation) in addition to either medical therapy or botulinum toxin injection or bladder augmentation
- High-pressure bladder and sphincter not intact: same as with sphincter support (urethral bulking agents, or tapes, AUS, or bladder neck closure and Mitrofanoff)
- Low-pressure bladder and sphincter intact: catheterisation techniques
- Low-pressure bladder and sphincter not intact: sphincter support

Conservative treatment or lifestyle modification
Containment devices such as pads and conves, indwelling catheters (urethral or suprapubic), or ISC are used in the majority of neuro-urological patients, either alone or alongside other treatments. ISC is usually the preferred choice out of these, if possible. Reflex voiding or Valsalva voiding are not recommended due to high-bladder pressures.

Pelvic floor exercises and bladder training may be possible in some patients with ‘safe’ (i.e. low-pressure bladders, who have sufficient neurological control).

Intermittent Self-Catheterization ISC has transformed the management of neurogenic bladder disorders. The frequency of catheterisation is often best determined by the patients themselves, but in general the volumes drained on each occasion should be less than 500 ml. A nurse specialist or continence advisor is normally responsible for providing information and teaching the technique. Learning is more difficult for females and a mirror is useful at first. The majority master the method with adequate advice and training even if they greet the prospect with expressions of revulsion.

Benefit from ISC depends on the volume of urine that can be held within the bladder before incontinence occurs. A weak urethral sphincter or severe detrusor hyperreflexia will reduce the functional capacity of the bladder. Urinary infection is a surprisingly infrequent complication of this procedure. By draining the residual urine from the bladder, the incidence of symptomatic urinary infection may actually be reduced, although asymptomatic bacteriuria may be a more frequent finding. Manual dexterity is an important factor and may determine a patient’s ability to carry out clean ISC. Many patients find it helpful to talk to another patient who has already mastered the technique.

Clean Intermittent Catheterisation For some patients, poor hand function and the want of a suitable carer, may make an indwelling CIC impossible. It may be unsuitable for patients whose main bladder disorder is hyperreflexia but for these patients an add-on ‘clam’ cystoplasty using opened-out bowel, may lower the pressure inside the bladder despite the detrusor contractions and make CIC feasible. This is especially valuable in children with the neuropathic bladders that occur with spina bifida.

There remain some patients for whom a CIC is the only means of ensuring adequate urinary drainage and personal hygiene.

The main complications of LTC are leakage alongside the catheter, intermittent blockage and chronic urinary infection. Stone formation may occur in association with the presence of the catheter and infection. Treatment of infection with antibiotics and antiseptic washouts is unlikely to be complete and may lead to colonisation of the urinary tract with resistant organisms. Bypassing around the catheter is common, usually as a result of uninhibited detrusor contractions. Logically, one may attempt to manage this with anticholinergic medication. The use of increasingly bigger balloons only worsens the detrusor instability, and large catheters result eventually in a grossly patulous urethra.
Suprapubic Catheterization  An indwelling suprapubic catheter offers effective urinary diversion which is less liable to expulsion or bypassing and improves the QoL as compared to CIC.

Risks of the procedure includes infection and sepsis, bleeding if on antiplatelet, bladder discomfort and pain, persistent urethral leakage of urine, catheter blockages and encrustation or stone formation, and rarely bowel injury, especially if the patient has had previous abdominal surgery, is obese, or the bladder is not palpable due to underfilling (Figure 23.12).

The procedure is done under guidance, either a flexible cystoscopy under local anaesthetic (as majority of these patients will be comorbid with high risk from general anaesthetic), rigid cystoscopy under a general anaesthetic, or especially in an emergency setting, under USS guidance. However, if the bladder is easily palpable, blind insertion can be done, bearing in mind bowel injury can still occur (Figure 23.12).

Medical treatment  Neurogenic DO should be treated as for OAB/DO (Section 23.7.1.1). Combining antimuscarinic agents can be considered. Alpha-blockers can be given to reduce outlet resistance.

The use of antibiotics to prevent recurrent UTIs should be kept to a minimum. Asymptomatic bacteriuria does not need treatment and long-term antibiotics should be avoided. Recurrent UTIs should trigger a search for bladder stones or foreign bodies.

Surgical treatment  All patients will need video urodynamics prior to surgery to determine bladder as well as sphincter actions; however, the bladder is the focus of treatment.

a) Botulinum toxin injections for neurogenic DO if failed medical treatment. The patient must be able to perform ISC, or have a caregiver who is willing and able to perform CIC for the patient. Refractory neurogenic DO can be treated by bladder augmentation.

b) Bladder neck incision can be used to treat a fibrotic bladder neck.

c) Neurogenic stress incontinence due to intrinsic sphincter deficiency can be treated with an autologous urethral sling or an AUS.

d) When symptoms have failed to respond medical therapy and have become intolerable, or there is any suggestion of high-pressure damage to the kidneys despite pressure-reducing measures, a cystoplasty should be considered whereby a detubularised patch of bowel is let into the wall of the bladder to reduce the pressure.

23.4.4.1.5  Follow-up

Any significant clinical change should prompt reinvestigation of the patient with neuro-urological symptoms.

Patients at high risk need routine follow-up every six months, including physical examination, serum creatinine, renal USS, and yearly urodynamics. Intervals can be extended for lower-risk patients.

23.4.4.2  Pelvic Organ Prolapse

23.4.4.2.1  Definitions and Aetiology

Anterior wall prolapse (50%) results from herniation of the bladder (cystocele) or urethra (urethrocele) through the vaginal wall.

Posterior wall prolapse (30%) results from herniation of the rectum (rectocele) or bowel or omentum (enterocele) through the vaginal wall.

Middle compartment prolapse (20%) occurs when the the uterus or the vaginal vault descends.

Nearly half of all prolapses are caused by normal vaginal deliveries. Other causes include old age (due to lack of oestrogen), obesity, constipation, smoking, and chronic obstructive pulmonary disorder (regular coughing

Figure 23.12  Suprapubic catheter inserted into bowel, note the distance from the urinary bladder. Source: Photographs courtesy of Dr Neil Collins Southmead Hospital.
causes chronic strain), previous pelvis or vaginal surgery, or radiotherapy.

POP is commonly associated with UI and LUT symptoms, although there is no established causative relationship either way.

23.4.4.2.2 History and Examination
The history should be aimed to look for causative factors as well as LUTS and bowel and sexual dysfunction.

The examination is best performed in three positions: lithotomy, left lateral position, and standing. Pressure test to demonstrate prolapse (e.g. coughing, straining, or bearing down) and UI. POP can be classified either by the classical Baden-Walker system or the more detailed POP-Q system.

23.4.4.2.3 Baden-Walker
By degree of descent of prolapsing structure in relation to the hymen.

- Grade 0 – no prolapse
- Grade 1 – halfway to hymen
- Grade 2 – up to hymen
- Grade 3 – halfway past hymen
- Grade 4 – maximum descent or complete prolapse (procidentia)

23.4.4.2.4 POP-Q
The POP-quantification (POP-Q) system is a detailed anatomical representation of a prolapse.

Investigations
Bladder diary, urine dipstick, PVR, and urodynamics if surgery is contemplated.

Treatment
1) Conservative management or life-style modifications
   To reverse any predisposing factors, such as obesity, smoking, vaginal atrophy, and constipation. Supervised PFMT. Vaginal pessaries.

2) Surgery
   Anterior and posterior walls: Repairing the prolapse encompasses suturing the defect in the vaginal wall with interrupted suture with or without the use of a mesh.

   There is ongoing debate as to the utility of prophylactic anti-incontinence surgery in women with POP irrespective of continence status. There is also significant discussion about the role of artificial mesh in POP repair. These discussions are outside the scope of this chapter and would be a topic of subspecialist interest.

   From the point of view of a general urologist or trainee: an adequate evaluation of the patient including a through history of incontinence and prolapse symptoms, along with appropriate examination and clear documentation along the lines stated previously, would be more than adequate.

   Middle-compartment prolapse repair entails either a hysterectomy, a sacrohysteropexy, or sacrocolpopexy if the uterus was previous removed.

References


24  

Fistulae and Sinuses  

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Abstract  

A fistula is a communication between two epithelialized surfaces – usually between one hollow viscus and another or between a viscus and the skin. A sinus is an abnormal blind-ending track which communicates with the skin. In this chapter we describe urological fistulas and sinuses.  

Keywords ureterovaginal; ureteroenteric; colo-vesical; vesicovaginal; vesicouterine; fistula; sinus  

Key Points  

This chapter covers the following topics with regards to fistulae and sinuses:  

- Ureterovaginal  
- Ureteroenteric  
- Colovesical  
- Vesicovaginal  
- Vesicouterine  

24.1 Principles and Definitions  

A fistula is defined as an abnormal communication between two epithelial surfaces – usually between one hollow viscus and another or between a viscus and the skin. A sinus is an abnormal blind-ending track which communicates with the skin. Fistulae can be found anywhere throughout the body and are named after the organs they communicate between (e.g. a vesicovaginal fistula is one which tracts between the bladder and vagina). Further definitions can be given once the aetiology of the fistula is understood and considering the physiological output or function of the existing fistula. Different locations of fistulae are associated with different aetiologies, and these factors of their development will provide predictive information regarding the likelihood of spontaneous closure or the requirement for operative repair and overall prognosis.  

Within urology, the most common fistulas encountered are between the genitourinary organs (i.e. ureter, bladder, urethra) and either the gastrointestinal organs (i.e. small or large bowel), the lower reproductive tract most commonly in females (i.e. uterus, cervix, vagina), or the skin. Fistula and sinus formation can be considered a consequence of one or a combination the following processes: trauma (including surgery), infection, inflammation, malignancy, radiation damage, or congenital abnormalities.  

24.2 Pathophysiology  

Overall the incidence of fistula disease within the urological tract is low and the cellular-level changes that occur to cause and promote fistula remain poorly investigated and understood. However examining relevant granulomatous disease processes such as Crohn disease where there is a high incidence of fistulae (including to the urological organs), the working hypothesis is that the intestinal epithelial cells undergo epithelial to...
mesenchymal transformation (EMT). EMT is driven by inflammation, which then drives the production of matrix metalloproteinases which then cause further local tissue damage, and this, along with impairment of normal repair process such as fibroblast migration, leads to fistula formation [1].

Figure 24.1 illustrates organ-specific factors within the urological organs which predispose to non-healing of developed fistula (Figure 24.1):

1) There is obstruction to the viscus (e.g. to the ureter or urethra) downstream to the opening of the fistula.
2) The fistula or sinus has been present for so long that the track is lined by epithelium.
3) The fistula or sinus contains or leads down to a foreign body (e.g. a nonabsorbable suture or a calculus).
4) The underlying cause is a chronic granuloma (e.g. tuberculosis, xanthogranuloma, actinomycosis, Behçet syndrome, Wegener granuloma, or in the perineum, Crohn disease).
5) The tissues have been rendered ischaemic by previous radiotherapy.
6) The fistula or sinus leads down to a cancer.

24.3 General Complications

A fistula leading from the urinary tract to the skin will leak urine. This may be intermittent or continuous according to the site of the internal opening of the fistula. The urine is often cloudy from infection and resembles lymph or serous fluid, but the diagnosis can easily be made by measuring its content of urea or creatinine because only urine can have a concentration of these substances greater than that of plasma. If the communication is between the bowel and the urinary tract, the main danger is from infection by faecal organisms, which can be lethal.

If there is a large surface area of granulation tissue in contact with the urine as it escapes from a fistula or if the urine enters the bowel, then urine will be absorbed, and lead to hyperchloraemic acidosis. Also calcification can occur around chronic fistulae, and stones often form in them.

24.4 Organ-Specific Fistulae

24.4.1 Kidney

Of all fistulae in the urological tract, renal fistula represents the rarest variety, and if found, they are usually secondary to traumatic injury or surgical misadventure, although rates of these fistulae have risen in the advent of minimally invasive surgical techniques [2]. A very rare group of fistulae can occur between the renal pelvis and the gastrointestinal tract. The underlying cause is usually infection caused by a calculus, leading to a perinephric abscess, often complicated by xanthogranuloma. Transitional cell carcinoma may also give rise to such a fistula. The presentation is that of a painful mass in the loin, accompanied by fever. X-rays may show gas in the renal pelvis. Radical surgical excision of the involved kidney and bowel can provide a permanent cure.

24.4.2 Ureter

As with renal fistula, ureteric fistula is an uncommon condition. In developed countries, the most common cause of ureteric fistulae is because of missed ureteric injuries and delayed presentation following major abdominal and pelvic surgeries. Fistulae are more commonly found in the lower half of the ureter, although this often depends on the extent of the caudal dissection and identification of the ureter during dissection of the
In disease states that interfere or obliterate the normal fascial planes (e.g., invading tumours, inflammatory processes), identification of the ureter and safe preservation can be difficult, so there must be a high index of suspicion of ureteric damage at the time of surgery to prevent fistulous complications postoperatively.

24.4.2.1 Ureteral-Arterial Fistulae

In a brief reminder of ureteric anatomy: the ureters cross the common iliac or proximal portion of the external iliac artery at the level of the pelvic brim. The development of these fistulae tends to be considered a rare iatrogenic complication of usually a combination of features including, pelvic radiotherapy, pelvic surgery, ureteric stenting, or ureterolysis or the presence of prosthetic arterial grafts. The combination or some of these features leads to fistulation by increasing the adherence of the ureter to the underlying iliac vessels and damaging the integrity of those vessels [3]. There are case reports of uretero-aortal fistulae, but these are much rarer than iliac fistule. All patients present with haematuria, although this is reported to be significant haemorrhage with haemodynamic instability (defined as ongoing bleeding with a systolic blood pressure of <90) in the majority of cases [3].

Computed tomography (CT) angiography and cystoscopy are the main methods of investigation, although cystoscopy is not appropriate in the presence of life-threatening haemorrhage (i.e., pulsatile bleeding coming from a ureteric orifice or fresh thrombus around a ureteric stent have been reported cystoscopic findings) [4].

Before the introduction of endovascular intervention in the 2000s, these cases required open surgical repair with either direct surgical arterial repair or arterial bypass grafting. In the last decade, the use of endovascular stents has become the mainstay of management in these patients [3–6]. Without prompt treatment, these fistulae are universally fatal, and even with treatment, these patients face significant morbidity and mortality, although this has improved with the switch to endovascular management.

24.4.2.2 Ureterovaginal Fistulae

Fistulae between the ureter and the vagina are an uncommon but well-recognised complication of hysterectomy and other pelvic operations including Cesarean section. Fistulae have also been described between the ureter and the fallopian tube or uterus. Cases of fistulation have been reported not only from open or laparoscopic gynaecological procedures, but there are also several case reports of ureterovaginal fistulae formation post-transvaginal ultrasound-guided extraction of oocytes for fertility treatments [7, 8]. The highest rates of ureteric injuries are found in surgeries for uterine cancers (10%), with similar but lower rates for cervical and ovarian cancers (1–4%), and around 1% for benign surgeries, although this is slightly higher in women undergoing procedures from endometriosis (1.7%) [9].

Whatever the cause of the fistula, the ureter is usually at least partially if not completely obstructed, and the presenting clinical picture is often that of upper tract obstruction (e.g., loin pain, systemic sepsis, acute kidney injury), although sometimes it is more an indolent presentation of recurrent urinary tract infections (UTIs). There can be some immediate leakage of urine from the vagina, although this may or may not be a significant finding on clinical assessment, and if present, is often described as intermittent or positional [10].

CT urography is a useful assessment if a fistula is suspected, although this only illustrates a fistula in around 60% of cases [11]. This may illustrate active leakage of urine into the vagina (or uterus or fallopian tubes); however, it may just show proxy markers of ureteric obstruction; hydronephrosis, stranding around the ureter, urinoma, lack of contrast passage, or hypoperfusion of the kidney. Alternatively, cystoscopy and retrograde pyelography may be of more use to assess the exact level of injury and extent of leakage.

Initial management depends on the clinical condition of the patient and the time since the primary surgical intervention. Prompt diagnosis followed by repair using a Boari flap, psoas hitch, or primary uretero-neocystostomy gives the best results in the acute setting.

In patients who are profoundly unwell because of urinary sepsis, initial diversion of urine with a nephrostomy may be appropriate, followed by nephrostogram and definitive intervention once any sepsis has resolved. Alternatively, a ureteric stent can be placed for a period as a conservative management strategy. Surgical excision and repair has a success rate of 70–100%, whilst with conservative measures the success rate is around 70% [11–13]. The choice of management strategy must consider previous therapies the patient has undergone; those who have had radiotherapy are likely to have ureteric strictures and the success of conservative measures is usually low due to poor healing, although primary may be more challenging in the postradiotherapy setting. If the lesion has been neglected and the diagnosis is made only after several months, the kidney may be hopelessly damaged by obstruction and necessitate nephrectomy.

24.4.2.3 Ureteroenteric Fistulae

Due to the retroperitoneal position of the ureters, fistulae between ureters and bowel are rare. However, they may occur between the ureter and colon or small intestine and occasionally between the ureter and appendix, from which urine enters both the colon and ileum. The most common cause for ureteroenteric fistulae is iatrogenic injuries during abdominal surgery or because of
penetrating abdominal trauma [14–17]. Inflammatory bowel conditions such as Crohn disease or diverticulitis can also envelope the ureters in the inflammatory process, although fistulation to the bladder is far more common.

In patients with renal transplants ureteroenteric fistulae can develop as a consequence of chronic rejection many years after transplantation, although there is an earlier peak in incidence in this population within a week of transplantation (due to avascular necrosis of the ureter) [18–21]. There have also been reports of ureteroenteric fistulae developing post-extracorporeal shock-wave lithotripsy (ESWL) [22]. Historically, the most common cause for ureteroenteric fistulae were as a complication of tuberculosis [23].

The presenting complaint in these patients can be an indolent history of gastrointestinal disease, previous surgeries, or recurrent UTIs. The main clinical problem arises from absorption of urine leading to hyperchloraemic acidosis. This occurs as the when the bowel epithelium is exposed to urine it reabsorbs the ammonia, hydrogen, and chloride content which does not usually occur with urothelium. To do this it cotransports out sodium and bicarbonate in exchange for hydrogen and chloride, respectively. Symptoms of hyperchloraemic acidosis include high respiration rate, fatigue, nausea and vomiting, confusion, headache, atrial fibrillation, pulmonary oedema, and osteopenia. It is also common for patient to develop renal stones due to the patient becoming hypercalciuric and to see a reduction in urinary citrate levels.

CT imaging of the abdomen and pelvis with contrast and separate delayed urogram phase can be helpful to identify the underlying pathological process and assess for ureteric obstruction, gas may be visible within the renal pelvis; however, often cystoscopy, retrograde pyelography, and ureteroscopy may be required to confirm the presence of a fistula.

Initially it is helpful to insert a nephrostomy, especially if there is hydrenephrosis, to allow urinary diversion. This will improve any metabolic disturbance and allow further antegrade imaging to assess for drainage and fistulation and potentially dilate any concomitant ureteric strictures. A ureteric stent can be placed ante- or retrogradely. Often, the ultimate management depends on the underlying pathology. In the case of neoplasms, these will generally require surgical excision. For Crohn disease, a trial of antibiotics and immunosuppressants along with ureteric stenting or nephrostomy has been advocated as a conservative approach to these patients [22]. It may be appropriate to trial endoscopic therapies in the first instance; however, surgically, the best management is excision of the diseased segment of bowel and performing a uretero-ureterostomy or ureretero-neocystostomy [22]. In some instances, it may be required to consider urinary diversion.

24.4.2.4 Ureterocutaneous Fistula
These are very rare fistulae, and there are only a few anecdotal reports within the literature. Most seem to be a consequence of chronic renal tract sepsis, chronic granulomatous diseases, or trauma or iatrogenic injuries [24–26]. If a ureterocutaneous fistula is suspected, the easiest diagnostic test is to check fluid electrolytes to confirm the fluid is indeed urine. Formal CT imaging of the urinary tract is then required to further assess the disease. Nephrostomy drainage allows diversion of urine away from the site of fistula. Depending on the nature of the fistula, further endourological or open surgical approaches may be required to manage any underlying disease process such as obstructing stones.

24.4.3 Bladder
Fistulae to the bladder are the most common types of fistula encountered within urology and their presence, particularly those between bladder and vagina, can be found to go back millennia. The most common sites for fistulation are the colon and the vagina. In the developing world and historically, the most common cause of vesical fistulas is prolonged, obstructed labour. In the developed world, this has become less common with current advances in obstetric care and the access to Caesarean sections, although as detailed throughout this chapter, this is also a risk factor for injury to the urological organs and fistula formation. Otherwise, and as with other fistulae, the most common causes are abdominal and pelvic surgeries, radiotherapy, inflammatory conditions, and malignancies.

24.4.3.1 Colovesical Fistula
Colovesical fistulae are most commonly found as a consequence of complicated diverticular disease and seen between the sigmoid colon and bladder; however, they can arise because of a number of common conditions including inflammatory bowel disease (typically, Crohn disease) and colorectal tumours (predominantly sigmoid and rectal tumours). Rarer causes of these fistula include both open and laparoscopic inguinal hernia repair, foreign bodies within the colon (with several reports of fistulae caused by chicken bones), or as a result or appendicitis. There are even reports of fistulae formation after transurethral resection of bladder tumour (TURBT) and Mitomycin C instillation [27–36]. Colovesical fistulae are more commonly seen in men, with the uterus acting as an additional barrier to fistulation in females (although colouterine fistulae can develop).
Often the presentation can be more indolent than with another urological fistula. Patients will often report recurrent UTIs, although some patients will present with recurrent urinary sepsis or pyelonephritis. They may report altered bowel habit and perirectal bleeding if they have active diverticulitis. Classically patients with a colovesical fistula will report pneumaturia, which air bubbles in the urine that bubble throughout the stream. Pneumaturia, however, is often only elicited by direct questioning and infrequently volunteered by patients, although on direct questioning is present in more than 90% of patients [28]. Examination may reveal a tender mass in the lower abdomen, although it is often unremarkable, particularly in patients with a chronic fistula. Urine cultures will contain profuse faecal contamination and can also contain particulate food or faecal matter. Often patients will experience frank haematuria because of severe cystitis.

Definite visualisation of a fistula is notoriously difficult in practice and often patients undergo both radiological and endoscopic evaluation of the bladder and colon. Cystoscopically it is often very difficult to see the fistula, which is usually on the posterior wall or towards the left side of the dome of the bladder because it is often concealed by oedema. Biopsies will confirm the presence of inflammatory infiltrate only but do exclude a bladder malignancy. Pressure over the suprapubic region may cause pus to issue like toothpaste from the fistula, and occasionally faeces and gas are seen to emerge. Occasionally the irrigation fluid will leak perirectally during cystoscopy, although this indicates a significant deficit and can make good views of the bladder difficult.

A formal cystogram may show the communication, but the pressure in the sigmoid is usually much greater than that in the bladder so that the fistula is usually better seen with a contrast enema, typically a CT with intravenous and rectal contrast. This has the benefit of examining the extraluminal features of the organs as well the fistulous tract, although sometimes the only evidence of communication is the presence of air within the bladder; this is relevant in patients who have not had recent bladder instrumentation or catheterisation. It can be difficult to distinguish between complicated diverticular masses and recto-sigmoid tumours on CT and so many patients will additionally require colonoscopy and biopsy to confirm the underlying pathology.

The treatment then depends on the severity of the inflammation in the pelvis. The classical method was to perform a diverting colostomy, wait three to six weeks, and then carry out a colonic resection. The purpose of defunctioning was purely to aid in the resolution of pelvic sepsis and not aid in the closure of a fistula; the tract must be excised and the primarily affected segment of bowel resected. Today, with antibiotics and a more-effective and precise preoperative diagnosis, the affected bowel can usually be resected and anastomosis performed in a single stage without the need for any colostomy. Once the affected bowel has been removed, omentum is brought down and interposed between bladder and bowel, and the hole in the bladder is closed in two layers with absorbable sutures and a catheter left indwelling for five or six days. This is possible for more than 90% of patients requiring surgical resection in modern practice [28]. Thought should be given to the ureters in preoperative planning, and it may be useful to cannulate or stent the ureters to delineate anatomy and prevent further iatrogenic injury intraoperatively.

As discussed in the previous section, the only category of fistulae that may improve without surgical input are those as a consequence of Crohn disease. The nature of Crohn disease means that the fistulae can be either small or large bowel in origin, and often the long-term treatment aim is to preserve as much bowel as possible, particularly if the fistula is vesico-ileal. Once again, longer-term antibiotics and immunosuppression may produce resolution without the need for surgery but requires the specialist input of a gastroenterologist.

### 24.4.3.2 Vesicovaginal Fistula

Vesicovaginal fistulae (VVF) are often a socially debilitating consequence of a prolonged obstructed labour in low-resource countries. In countries where emergency obstetric provision is greater, they tend to be due to iatrogenic injuries from gynaecological or pelvic surgeries and radiotherapy. Whilst in Western nations the incidence of VVFs is low at 0.3–2%, it is estimated that in some sub-Saharan countries the incidence of VVFs is between 1.6–3 per 1000 women [37, 38], and many of these are untreated. Obstructed labour leads to fistulation due to the pressure of the foetus within the true boy pelvis causing pressure necrosis of the bladder and vagina.

Of the iatrogenic injuries that cause VVF, transabdominal hysterectomy (simple and radical) and transvaginal hysterectomy are the most common, although laparoscopic hysterectomy, colporrhaphy, Caesarean sections, urethral surgery, bladder traumas, periurethral bulking, and anti-incontinence surgeries are amongst the procedures. Radiotherapy is another frequent cause of VVFs [39]. The mechanism of fistula formation is generally one of tissue ischaemia and necrosis following external pressure (e.g. clamping, clipping), inflammation, and tissue fibrosis or direct puncture or laceration of the urinary tract [10]. Pelvic radiotherapy has a 5% risk of VVF formation even years after radiotherapy. Postradiotherapy fistulas are attributable to persistent
small-vessel arteritis obliterans which reduces blood flow and leads to tissue necrosis [40]. Most VVFs are found at the vaginal cuff post-hysterectomy.

The main symptom of a vesicovaginal is a painless constant leakage of urine from the vagina, although additionally women may experience recurrent UTIs and local vulval irritation. Examination with a Cusco speculum may reveal pooling of urine, the fistula itself often appears as a raised red granulomatous area with no visible opening. Usually clinical examination and examination under anaesthesia is often satisfactory to diagnose a VVF, but if in doubt, the patient can be injected with methylene blue which is renally excreted and turns urine blue – any blue PV loss confirms the diagnosis. The main differential diagnosis is a uretero-vaginal or uterine fistula. Upper tract imaging with a CT urogram should be performed regardless because up to a quarter of patients will have hydronephrosis, and there is a risk of concomitant ureterovaginal fistulae [10].

Ultimately the best treatment of VVF is prevention – the provision of adequate emergency obstetric care and good surgical techniques and practices. There are some patients who have small, nonmalignant fistulas in whom conservative management may be appropriate; urethral catheterisation to prevent vaginal leakage, anticholinergic drugs to prevent bladder spams to ensure urine is diverted from the fistula track, and topical oestrogens for postmenopausal women to promote healing. Additionally, it is possible to diathermy and ablate a small fistula via a cystoscope [10].

With regards to surgical management, there are variations in terms of the approaches undertaken. For an uncomplicated VVF post-surgery then often early closure is as effective as delayed repair. However, for radiotherapy or obstetric fistulae then it has been typically advocated to delay repair to allow for total tissue loss and regeneration to occur, with the aim to repair fistulae in a single procedure. More contemporary data however now supports early repair of obstetric fistulae. The general definition of ‘early’ repair seems to be accepted as within six weeks of injury [19].

There are a variety of techniques to repair VVF, and often, these are dependent on individual surgeon’s experience. Transvaginal approach is suitable for distal fistulae. The dissection needs to be wide enough to allow for a tension-free closure, which is performed in three layers with absorbable suture material and must not overlap (i.e. bladder mucosa, perivesical fascia, and undermined vagina or flap). In post-radiotherapy fistulae or if the tissue quality is poor, a Martius flap may be required (i.e. a vascularised adipose tissue flap with bulbospongious muscle from the labium majus). A transabdominal approach may be required if there is ureteric involvement, and the requirement for ureteroneocystostomy or a proximal fistula in a deep or narrow vagina. There are several techniques but all involve dissecting off the bladder and excising the fistulous tract. The bladder usually opened to obtain adequate access (either cystotomy to bivalved) to tissue layers and to allow a layered tissue repair (double-layered closure) and also omentum is interposed to prevent recurrence [41].

Both laparoscopic and robotic techniques have been presented which are modified versions of the open approach. These techniques are for benign VVF, for post-radiotherapy, or malignant fistulae an open approach is advocated [41–47]. For large VVF, it may be necessary to consider ileocystoplasty or urinary diversion to prevent vaginal losses. Often a suprapubic and urethral catheter are placed at the end of VVF repair and the suprapubic catheter left in situ for several weeks whilst the urethral catheter is removed 5–7 days postoperatively. Patients should be discharged with laxatives and anticholinergics for bladder spasms if required.

Success rates for primary repair are around 90% [39]. Commonly women will experience urinary frequency and urgency postoperatively and some have issues with stress or urge urinary incontinence, although this is often not clinically significant and improves with time from surgery. There is an impact on sexual function and women will often report vaginal dryness or dyspareunia [48].

### 24.4.3.3 Vesicouterine Fistula (Youssef’s Syndrome)

This rare fistula is characterised by cyclical haematuria and amenorrhea with no leak of urine PV [49]. These fistulas typically develop in women who have history of Caesarean section or assisted vaginal deliveries. However, they can develop after any gynaecological procedure during which the uterus is instrumented. The woman will only develop urinary incontinence if the cervical os sphincter is incompetent or if the opening is below the level of the cervical os [50]. Magnetic resonance imaging (MRI) is helpful at identifying the fistula tract and will allow reveal urine within the endometrial cavity.

Treatment options include a conservative approach with urethral catheterisation to prevent urine entering the uterus and medical induction of amenorrhoea to prevent mensuria which has been shown to produce spontaneous closure [51]. The surgical principles for repair are identical to that of VVF repair: a tension-free layered closure and are generally done via an open approach, although laparoscopic and robotic cases have been published [51].

### 24.4.3.4 Vesicocutaneous Fistula

These uncommon complex fistulae are usually iatrogenic from pelvic surgeries or arthroplasties, although can
occur secondary to pelvic fractures, or in the presence of large bladder calculi. Very rarely they can follow pelvic radiotherapy [52]. They can also be seen in the paediatric and adult population of those who have undergone congenital bladder extrophy repairs. They are perhaps most commonly encountered in patients with previous long-term suprapubic cystotomies that have failed to close.

24.4.4 Urethra

As with the rest of the urological tract, fistulae can develop between the urethra and adjacent organs, and more commonly in men, the skin of the perineum and penis. As with previous sections one of the most common causes of urethral fistulae are iatrogenic complications from primary instrumentation or surgery on the urethra, although they can also develop after radiotherapy for prostate or rectal cancers, as a complication of pelvic trauma, or present in the paediatric populations as a primary congenital defect.

24.4.4.1 Rectourethral Fistula

These are a complex and uncommon fistula that are usually iatrogenic, although there are reported cases of congenital fistulae. They can develop as a consequence of prolonged pelvic sepsis in patients with diverticular disease or inflammatory bowel disease or from deep pelvic surgery. They are most commonly seen as a complication of radical prostatectomy for prostate cancer (PCa), whereby an inadvertent rectal injury has occurred during the dissection of the plane between Denovilliers fascia and the rectum, leading to a rectourethral fistula [53]. They have also been reported to develop post transurethral resection of prostate where the anatomy has been difficult to distinguish. Of note they can also develop as a complication of the newer ablative prostate cancer treatments such as brachytherapy, cryoablation, and high-intensity focused ultrasound [54–58].

Patients typically present with the passage of faecal material per urethra, and this can result in subsequent recurrent UTIs. Investigations include both sigmoidoscopy and ureteroscopy, as well as formal imaging with CT scanning with rectal contrast. A urethrogram may illustrate contrast flow into the rectum (although this may be of better value in delineating concomitant urethral strictures), although often the pressure in the rectum is higher and so contrast often flows better from the rectum to urethra.

Traditionally the main approach to managing these cases was first to perform a defunctioning colostomy. This aids in resolution of pelvis sepsis and alleviates symptoms. It is generally insufficient as treatment alone, except in small fistulae formal, surgical repair is required and should be supplemented with a low-residue diet and antibiotics. There is a choice of methods for closing fistulae between urethra and rectum with more than 40 different methods described and a variety of surgical approaches including trans-anal, transperineal, laparoscopic, and robot-assisted [59].

24.4.4.2 Urethrovaginal Fistula

These fistulas have increased in incidence, although remain uncommon, in the era of midurethral incontinence procedures such as transvaginal and transobturator tapes, although remain rare. Women present with new or worsening urinary incontinence and may have a history of previous incontinence-surgery. Clinical examination may be unremarkable, although a red granulomatous area may be seen on the anterior vaginal wall on speculum examination. Patients require cystoscopy and examination under anaesthetic, and this is usually sufficient to confirm diagnosis.

Surgical repair is preferred and generally involves a transvaginal approach and follows the same principles and approach of vesicovaginal fistula repair: a multilayer repair with the placement of a Martius flap. If previous tapes have been placed, these should be removed and thought should be given to whether further incontinence surgery is also required; some have also performed a synchronous pubo-fascial sling procedure [60, 61].

24.4.4.3 Urethrocutaneous Fistula

These fistulae are very uncommon, although are most commonly encountered in the cohort of patients with congenital urogenital defects particularly after hypospadias repairs, in patients with bladder extrophy, and in those undergoing penile constructive or reconstructive surgery, including gender reassignment and urethroplasty. It has been reported as a rare consequence of tuberculosis [62].

Cystoscopy alone is often diagnostic. Surgical repair can vary in complexity to primary repair with multilayer closure to the use of tunneled tunica vaginalis flaps which have been shown to be effective and with few complications [63, 64]. Regardless of the technique a period of urinary diversion is required for several weeks postoperatively, and this is usually achieved by the placement of a suprapubic catheter at the time of surgery.

24.4.5 Sinuses

Idiopathic sinuses developing within the urinary tract are rare, and most cases are iatrogenic. Persistent sinuses after operations on the urinary tract are nearly always due to the use of nonabsorbable suture material or placement metal clips. One particularly difficult type is seen when the renal vessels have been ligated with nonabsorbable material at nephrectomy in the presence of infection (e.g. in calculi or pyonephrosis). The sinus
typically tracks up and down the psoas muscle and may even point in the groin to resemble a femoral hernia. Attempts to deal with the sinus by drainage and antibiotics are always followed by relapse; the only way to cure the condition is to reopen the old incision, reflect the bowel, and remove the offending material.

Persistent sinuses after operations on the kidney may also be caused by tuberculosis or actinomycosis, and the diagnosis only made by sending pus from the sinus for culture.

### References

References


24 Fistulae and Sinuses


Part IV
25

Prostate Structure and Function

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Abstract

The prostate gland is a largely androgen-sensitive exocrine gland of the male mammalian reproductive system. A sound understanding of its structure and function will equip the urologist with the foundation on which to build experience in open, endoscopic, laparoscopic, and robotic-assisted laparoscopic prostate surgery, all of which are relevant in the emergency and elective setting alike. The following chapter focuses on the embryology, anatomy, physiology, and histology of the normal human prostate.

Keywords prostate; prostate development; prostate anatomy; prostate physiology; prostate capsule

Key Points

- The prostate is a male exocrine gland under the control of testosterone for both embryological development and maintenance of homeostasis.
- It consists of fused zones that are anatomically distinct, have characteristic histological features, and importantly, have typical predisposition to benign or malignant change.
- The periurethral transitional zone is the main site of benign enlargement, and the peripheral zone is the main site for malignant change.
- Its primary function is to produce prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), which liquefy the semen, facilitating sperm passage in the female reproductive tract.

25.1 Comparative Anatomy

Our closest mammalian kin are the primates. Here we find variations on a common underlying theme (Figure 25.1). There are two distinct ‘prostates’ – cranial and caudal – shaped like croissants rather than doughnuts. There is a gap between them for the vasa deferentia and common ejaculatory ducts to enter the urethra on either side of the verumontanum which also contains the vestige of the fused müllerian ducts, the utriculus masculinus.

Just downstream of the cranial prostate is the external sphincter; it is made of two muscular components – unstriated and striated – which are both cephalad and distinct from the levator ani sheet of the pelvic floor.

In man, the cranial prostate fits into the caudal prostate like an egg in an egg-cup (Figure 25.2); both prostates are deficient in front where glandular tissue is replaced by a fibromuscular septum (Figure 25.3).

25.2 Maturation of the Prostate

The normal pattern of growth and development of the prostate gland depends on testosterone. To become activated, testosterone must be converted to
dihydrotestosterone by the enzyme 5-alpha-reductase within the prostatic cells.

In early foetal life, the mesenchyme of the prostate differentiates into fibrous tissue and muscle, but there are few glandular elements. During the postnatal period and under the influence of androgens, glandular elements bud out to form ducts from the posterior wall of the urethra on either side of the verumontanum, and displace the urethra forwards (Figure 25.4). Ducts form true patent lumens, and the epithelial cells lining the acini fully

Figure 25.1 The fundamental 'blueprint' of the primate prostate. There are two distinct prostates, cranial and caudal between which pass the ejaculatory ducts. Note also the two distinct parts to the external sphincter.

Figure 25.2 The cranial prostate is fitted into the caudal prostate like an egg in an egg cup.
differentiate to synthesise a variety of secretory products essential for sperm survival. During puberty, serum testosterone increases to induce epithelial proliferation and the formation of a mature adult prostate, resulting in elongation of the urethra (Figure 25.5) [1, 2].

At around the age of 40 years, small nodules of hyperplastic acini and muscle begin to appear in the transitional zone of the gland (Figure 25.6). These nodules grow and coalesce to become the common pathological entity benign prostatic hyperplasia (BPH).

25.3 Anatomy of the Prostate

25.3.1 Topographical Anatomy

The size of the ‘normal’ prostate is difficult to quantify because the prostate volume increases with age under the effect of androgens. In the young adult male, the
Prostate Structure and Function

The prostate is about the size of a chestnut, weighing 10–15 g, and by age 50 years its size could be likened to that of a ping pong ball (approximately 30 g). The urethra bends slightly (by about 30°) as it passes through the gland (Figure 25.7). The prostate is thin in front (the fibromuscular septum) where it is devoid of acini. The openings of the prostatic ducts are found along the posterior half of the prostatic urethra, and the glands curve round on either side. There is virtually no glandular tissue in the midline anteriorly.

Most of the normal adult gland lies behind the urethra. It is separated into an inner cranial and an outer caudal zone by the entry of the ejaculatory ducts. The innermost part of the inner cranial part is the paraurethral zone.

Cranial to the prostate within the true bony pelvis are the trigone, ureters, and base of the bladder, and behind lie the seminal vesicles and vasa deferentia. The two layers of peritoneum that form the fascia of Denonvilliers separate the prostate and vesicles from the rectum behind. The deep veins of the penis and the symphysis pubis are located anterior to the gland.

Posterolateral to the prostate are the neurovascular bundles which supply the corpora cavernosa of the penis (Figure 25.8) [3]. The inferior-most aspect of the prostate, the apex, is directed downward and is intimately related to the superior part of the urogenital diaphragm.

The adult prostate consists of fused zones that are anatomically distinct, have characteristic histological features, and importantly, have typical predisposition to benign or malignant change [4]. These are the anterior fibromuscular stroma, which is devoid of glandular components, the periurethral transitional zone (TZ), which comprises of about 5–10% of the glandular tissue, the central zone (CZ; 20–25%), and the peripheral zone (PZ; 70%) (Figure 25.9) [5, 6]. The central zone surrounds the ejaculatory ducts and comprises the portion of the prostate that extends from the base proximally to where the ejaculatory ducts enter the urethra, near the prostatic utricle at the verumontanum distally. The TZ is located interiorly between the urethra and the surrounding peripheral and CZs, while the PZ is found on the posterolateral aspects of the prostate. The main morphological differences between the TZ and PZ are few; however they are easily identifiable pathologically because the TZ is chiefly affected by BPH.

Although lobes are recognisable in the developing human prostate, the lobar classification is still employed by urologists, particularly when describing the prostate at transurethral resection (TUR; Table 25.1).
**Figure 25.7** Sagittal section through the prostate showing anatomical relations.

**Figure 25.8** Diagrammatic cross-sections through the prostate at two levels showing the situation of the neurovascular bundles to the penis.

**Figure 25.9** Anatomy of the normal human prostate. (a) Sagittal section through the prostate demonstrating the orientation of the base (most cranial aspect) and the apex (most caudal aspect). Source: Adapted from McNeal [7] in Valkenburg and Williams [8] (b) Axial section through the base, illustrating its intimate relation to the pubis (anteriorly) and rectum (posteriorly). Source: Adapted from Walz, Burnett, Costello, et al. [9]. (c) A haemotoxylin and eosin (H&E) section through the base of a prostate removed following an open radical retropubic prostatectomy for localised prostate cancer. The impressive demarcation delineating the transition (T) and peripheral (P) zones are due the patient's young age. In older men, these planes would be more indistinct. A, anterior fibromuscular stroma; ED, ejaculatory duct; U, urethra. H&E slides courtesy of Dr. David Griffiths, consultant histopathologist, UHW, Cardiff.
Table 25.1 Each prostate lobe corresponds to part(s) of an anatomical zone.

<table>
<thead>
<tr>
<th>Prostate lobe</th>
<th>Corresponding prostate zone</th>
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<tbody>
<tr>
<td>Anterior</td>
<td>Mainly transitional zone</td>
</tr>
<tr>
<td>Median</td>
<td>Central and transitional zones</td>
</tr>
<tr>
<td>Lateral</td>
<td>Spans all zones</td>
</tr>
<tr>
<td>Posterior</td>
<td>Predominantly the peripheral zone</td>
</tr>
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</table>

The terminology relating to prostate lobar anatomy is commonly used for surgical description. Prostate lobes do not precisely correspond to individual prostate zones; indeed the lateral lobes (readily visible during TUR) span all zones.

25.3.2 Capsule of the Prostate

There are three separate entities that share the term ‘prostate’, with potential to confuse the urologist.

25.3.2.1 Anatomical Capsule

The prostate is surrounded by a capsule that is ill-defined in an anatomical sense. It consists of concentrically layered fibromuscular fascicles that are inseparable from the prostatic stroma anteriorly [10–12]. Vessels and nerves penetrate the capsule laterally [11, 12]. The prostatic capsule is discontinuous: it is non-existent at both the apex and the base of the prostate [11]. At its apex, the prostate stroma merges with the muscle fibres of the urinary sphincter and at the base with the smooth muscle fibres of the detrusor [11, 13].

25.3.2.2 Capsule at ‘Simple’ Open Prostatectomy for Benign Prostate Hyperplasia (Millin Prostatectomy)

In the early days of prostatectomy after the adenoma was enucleated from its shell with the finger, at first it was thought that the entire prostate had been removed from within its anatomical capsule [14]. Before long the error was recognised, and it became clear that the shell left behind was a layer of compressed prostatic tissue, often containing adenomatous nodules [15]. This technique was subsequently adopted by surgeons such as Millin [16, 17] to enucleate adenomas causing symptoms in BPH, prior to the advent of TUR. TUR later became, and continues to be, the gold standard surgical procedure for BPH. To this day, ‘simple’ open prostatectomy (which can be anything but!) remains an important technique for large, vascular prostates causing bothersome symptoms or haematuria. Endoscopically, this capsule is the limit of enucleation to the urologist that practices holmium laser enucleation of the prostate (HoLEP).

25.3.2.3 Capsule at Transurethral Resection

This is the term given to the lacy veil of tissue recognisable at TUR. The skill of TUR rests on being able to remove all the adenoma without perforating this ‘capsule’, outside which lies fat and veins. The layer of tissue is in fact thinner than the wire of the resectoscope loop. Capsular perforations at TUR are identifiable by persistent bubbles adherent to the fat outside the capsule, whereas bleeding from peri-prostatic veins is not so difficult to identify. They can cause bleeding which is not seen when the bladder is full but brisk when the bladder is empty. This should be managed with careful diathermy in the first instance, with or without a large catheter balloon (up to 30–40 ml) or intermittent catheter traction. If refractory or heavy bleeding ensues then open packing of the prostate is occasionally required [18].

25.3.3 Arteries

The prostate has a rich blood supply entering the gland in two main leashes on either side from the inferior vesical branches of the anterior branch of the internal iliac (hypogastric) arteries. The prostate artery then divides into the urethral and capsular arteries. From the urethral group arise Flock’s and Badenoch’s arteries, both of which supply the TZ. Flock’s arteries approach the bladder neck at 1 and 11 o’clock and Badenoch’s approach it at 5 and 7 o’clock (Figure 25.10). Awareness of these arteries is useful when performing a transurethral resection of the prostate (TURP) to help prevent bleeding. The capsular branches of the prostatic artery run with the cavernosal nerves [19, 20]. In addition to the prostatic arteries, the prostate is supplies by a small branch of the middle rectal artery.

25.3.4 Veins

Initially, the dorsal vein of the penis passes beneath the symphysis pubis emerging in between the puboprostatic ligaments. The dorsal vein then trifurcates into a central superficial branch that runs in the midline over the prostate and two lateral plexuses that runs along the side of the prostate running within the pelvic fascia. During a radical retropubic prostatectomy, after division of the puboprostatic ligament, to avoid blood loss the dorsal vein should be divided distally, before it trifurcates. The superficial branch drains the anterior prostate. The lateral plexuses drain the remaining prostate as well as the rectum and communicate with numerous vesical veins prior to draining into the internal iliac (hypogastric) vein. In the pelvis, numerous venous communications exist via valveless veins between the prostatic plexus and veins draining the pelvic bones and the vertebral plexus, affording an easy route for spread of cancer [21].
25.3.5 Lymphatics

The lymphatic drainage of the prostate primarily drains to the obturator and the internal iliac lymphatic chains that travel with their accompanying vessels; they also communicate directly with the bone marrow of the vertebrae, pelvis, and femora. This explains why bone metastasis to these areas is more common. There is also lymphatic communication with the external iliac, presacral, and the para-aortic lymph nodes.

25.3.6 Nerves

The autonomic innervations of the prostate arise from the pelvic plexus formed by the parasympathetic fibres that arise from sacral levels (S2–S4) and sympathetic fibres from lumbar levels (L1–2). The parasympathetic and sympathetic fibres travel to the prostate via the cavernous nerves, running postero-lateral within then pierce the thin capsule along with the fine branches of the arteries. The parasympathetic nerves end on the acini leading to increased prostatic secretion during sexual arousal. The sympathetic nerves end on α-1 receptors on smooth muscle of the capsule which are stimulated during ejaculation and closing the prostatic sphincter and relax during voiding. Nerve supply to the prostate is involved in glandular secretion and emission, with no active role in continence. The adrenergic fibres end in the stromal tissue (98%), being mainly α1 (90–60% are α1a) and α2 (10%). Cholinergic fibres end in the epithelium and help regulate secretions.

The pudendal nerve is the major nerve supply, leading to somatic innervations of the striated sphincter and the levator ani.

25.4 Prostate Physiology

25.4.1 Function

The function of the prostate gland is often overlooked by its association with benign enlargement and malignancy. Its main function, however, is the production of an acidic secretion (pH ~6) containing zinc, citrate, and polyamines, in addition to strong proteolytic enzymes such as prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) which liquefy the seminal coagulum.

25.4.2 Prostate-Specific Antigen

PSA is an androgen-regulated 34 kDa glycoprotein enzyme belonging to the kallikrein family of serine proteases. It is produced primarily by prostate ductal and acinar epithelium and is secreted into the lumen, where its function is to cleave semenogelin I and II in the seminal coagulum [22]. As the coagulum dissolves, the sperm simultaneously become highly motile, facilitating its journey from the vagina to the ova.

Nearly 75% of PSA is bound to plasma proteins (i.e. α-1 anti-chymotrypsin and α-2 macroglobulin) and metabolised in the liver with the remaining 25% free and is excreted in the urine.

Its major relevance in oncology is as a biomarker to detect prostate cancer (PCa) and to assess responses to treatment. With PCa, there is less PSA production; however, a characteristic of early PCa is disruption of the basal cell layer and basement membrane, causing loss of normal glandular architecture and allowing PSA direct access to the peripheral circulation as oppose to the lumen, giving rise to a significantly higher serum level count [23, 24]. It is measured by radioimmunoassay in the serum and identified by immunohistochemistry of histological section, thus clearly identifying metastases that have risen from the prostate. Serum PSA's half-life is nearly two. Two days and levels vary with age (Table 25.2) and race [25].
One must remember that the PSA is prostate specific and not PCa specific, with many factors causing PSA levels to read high. More common factors include, BPH, urinary retention, catheterisation, prostatic biopsies or TURP, and UTIs, especially prostatitis.

### 25.4.3 Prostatic Acid Phosphatase

PAP is a prostate epithelium-specific secretory protein that is found in large amounts in the seminal fluid. PAP was the first tumour marker used for prostate cancer [26] and used in the pioneering work by Huggins and Hodges, demonstrating the beneficial effects of castration on PCa bone metastases [27]. Elevated PAP levels have been reported in 70% of metastatic disease [28]; however, it is reported to be elevated in only 1% of patients with localised disease [29] and may be significantly artefactually elevated after digital rectal examination (DRE).

### 25.4.4 Emission and Ejaculation

During sexual arousal, spermatozoa are transported from the ampulla of the vasa into the prostatic urethra, this is called ‘emission.’ The sperm mixes with fluid from the prostate, seminal vesicles, and bulbar-urethral (Cowper) glands to form semen.

During ejaculation, the smooth muscle of the prostate capsule contracts synchronously with the bulbospongiosus muscle, along with the pelvic floor muscles and the ischocavernosus muscles. The rhythmic contractions propel the semen distally through the urethra.

During erection, the bladder neck (prostatic sphincter) closes (under sympathetic stimulation) and prevents retrograde flow of semen into the bladder; bladder neck closure is more marked just before ejaculation. Hence why it is difficult to urinate with an erection or after ejaculating. If the bladder neck has been cut, the sympathetic nerves have been divided or the $\alpha$-1 drive to the bladder neck has been blocked by medication, then semen will leak back into the bladder (retrograde ejaculation) producing a more or less ‘dry ejaculation.’

The fructose-rich seminal fluid provides the nourishment for the sperm and helps to wash the sperm through the ejaculatory duct and urethra. The seminal secretions contribute to approximately two-thirds of the semen volume. The bulbar-urethral glands produce a pre-ejaculate that lubricates the urethra to facilitate sperm passage.

### 25.4.5 Prostate and Sphincters

At the neck of the bladder there is a ring of $\alpha$-1 adrenergic smooth muscle intertwined with prostatic acini and fibrous tissue (Figure 25.11). In middle age, this ring of muscle, often referred to as the bladder neck, although distorted by adenoma, remains under the influence of $\alpha$-1 agonists. Stimulation of the presacral nerve causes it to contract, whereas $\alpha$-1 blockers cause it to relax.

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**Table 25.2** Age-specific reference range guide.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>PSA (ng ml$^{-1}$)</th>
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<tbody>
<tr>
<td>40–49</td>
<td>2.5</td>
</tr>
<tr>
<td>50–59</td>
<td>3.5</td>
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<tr>
<td>60–69</td>
<td>4.5</td>
</tr>
<tr>
<td>70–79</td>
<td>6.5</td>
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</table>

PSA, prostate-specific antigen.
Caudal to the verumontanum, there is a second sphincter, the external sphincter, and hence why the ‘veru’ is a key landmark in TUR (i.e. to prevent resection distally risking damage to the sphincter). It is contained in the few millimetres of tissue immediately surrounding the urethra and is quite distinct from the striated pubo-coccygeal part of the levator ani. During operations on the bulbar urethra (e.g. resection for cancer or repair of a ruptured posterior urethra), this intramural external sphincter can be clearly seen above and moving independently from the hiatus in the levator ani sheet (Figure 25.12).

The external sphincter has two components: (i) an inner sleeve of smooth muscle which is continuous with that of the prostate (and thought to be supplied by α-1 adrenergic nerves) and (ii) an outer layer of striated muscle (Figure 25.13), a special striated muscle made up of small cells, classified as the slow-twitch type and can maintain contraction for long periods. Electron microscopy shows these small slow-twitch fibres to have a high content of lipid and mitochondria which make them able to maintain contraction for a long period.

Every urologist should appreciate how small and vulnerable is this precious sleeve of muscle on which male continence depends after operations on the bladder neck or prostate.

At the beginning of normal micturition the bladder neck relaxes, and at the same time, the detrusor contracts.
When the bladder is empty, the external sphincter closes first and the prostatic urethra is emptied by milking back the small quantity of urine it contains into the bladder and then the bladder neck closes (Figure 25.14).

Both components of the intramural sphincter are innervated by the pelvic splanchnic nerves.

**References**


26

Prostate Inflammation

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Abstract

Prostatitis is an umbrella term encompassing a spectrum of disease from asymptomatic inflammatory prostatitis to bacterial prostatitis and chronic pelvic pain syndrome. The estimated prevalence is between 10 and 14% [1]. Prostatitis can occur in all age groups but is most common in younger men, causing significant morbidity and subsequent economic impact [2, 3]. Chronic prostatitis has recently been considered an important factor in the progression of benign prostatic hyperplasia (BPH) [4] and is thought to be one of the most common reasons for a man younger than 50 years to go to a urologist. During the last decade, we have seen an increase in the incidence of acute bacterial prostatitis and urosepsis after transrectal ultrasound (TRUS)-guided prostate biopsies [5].

Keywords prostate; prostatitis; classification; inflammation; abscess

Key Points

- Recent classifications of prostatitis describe four distinct categories: (i) acute bacterial prostatitis, (ii) chronic bacterial prostatitis, (iiia) inflammatory and (iiib) non-inflammatory chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and (iv) asymptomatic inflammatory (histological) prostatitis.
- The Meares and Stamey four-glass urine collection with microscopy and culture is the gold standard for localisation of infection to bladder, prostate, and urethra.
- Intravenous aminoglycosides followed by second-generation fluoroquinolone antibiotic treatment for two to four weeks is the preferred treatment for acute bacterial prostatitis.
- If a prostatic abscess is confirmed on imaging, a transurethral abscess de-roofing is the preferred drainage method. Surgical treatment options for CP/CPPS remain experimental.

26.1 Classification of Prostatitis

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) updated the classification of prostatitis in 1999 to the current definitions of four distinct categories of prostatitis (summarised in Table 26.1) [6]. Acute and chronic bacterial prostatitis (NIH I/II) are thought to account for only 5–10% of all cases of prostatitis; the remainder are chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) which represents more than 90% of patients with a diagnosis of prostatitis [1].

26.1.1 Category I: Acute Bacterial Prostatitis

Acute bacterial prostatitis used to be a rare condition, resulting from acute ascending infection of uro-pathogenic faecal flora, commonly Escherichia Coli; other gram-negative pathogens include Proteus, Klebsiella, Pseudomonas, and Serratia spp., and rarely, gram-positive organisms such as Enterococcus faecalis. Urinary tract infections (UTIs), urethral strictures, phimosis, indwelling urethral catheters, instrumentation of the lower urinary tract, prostatic stones, and unprotected anal sexual intercourse are predisposing factors.
Clinically, sepsis and localised pain (e.g. perineal, suprapubic, penile, or genitalia) can elude to the diagnosis. Some patients may present with significant worsening of lower urinary tract symptoms (LUTS). Acute urinary retention (AUR) is seen in nearly 10% of cases requiring suprapubic or urethral catheterisation. Examination elicits a tender swollen prostate on digital rectal examination (DRE). Urethral catheterization can be extremely painful, and in such cases, suprapubic catheterization is recommended. Prostatic massage is contraindicated because it can provoke septicaemia. Bed rest, analgesia, and laxatives are also an important part of the management to aid recovery.

Today, acute prostatitis is seen more often due to an increasing number of transurethral ultrasound (TRUS) biopsies being taken. Patients must be informed about this complication before TRUS biopsy, and in case of a febrile reaction, they should be hospitalised as an emergency for intravenous treatment with antibiotics [7].

Acute prostatitis can lead to the chronic form or to abscess formation if antibiotics treatments fail. Abscess should be considered if symptoms persist despite appropriate antibiotics, especially in patients who are diabetic, or those who are immunocompromised, have renal failure, or are catheterised.

### 26.1.2 Category II: Chronic Bacterial Prostatitis

This form of prostatitis accounts for about 10% of cases and can be associated with recurrent UTIs. Similar organisms may be isolated as in acute prostatitis. The infection is thought to occur in the peripheral zone as ducal drainage here allows more reflux. Infected urine refluxes into the prostatic ducts that drain into the posterior urethra, causing oedema and inflammation, which can obstruct the ducts, leading to deep rooting and trapping of bacteria. It can also be associated with prostatic calculi, creating a nidus for recurrent infection. Patients may complain of painful ejaculation, perineal or suprapubic pain, and obstructive LUTS lasting for more than three months.

### Table 26.1 Definitions of four distinct categories of prostatitis.

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms / Signs</th>
<th>WBCs in EPS</th>
<th>NIDDK Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pain, bacteraemia, leucocytosis with or without systemic sepsis</td>
<td>Positive</td>
<td>Acute bacterial prostatitis</td>
<td>Bacterial infection of the prostate causing systemic sepsis.</td>
</tr>
<tr>
<td>II</td>
<td>Intermittent pain, bacteriuria, and pyuria</td>
<td>Positive</td>
<td>Chronic bacterial prostatitis</td>
<td>Intermittent symptoms &gt;3 months. Rare cause of recurrent UTIs.</td>
</tr>
<tr>
<td>IIa</td>
<td>Pain + sterile pyuria</td>
<td>Positive</td>
<td>Inflammatory CP/CPPS</td>
<td>Encompasses &gt;90% of prostatitis diagnosis. Aetiology is unknown. Associated with sexual dysfunction and psychological issues.</td>
</tr>
<tr>
<td>IIb</td>
<td>Pain + no pyuria</td>
<td>Negative</td>
<td>Noninflammatory CP/CPPS</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>No pain only pyuria with or without bacteriuria</td>
<td>Positive</td>
<td>Asymptomatic inflammatory prostatitis</td>
<td>Incidental evidence of prostatitis on TRUS biopsy</td>
</tr>
</tbody>
</table>

(Source: Adapted from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Classification of prostatitis [6]).

CP, chronic prostatitis; CPPS, chronic pelvic pain syndrome; EPS, expressed prostatic sections; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; TRUS, transrectal ultrasound; UTI, urinary tract infection; WBCs, white blood cells.)

### 26.1.3 Category IIa: Inflammatory Chronic Prostatitis/Chronic Pelvic Pain Syndrome and Category IIb: Non-inflammatory

Categories IIIa/b together represent about 90% of patients with a diagnosis of prostatitis. Prostatitis is most common between the ages of 36 and 65 years [3]. Its aetiology remains unclear; however, high-pressure voiding and reflux of urine into prostatic ducts, non-culturable microorganisms [8], autoimmune disease [9], and neuropathic and interstitial cystitis-like processes have been suggested. Symptoms include localised pain, pain with ejaculation, LUTS, and erectile dysfunction lasting for more than three months. Diagnosis of inflammatory prostatitis (NIH IIIa) justifies using a test course of antibiotics, which may be prolonged in the case of symptom relief. Diagnosis is made by means of microscopy (two-glass or four-glass tests) in patients presenting with chronic pelvic pain and negative culture tests.

The inflammatory subset (NIH IIIa) is characterised by leucocytes in expressed prostatic secretions (EPS) or postmassage urine. Associated LUTS, sexual dysfunction, and mental health problems are common and can have a huge impact on the patients’ quality of life (QoL). The Chronic Prostatitis Symptom Index (NIH-CPSI) was developed to quantify three symptom domains: pain, LUTS, and QoL and is useful in both clinical practice and research to quantify these symptoms [6].

### 26.1.3.1 Category IIIb: Non-inflammatory Prostatitis

This form of prostatitis accounts for about 10% of cases and can be associated with recurrent UTIs. Similar organisms may be isolated as in acute prostatitis. The infection is thought to occur in the peripheral zone as ductal drainage here allows more reflux. Infected urine refluxes into the prostatic ducts that drain into the posterior urethra, causing oedema and inflammation, which
26.1.4 Category IV: Asymptomatic Inflammatory (Histological) Prostatitis

Approximately 20% of asymptomatic infertile men have evidence of prostatitis in EPS or semen. Histological evidence of inflammation in prostatic biopsies signifies asymptomatic inflammatory prostatitis. Patients lack any LUTS or pain, and no treatment is required.

26.2 Investigations

26.2.1 Microbial Localisation

The four-glass urine collection method described by Meares and Stamey in 1968 remains the gold standard of investigation [10]. This involves collecting urine and EPS for microscopy and culture from the urethra, prostate, and bladder as outlined in Table 26.2.

An alternative to this method is the two-glass technique suggested by Weidner in 1985. This assumes that urethritis can be ruled out clinically and that postprostatic massage urine reflects the EPS. This simpler technique involves only pre- and postprostatic massage urine samples and correlates with the four-glass technique in 90% of cases [8].

26.3 Imaging

Further imaging may be indicated in persisting acute and chronic bacterial prostatitis (NIH I/II) and when a prostatic abscess is suspected. Magnetic resonance imaging (MRI) or high-resolution computed tomography (CT) of the pelvis provides a noninvasive method to image the prostate. MRI is preferred for its soft-tissue differentiation and lack of exposure to ionising radiation in young patients (Figure 26.1). Despite associated discomfort, TRUS may allow transrectal or perineal aspiration of a prostatic collection [11]. Additional imaging in chronic prostatitis remains debatable; however, some series have suggested that low signal intensity (SI) regions in T2-weighted images can be correlated

<table>
<thead>
<tr>
<th>Sample</th>
<th>Localisation</th>
<th>Method</th>
<th>Active UTI or acute prostatitis All samples positive (NIH I)</th>
<th>Chronic bacterial prostatitis (NIH II)</th>
<th>CP/CPPS and AIP All samples negative (NIH IIIa/b and IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VB1</td>
<td>Urethra</td>
<td>1st 10 ml urine</td>
<td>&gt; $10^3$ CFU ml$^{-1}$</td>
<td></td>
<td>&lt; $10^3$ CFU ml$^{-1}$</td>
</tr>
<tr>
<td>VB2</td>
<td>Bladder</td>
<td>2nd 10 ml urine</td>
<td>&gt; $10^3$ CFU ml$^{-1}$</td>
<td></td>
<td>&lt; $10^3$ CFU ml$^{-1}$</td>
</tr>
<tr>
<td>EPS</td>
<td>Prostate</td>
<td>EPS fluid</td>
<td>&gt; $10^3$ CFU ml$^{-1}$</td>
<td>&gt; $10x$ CFU ml$^{-1}$ of VB1</td>
<td>&lt; $10^3$ CFU ml$^{-1}$</td>
</tr>
<tr>
<td>VB3</td>
<td>Prostate</td>
<td>3rd 10 ml urine</td>
<td>&gt; $10^4$ CFU ml$^{-1}$</td>
<td>&gt; $10x$ CFU ml$^{-1}$ of VB1</td>
<td>&lt; $10^4$ CFU ml$^{-1}$</td>
</tr>
</tbody>
</table>

*Greater than $10^3$ CFU per ml is usually considered a positive sample. EPS must be greater than 10 times the CFU ml$^{-1}$ of VB1 for the diagnosis of chronic bacterial prostatitis (NIH II) [6].
AJIP, asymptomatic inflammatory prostatitis; CFU, colony-forming unit; CP, chronic prostatitis; CPPS, chronic pelvic pain syndrome; EPS, expressed prostatic secretions; NIH, National Institutes of Health; UTI, urinary tract infection.

Figure 26.1 Contrast-enhanced magnetic resonance imaging (MRI) showing multiple prostatic abscesses. T1-weighted coronal image with a low attenuation region highlighted in the left lobe of the prostate representing a prostatic abscess (a). T2-weighted coronal image showing the corresponding high attenuation abscess region (b).
to regions of histologically confirmed chronic prostatitis from TRUS biopsy [12].

26.4 Serum Prostate Specific Antigen

Prostate-specific antigen (PSA) testing is not recommended for patients with suspected prostatitis. It is certainly not advised in the acute setting. The level of PSA does not appear to correlate well with resolution of prostate inflammation, and its use is to be avoided in acute febrile prostatitis [13].

26.5 Histology

Suspected prostatitis is not an indication for prostate biopsy. However, inflammatory prostatitis is often seen in diagnostic prostatic biopsies for prostate cancer due to elevated PSA levels. The biopsy shows regions of microscopic inflammation characterised by diffuse inflammatory infiltrates. Retrospective studies have shown that most patients with CP or CPPS have only mild inflammation, the extent of which does not correlate with the severity of symptoms, suggesting an alternative aetiology may play a greater role than inflammation alone [14].

26.6 Treatment Options

In the acute setting, patients who are septic might need hospitalisation and intravenous antibiotics and analgesics. Once the patient is stable and well, oral antibiotics can be given. While in the chronic forms, it can be beneficial for the patient to have a multidisciplinary approach with a focus on the predominant symptom and the impact on QoL. Psychiatric teams, psychologists, and physiotherapists can help with counselling, education, biofeedback techniques, stress and anxiety relief, pelvic floor exercises, or even support groups. The pain team can be of vital help for pain management.

26.6.1 Antibiotics

Antibiotics for acute and chronic bacterial prostatitis are broad spectrum with activity against gram-positive and -negative pathogens. The intravenous aminoglycoside, gentamycin with a broad-spectrum penicillin or a third-generation cephalosporin, is administered in the acute setting in patients who are unwell with urosepsis. Otherwise current recommended regimens use the second-generation fluoroquinolones (i.e. ciprofloxacin, ofloxacin, and norfloxacin) [15, 16]. The optimal duration of treatment for acute prostatitis (NIH I) remains unclear but is commonly in the region of four weeks to prevent progression to chronic prostatitis.

Consensus for the treatment of chronic prostatitis (NIH II) is a similarly prolonged treatment course of at least four weeks. Up to 80% of patients are rendered free of infection by culture following treatment with fluoroquinolones, while the infection-free rate is lower with trimethoprim at about 40% after similar treatment duration [17]. Both of these antibiotics are able to penetrate into the deep prostatic tissue. Trimethoprim has no activity against Pseudomonas and some Enterococci and Enterobacteriaceae.

More recently, resistance to ciprofloxacin is becoming more common and may result in greater use of third-generation fluoroquinolones such as levofloxacin [18]. Toxicity (including prolonged QT syndrome), side effects (including tendon rupture), and drug interactions (including Warfarin) of fluoroquinolones should be considered carefully when prescribing prolonged courses.

Tetracyclines and macrolides also have good prostatic penetration and are used if culture sensitivity dictate it.

26.6.2 Tamsulosin and Finasteride

The use of alpha-blockers may have a role in reducing symptom recurrence and bacteriuria in chronic bacterial prostatitis, with one retrospective study suggesting a reduction of as much as 50%. They can also be of use in treating the obstructive LUTS element of CP/CPPS (NIH IIIa/b). By improving urinary flow, reducing reflux, and therefore inflammation, a 5-alpha reductase inhibitor has also been shown to possibly have a role in the management of CP/CPPS. A small placebo randomised controlled trial [19] showed a beneficial effect in inflammatory CP/CPPS (NIH IIIa), with 33% of men improving in NIH-CPSI by >25% (defined as a responder) at six months compared to 16% responding with placebo, but this was not statistically significant. There may be an additive effect in combining finasteride and Tamsulosin in CP/CPPS, but it is currently only recommended in patients with concurrent benign prostatic hyperplasia (BPH) [20] as prostatitis can lead to BPH disease progression.

26.6.3 Pain Relief

A stepwise approach is taken with analgesics to help alleviate pain. Chronic pain may respond to neuro-modulatory therapies such as amitriptyline, gabapentin, and pregabalin.

26.6.4 Pentosan Polysulphate

This is a heparin-like molecule which resembles aminoglycosides and is thought to provide a barrier-like protection on the uro-epithelium. Its use is more
common for interstitial cystitis. A randomised controlled trial for treatment of CP/CPPS with pentosan polysulphate was negative when compared to placebo [21].

26.6.5 Other Therapies

Because CP/CPPS is a common but poorly understood ‘condition’, and there is little proof to support the effectiveness of conventional therapies, many alternative treatments have been suggested. Herbal supplements such as quercetin and acupuncture have been used with limited evidence of efficacy [22]. Biofeedback, psychotherapy and relaxation exercises including lifestyle changes have also been tried. In 1999, Nickel advocated ‘triple-therapy’, combining an alpha blocker, a nonsteroidal anti-inflammatory, and a muscle relaxant such as diazepam as initial treatment for noninflammatory CP/CPPS (NIH IIIb) [23].

26.7 Upoint Phenotypic Classification of CP/CPPS

This clinical tool has been developed to further classify CP/CPPS into six phenotypic domains [24]. Theory behind this is that patients with CP/CPPS are a heterogeneous group, and as discussed previously, the aetiology remains unclear and may include many different causal factors. Failure to show a benefit in many randomised trials in CP/CPPS cohorts have led to the conclusion that to successfully treat these patients, they must be further characterised phenotypically. This developed into the ‘Snowflake Hypothesis’ in which patients with CP/CPPS can be classified by six domains (the six points of a snowflake, Figure 26.2). These are urinary, psychosocial, organ specific, infection, neurologic/systemic pain and tenderness of skeletal muscle (UPOINT). One study in a cohort of 90 men with documented CP/CPPS suggested that only 22% are positive for only one domain and the proportion positive for each domain was urinary (52%), psychosocial (34%), organ specific (61%), infection (16%), neurologic/systemic pain (37%), and tenderness of skeletal muscle (53%) [25].

A prospective study of 100 patients with CP/CPPS treated with this multimodal approach has shown promising results with more than half improving in NIH-CPSI by greater than 50% with an average follow up period of 50 weeks. Specific treatment regimens employed for each positive domain included urinary (α-blocker or antimuscarinic), psychosocial (stress reduction/psychological support), organ specific (quercetin), infection (antibiotics), neurological/systemic pain (amitriptyline or pregabalin), and tenderness of skeletal muscle (pelvic floor physiotherapy) [26]. An online algorithm based tool for urologists has been created to enter patient factors and provide the UPOINT phenotype [27] with suggested therapies to help manage this difficult condition using a multimodal and multidisciplinary approach.

26.8 Surgical Options

Transurethral resection or deroofing can be useful to drain a prostatic abscess (Figure 26.3). Transurethral resection of the prostate (TURP) may provide a benefit in chronic bacterial prostatitis (NIH II) due to drainage of abscesses and removal of prostatic calculi, but this has not yet been proven. A modified TURP technique, avoiding resection of the bladder neck and anterior zone for prostatic abscess drainage, has been suggested to minimise any risk of incontinence, which may in part be due to bladder overactivity [28]. It is recommended that TURP is reserved only for refractory cases of chronic prostatitis and in the context of trials. A combination of prostatic massage and antibiotic therapy regimens may also improve symptoms in the short term, but its longer-term efficacy remains unproven [29].

26.9 Heat Therapies

Transurethral microwave thermotherapy (TUMT) involves increasing the temperature of the prostate, which is thought to have a numbing effect on prostatic sensory nerves resulting in symptom relief. It has been shown in a small randomised double-blind sham controlled trial to provide a beneficial effect in CP/CPPS (NIH IIIa/b) by reducing symptom score from 48.4 to 27.3 over three months using a validated severity index
Prostate Inflammation

(0–100); this is a statistically significant improvement compared to sham [30]. Responders were then followed up for 21 months without deterioration in symptoms, suggesting long-term maintenance of the effects [30]. Transurethral needle ablation (TUNA) of the prostate has also been shown to provide improvement in symptom score in a study of 32 patients with inflammatory CP/CPPS. Symptoms resolved in 60% of patients at six months and reduction in leucocytes present in EPS was seen in all patients [31]. Despite promising results, studies are small, and these forms of thermotherapy remain experimental.

26.10 Prostate Tuberculosis

Prostate tuberculosis (PTB) is a form of extrapulmonary tuberculosis (EPTB) and rare in developed countries, accounting for only 2–5% of all cases of EPTB. Before anti-tuberculosis (TB) drugs, the prevalence of PTB was much greater because it is spread by sexual transmission [32]. In patients with active TB and LUTS, a diagnosis of PTB should be considered. An early diagnosis can be aided by TRUS biopsy staining for acid-fast bacilli as well as TB culture or polymerase chain reaction (PCR) of prostate tissue. Treatment with standard anti-TB combination therapy with the addition of ofloxacin to better penetrate prostate tissue showed improvements in pain, dysuria, and negative cultures following therapy at eight months in a 2014 Russian study of 93 patients with suspected PTB [33]. By the time granuloma cavitation develop in the prostate, the disease cannot be fully cured with antimicrobial therapy. This late presentation is pathognomonic and may also present with a cold abscess draining into the rectum via a fistula tract.

26.11 Summary

Recent years have seen changes in the presentation and forms of prostatitis with acute prostatitis becoming more important as a complication of TRUS-guided prostate biopsies. This may lead to urosepsis and require emergency hospitalisation and intravenous treatment with broad-spectrum antibiotics.

CP/CPPS is as a common disease of younger men which may cause significant morbidity but remains poorly understood. There is limited evidence to support current treatments and surgery is reserved as a last resort. Further knowledge of the basic underlying processes may help to develop novel treatments and guide the management of these patients.
Symptomatology of prostatitis varies widely, ranging from severe symptoms (e.g., acute retention and septic shock) to vague LUTS, chronic pelvic pain, or asymptomatic as incidental findings. Diagnosis can therefore be challenging, requiring multiple investigations. In patients with acute prostatitis, possible complications include urinary retention (evidenced by palpation and bladder scan) and urosepsis with an exquisitely tender swollen prostate on DRE. Besides appropriate anti-microbial therapy, the insertion of a suprapubic catheter to decompress the bladder may be indicated to minimise the risk of epididymal spread and abscess formation.

TRUS-guided prostate biopsy is an important iatrogenic cause of infective prostatitis (and related sepsis). Typically within a week following biopsies, approximately 5% of patients present with UTI and about 3% need hospitalisation due to febrile UTI suspicious of urosepsis, despite the use of prophylactic antibiotics during prostatic biopsies.

Infective complications are increasingly related to ciprofloxacin-resistant bacteria in the rectal flora [34].

References

with lower urinary tract symptoms and a baseline total prostate volume of 25 ml or greater. *J. Urol.* 175: 217–220; discussion 220–221.


Prostate Benign Prostatic Hyperplasia

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Abstract

Lower urinary tract symptoms (LUTS) are common in the population but are not solely due to benign prostatic enlargement (BPE), instead age-related detrusor changes and other common medical conditions are the causative factor in many cases. Despite this, benign prostatic hyperplasia (BPH) is still a significant cause of LUTS, and this chapter attempts to explain the current evidence for the causes, investigation, complications, and management of patients with LUTS.

Keywords lower urinary tract symptoms (LUTS); benign prostatic enlargement (BPE); green light laser prostatectomy; urinary retention; benign prostatic hyperplasia (BPH)

Benign prostatic hyperplasia (BPH) is a pathological process that contributes to, but is not the sole cause of, lower urinary tract symptoms (LUTS) in ageing men [1]. Historically, LUTS have been related to bladder outflow obstruction (BOO), but the current literature attributes a significant proportion of LUTS to age-related detrusor changes and a variety of systemic medical conditions (e.g. congestive heart failure, diabetes, etc.). In this chapter, we will discuss all issues related to the current understanding and treatment of BPH and BOO.
27.1 Nomenclature

Use of the correct terminology cannot be stressed highly enough because use of incorrect terminology may result in the inappropriate treatment of men and treatment may not be focused on the correct cause [2]. Hald rings (Figure 27.1) describe the interplay of these terms and the International Continence Society (ICS) have standardised the terminology:

- LUTS is the accepted term, which replaces terms such as 'prostatism' and is used to describe the subjective indicator of a disease of the lower urinary tract, however, in general cannot be used to make a definitive diagnosis [3] (i.e. describes storage and voiding symptoms).
- Acute urinary retention (AUR) is 'defined as a painful, palpable or percussable bladder, when the patient is unable to pass any urine' [3].
- Chronic retention of urine is 'defined as a non-painful bladder, which remains palpable or percussable after the patient has passed urine. Such patients may be incontinent' [3].
- BOO 'is the generic term for obstruction during voiding and is characterised by increased detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous value of flow rate and detrusor pressure' [3].
- BPH 'is a term used (and reserved for) the typical histological pattern which defines the disease' [3].
- Benign prostatic enlargement (BPE) 'is defined as prostatic enlargement due to histologic benign prostatic hyperplasia. The term ‘prostatic enlargement’ should be used in the absence of prostatic histology' [3] (i.e. a clinical finding of an enlarged prostate).
- Benign prostatic obstruction (BPO) 'is a form of BOO and may be diagnosed when the cause of outlet obstruction is known to be BPE [3].
- Storage symptoms (formerly referred to as irritative symptoms) 'daytime urinary frequency, nocturia, urgency, urinary incontinence' [4].
- Voiding symptoms (formerly referred to as obstructive symptoms) 'slow stream, splitting or spraying, intermittency, hesitancy, straining, terminal dribbling' [4].
- Postmicturition symptoms 'sensation of incomplete emptying, post micturition dribbling' [4].

27.2 Aetiology

27.2.1 Hormonal Factors

27.2.1.1 Role of Androgens

The dependent relationship between the prostate and testosterone has been recognised for many years. The permissive role of dihydrotestosterone (DHT) in the pathogenesis of BPH is demonstrated by the fact that castration or hypopituitarism occurring in men prior to puberty prevents the development of BPH. Furthermore, individuals with congenital 5-alpha reductase deficiency do not develop BPH; prostatic levels of DHT remain high in ageing men, despite the fact that peripheral levels of testosterone decrease with age [5], and androgen withdrawal leads to partial reversal of established BPH [6].

Testosterone binds directly to androgen receptors; however, the more potent form DHT is what gives a greater effect. Testosterone is converted to DHT by 5α-reductase (5αR) II in the prostate or by 5αR I in the skin or liver. Once testosterone has diffused into the prostate and stromal epithelial cells, it binds to the androgen receptors. The majority of the testosterone binds to receptors on the cell membrane, where it is converted to DHT, which binds with greater affinity to the receptors (higher potency). The testosterone or DHT-androgen receptor complex then binds to the nuclear membrane, inducing transcription of genes and initiating protein production.

27.2.1.2 Role of Oestrogen

In ageing men, a change in the ratio of androgen to oestrogen in favour of oestrogens has been postulated to play an important role in the pathogenesis of BPH. Treatment of young dogs with androgen plus oestrogen hormones leads to early development and a greater prevalence of BPH [7]. The role of oestrogen in the development of BPH in humans is not as well understood as the role of androgens.

27.2.2 Stromal/Epithelial Interaction (Embryonic Reawakening) and Growth Factors

McNee noted that the histological appearance of stromal tissue in BPH nodules resembles the histologic appearance of developmental mesenchyme and hypothesised that BPH is caused by reawakening of embryonic processes in a distorted form in adult life [8, 9]. Cunha [10] has

![Figure 27.1 Hald’s rings. BPH, benign prostatic hyperplasia; BOO, bladder outflow obstruction; LUTS, lower urinary tract syndrome.](image-url)
demonstrated that prostatic epithelial development is dependent on androgen-sensitive and stromal mediators. Murine urogenital sinus mesenchyme cells will induce intact male murine bladder cells to proliferate, bud, and acquire a distinctly prostatic appearance when these cells are coincubated. This inductive process is androgen dependent, and it has been found that the stromal and epithelial cells are capable of producing growth factors (i.e. peptide molecules affecting cell division and differentiation) that bind to specific membrane receptors leading to cell division and differentiation process and at other times inhibiting these processes.

It appears that growth stimulatory factors such as the fibroblastic growth factors (FGF): FGF1 (acidic FGF-active in early life), FGF2 (basic FGF-active in later life), FGF7, and FGF17 families (also including the keratinocyte growth factors [KGF]), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and epidermal growth factors (EGF) including transforming growth factor-α (TGF-α), may play a role with DHT augmenting or modulating the growth factor effects. In contrast TGF-β, which is known to inhibit epithelial cell proliferation, may normally exert restraining influences over epithelial proliferation in BPH [11]. In health, there is usually a balance between the two (Figure 27.2), and an imbalance causes BPH.

27.2.3 Genetic Factors

Genetics have a role in the development of BPH. A retrospective case control analysis of patients who were treated surgically for BPH and control subjects at John Hopkins Hospital demonstrated that in 50% of men younger than 60 years of age undergoing prostatectomy had their BPH attributed to an inherited form of the disease, whereas only 9% of men older than 60 years of age undergoing prostatectomy had a familial risk [12].

The results are consistent with an autosomal-dominant inheritance pattern, but the specific gene(s) involved in familial BPH or contributing to the risk of significant prostatic enlargement in sporadic cases are still to be identified [12].

27.2.4 Role of Inflammatory Pathways

Recent research suggests that inflammatory cell infiltrates, which are seen in a high percentage of men with BPH, may provide an additional source of growth factors in human BPH. The cytokines (interleukin [IL] –6 to –8) may have a role in promoting cell growth and smooth muscle contraction [13].
27.2.5 Other Causative Relationships

It seems that there is no significant relationship between the incidence of BPH and religious or socioeconomic factors [14]. However, a recent study evaluating the metabolic syndrome or obesity and LUTS showed a statistical correlation between the two. The components of diabetes (i.e. elevated fasting glucose) and hypertension were most commonly associated with BPH, and this applied to men younger than 60 years of age [15].

27.3 Pathology of BPH

The embryological and anatomical studies of McNeal contributed greatly to the current understanding of BPH. According to McNeal, the adult prostate is made up of four distinct zones (i.e. McNeal's zonal anatomy of prostate; Figure 27.3). The peripheral zone makes up 70% of the prostate, whilst the central zone (20–25%) is the next largest zone and is cone shaped, with the base forming most of the base of the prostate and the apex located at verumontanum. The third zone is the interior fibromuscular stroma, and the periurethral transitional zone is the smallest zone but is the site where BPH develops (Figure 27.3) [8].

McNeal's studies demonstrated that the majority of early periurethral nodules are purely stromal, whilst the earliest transitional zone nodules represent proliferation of glandular tissue. The first phase of evolution of BPH is characterised by increased numbers of nodules, then the second phase is characterised by an increase in size of these nodules [10].

There is a significant variability in the stroma to epithelial ratio in BPH; resected tissue from small prostates demonstrates a predominance of fibromuscular stroma, while tissue from large glands removed by enucleation demonstrates primary epithelial nodules. As stated previously, BPH is primarily a stromal process associated with significant smooth muscle hyperplasia, the overall ratio of stroma to epithelium in BPH is 4:1 to 5:1 with the smooth muscle proportion of the hyperplastic stroma being approximately 40% [16]. The smooth muscle tone is regulated by the adrenergic nervous system and receptor-binding studies demonstrate the α1a is the most abundant adrenoceptor in the human prostate. One of the unique features of the human prostate is the presence of the prostatic capsule; it may be that the capsule provides resistance to tissue expansion caused by BPH nodules increasing in size, which in turn leads to increased urethral resistance [17].

Watanabe described the concept of presumed circle area ratio (PCAR), which is based on the theory that the change in prostatic shape, which can be observed as the prostate enlarges with BPH, is due to greater tension within the prostatic capsule with the forces within the prostate being distributed evenly including upon the

Figure 27.3 Diagram of McNeal's prostate zonal anatomy.
prostatic urethra. As the tension within the prostatic capsule increases, the prostate assumes a more spherical shape, this being the shape with the lowest surface tension for a given volume. Watanabe assigns the prostate a PCAR that describes how near a spherical shape the prostate has become, which he has correlated with infravesical obstruction in men with BPO [18].

27.3.1 Response to Obstruction

The bladder’s response to obstruction can be characterised in two ways. Changes that lead to detrusor instability (i.e. poor compliance) give rise to symptoms of frequency, nocturia, and urgency. This can then be followed by decreased detrusor contractility, which manifests clinically by poor stream, hesitancy, intermittency, and increase in residual urine [19].

The bladder responds to outflow resistance by muscular hypertrophy, increasing the thickness of muscle fibres and infiltration of collagen between the fibres leads to diverticular formation (Figures 27.4 and 27.5). The texture of the wall of the bladder changes from a fine felt to a course net, through the gaps of which the urothelium bulges out. The interior of the bladder develops a characteristic trabeculated appearance with saccules and diverticula formation from the herniated urothelium.

These structural changes affect the bladder function. There is an increase in voiding pressure within the bladder, unwanted contractions occur irrespective of bladder filling, and detrusor instability, leading to storage symptoms.

Failure to relieve the outflow obstruction will eventually lead to detrusor failure. Detrusor failure leads to inability to empty the bladder completely, leading to residual urine that can give rise to complications.

27.4 Complications of BPH

Diverticula are herniations of bladder mucosa between hypertrophied bars of detrusor muscle. Once prostatic obstruction has been corrected, they can usually be ignored; however, they should be surgically removed when stones or cancer develops within them or when they are so large that they fill up whenever the detrusor is trying to expel urine and so that symptoms persist (Figure 27.6).

---

**Figure 27.4** Diagram showing the radiographic appearances of the normal and the obstructed bladder.
Normal Hypertrophy with diverticulum formation
Detrusor failure with chronic retention
(a) Atonic detrusor
Hypertrophied detrusor
Saccules
Diverticulum
(b) Progressive failure of the detrusor.

Figure 27.5 (a) Diagram showing changes in the detrusor secondary to outflow obstruction. The urothelium is herniated between gaps in the trabeculae to form saccules and diverticula. The ureters are hooked up and obstructed. (b) Progressive failure of the detrusor.
The incidence of haematuria in patients with BPE is around 2.5%, and recent evidence suggests that those patients who develop haematuria have a higher microvascular density higher compared with controls [20]. Of course, when a patient with BPE presents with haematuria, the first concern is to rule out bladder cancer and upper tract causes. In some cases, benign enlarged prostates may bleed severely and bleeding may be the principle indication for intervention using medical (5-ARIs) or surgical (transurethral resection of prostate [TURP]) treatments.

Urinary tract infection (UTI) in residual urine is seldom cured unless obstruction is relieved; Hunter et al. reported an incidence of UTI of 5.2% in patients with BPH. The Medical Therapy of Prostate Symptoms (MTOPS) study reported an incidence of 0.1/100-year in patients treated with placebo [20].

The incidence of bladder stones was reported to be 0.7% in a cohort of Spanish men with BOO [21]. Stones that develop in residual urine either become rounded like pebbles or assume the characteristics of a Jack-stone.

The term ‘silent obstruction’ has been used to describe relatively asymptomatic patients who develop a variable degree of renal impairment as a result of BOO whenever the voiding pressure in the bladder exceeds about 40 cm H₂O. Fortunately, the incidence of this clinical picture is low at 2.4% [21].

The yearly risk for developing acute urinary retention (AUR) is about 0.6–1.8% [22]. From the clinical and prognostic point of view, spontaneous AUR should be separated from precipitated AUR. Precipitated AUR occurs after a triggering event such as anaesthesia, sympathomimetic, or anticholinergic drugs and constipation. All other AUR episodes are classified as spontaneous; after spontaneous AUR, 15% of patients have another similar episode and a 75% will require surgery. In precipitated AUR, on the other hand, only 9% have a further episode and only 26% will require surgery [1, 23]. Armitage reported that there was higher incidence of mortality rate in the first year after AUR compared to the general male population [24]. This was linked to the fact that as men got older their comorbidities increased contributing to the higher mortality rates (Table 27.1).

### 27.4.1 Chronic Retention of Urine

These patients present with a distended palpable bladder; renal function tests should be requested along with ultrasound of the upper urinary tract because the patient may have hydronephrosis, secondary to BOO with associated nephropathy. Obviously, these patients must be managed by inserting an indwelling urethral catheter, but one must be cautious about the possibility of postobstructive diuresis, which may lead to dehydration and electrolyte disturbances due to loss of sodium. Close monitoring of renal function and urine output are required as intensive fluid, and salt replacement may be indicated. Lying and standing blood pressure may be helpful until the patient’s urine output and overall condition stabilises. Following the relief of bilateral ureteric obstruction, tubular function usually recovers within two weeks, but full recovery of glomerular function may take up to three months. In this group of patients, catheter drainage should continue and surgery should be postponed until renal function recovery has been demonstrated because it has been proven that patients with renal failure have more complications after TURP (25 vs. 17%), and the mortality rate is increased sixfold [25].
There is a complex relationship between BPH, LUTS, BPE, and BOO. An understanding of this is important when managing a patient who presents with LUTS, to aid recognition of patients who have LUTS with or without BPE and with or without BOO. This relationship can be described using Hald rings (Figure 27.1). It shows the inter-relationship among LUTS, BOO, and BPE. BPE may be associated with symptoms with or without BOO; it may also be associated with obstruction with or without symptoms. Symptoms may occur with obstruction with or without BPE. It is the patient with all three (BPE, BOO, and LUTS) who will benefit maximally from therapy.

Autopsy studies showed that BPH never occurs before the age of 30 and progressively increases until it reaches a prevalence of 90% for men in their 80s [26].

A UK study which defined symptomatic BPH as the presence of enlarged prostate with a volume of more than 20ml, with LUTS or reduced urinary flow rate Q_max less than 15 ml s⁻¹ estimated the prevalence of BPH as 13.8% in 1000 members of a population ages 40–49 years (13.8%) and 50–59 years (24%), rising to 430 in 1000 members men ages 60–69 years (43%) [27]. While histological prevalence was more dramatic: <30 years (0%), 41–50 years (23%), 51–60 years (42%), 61–70 years (71%), 71–80 years (82%), and > 80 years (>88%) [28].

Studies of total prostate volume of men in their 30s revealed that total prostate volume averaged 25 cm³, and this increased to 45 cm³ for men in their 70s. A simple guide is that 50% of men will develop histologic BPH by the age of 60 and that 50% of men with histologic BPH develop clinical BPE, whilst 50% of men with BPE develop symptoms require treatment. A 50-year old (man) has a 25–30% lifetime chance of requiring surgical intervention for LUTS associated with BPH.

It has been shown that the concept of disease progression is also a reality. Indeed Lee et al. [29] reported the natural history of LUTS in a large cohort of symptomatic men followed for five years without treatment, which demonstrated that both storage and voiding LUTS get significantly worse with time [27].

Table 27.1 (a) One-year mortality rates after acute urinary retention (b) One-year mortality rates after acute urinary retention in patients with and without significant comorbidities.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Spontaneous acute retention</th>
<th>Precipitated acute retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>4.1%</td>
<td>9.5%</td>
</tr>
<tr>
<td>55–64</td>
<td>5.3%</td>
<td>12.5%</td>
</tr>
<tr>
<td>65–74</td>
<td>9.7%</td>
<td>17.8%</td>
</tr>
<tr>
<td>75–84</td>
<td>17.9</td>
<td>28.7</td>
</tr>
<tr>
<td>&gt;85</td>
<td>32.8%</td>
<td>45.4%</td>
</tr>
<tr>
<td>Any age</td>
<td>14.7%</td>
<td>25.3%</td>
</tr>
<tr>
<td>b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>1.8% without comorbidity</td>
<td>3.4% without comorbidity</td>
</tr>
<tr>
<td></td>
<td>14.7% with comorbidity</td>
<td>24.3% with comorbities</td>
</tr>
<tr>
<td>55–64</td>
<td>2.3% without comorbidity</td>
<td>4.5% without comorbidity</td>
</tr>
<tr>
<td></td>
<td>16.7% with comorbities</td>
<td>26% with comorbities</td>
</tr>
<tr>
<td>65–74</td>
<td>5.3% without comorbidity</td>
<td>8.1% without comorbidity</td>
</tr>
<tr>
<td></td>
<td>21% with comorbidity</td>
<td>30% with comorbities</td>
</tr>
<tr>
<td>75–84</td>
<td>12.5% without comorbidity</td>
<td>18.1% without comorbidity</td>
</tr>
<tr>
<td></td>
<td>28.8% with comorbities</td>
<td>40.5% with comorbities</td>
</tr>
<tr>
<td>&gt;85</td>
<td>27.3% without comorbidity</td>
<td>38% without comorbidity</td>
</tr>
<tr>
<td></td>
<td>44.3% with comorbities</td>
<td>54.7% with comorbities</td>
</tr>
<tr>
<td>Any age</td>
<td>9.9% without comorbidity</td>
<td>16.1% without comorbidity</td>
</tr>
<tr>
<td></td>
<td>27.2% with comorbities</td>
<td>38.1% with comorbities</td>
</tr>
</tbody>
</table>

27.5 Epidemiology and Natural History of BPH

There is a complex relationship between BPH, LUTS, BPE, and BOO. An understanding of this is important when managing a patient who presents with LUTS, to aid recognition of patients who have LUTS with or without BPE and with or without BOO. This relationship can be described using Hald rings (Figure 27.1). It shows the inter-relationship among LUTS, BOO, and BPE. BPE may be associated with symptoms with or without BOO; it may also be associated with obstruction with or without symptoms. Symptoms may occur with obstruction with or without BPE. It is the patient with all three (BPE, BOO, and LUTS) who will benefit maximally from therapy.
(0.2 ml s\(^{-1}\)), and a mean prostate growth of 2%/year (1–2 ml) [30].

Another study suggested that prostatic enlargement alone did not determine symptom severity, but the volume of transitional zone was the factor most strongly correlating with symptom severity [31]. This finding is consistent with Watanabe's theory of PCAR because the relationship between PCAR and BOO is also independent of total prostate volume. The transition zone index (TZI) is the ratio of the transition zone to total prostate volume, which has been shown to correlate with the extent of BOO. It should be noted that the total prostate volume does not correlate with the extent of BOO [32].

From these observations, it is clear that significant prostatic enlargement, elongation of transitional zone, and resulting tension within the prostate or prostate capsule are determinant factors of LUTS.

Many studies have assessed the relationship between LUTS and BOO. Netto et al. [33] performed urodynamic studies on 217 patients who had moderate and severe LUTS and identified obstruction in 53% and 83%, respectively. In another urodynamic study on 222 patients who had a clinical diagnosis of BPH and a maximum flow rate less than 15 ml s\(^{-1}\), 80% were obstructed [34]. These studies show that urodynamic evidence of BOO is prevalent in men who have moderate to severe LUTS.

AUR should not be viewed as an irreversible result of the bladder response to longstanding obstruction because many patients presenting with AUR have more than adequate detrusor function, with evidence of a precipitating event leading to obstruction. The overall risk of AUR has been estimated to be 0.5–2.5%/year; however, the risk is cumulative and increases with age and symptom severity. The MTOPS study [20] showed that the incidence of AUR increased threefold in patients who had a prostate volume greater than 40 ml. Furthermore when PSA levels were more than 1.4 ng ml\(^{-1}\), there was an eightfold increase in the incidence of AUR. Jacobsen et al. [35] estimated the risk of AUR for a 60-year old (man) who had moderate to severe symptoms was 13.7% over a 10-year period. It also identified that an age increase from fourth to seventh decade (eightfold), IPSS >7 (threelfold), flow rate <12 ml s\(^{-1}\) (fourfold), and postvoid residual (PVR) >50 ml (threelfold) increased the risk of AUR (Table 27.2) [36].

### 27.6 Investigations

The investigations for patients with LUTS start, as always, with a thorough history and clinical examination.

#### 27.6.1 History

History should include an assessment of the type of LUTS (storage or voiding), their severity, and importantly the impact on their quality of life (QoL) and bother. It is important to assess patient general medical history to help identify causes of LUTS and if there are any associated comorbidities (e.g. congestive heart disease, diabetes, Parkinson disease, etc.). A thorough review of the patient’s medications may also help identify contributing factors. Whilst there is little to no correlation between symptoms or urodynamics and prostate size [37–39], LUTS do correlate with urodynamically proven obstruction (correctly predicting nearly 90% of obstructive cases). Thus assessment of LUTS using validated self-assessed questionnaires such as the IPSS is useful [40]. Elicitation of red flag symptoms such as haematuria, incontinence, and dysuria may necessitate urgent investigations.

#### 27.6.2 Examination

Physical examination should focus on patient’s symptoms and comorbidities, including examination of the abdomen, external genitalia (i.e. meatal stenosis or phimosis), and digital rectal examination (DRE) of the prostate to assess for prostate cancer (PCA) and prostate size. Prostate size is estimated by feeling from side to side of

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**Table 27.2** Natural history of benign prostatic hyperplasia to cause acute urinary retention or disease progression.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Reference</th>
<th>Compared reference</th>
<th>Risk-fold increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70–79 years</td>
<td>40–49 years</td>
<td>8×</td>
</tr>
<tr>
<td>Qmax (ml s(^{-1}))</td>
<td>&lt;12</td>
<td>&gt;12</td>
<td>4×</td>
</tr>
<tr>
<td>PSA</td>
<td>&gt;1.4</td>
<td>&lt;1.4</td>
<td>3×</td>
</tr>
<tr>
<td>Prostate volume (measure by TRUS) (ml)</td>
<td>&gt;30</td>
<td>&lt;30</td>
<td>3×</td>
</tr>
<tr>
<td>Severity of LUTS (IPSS measured)</td>
<td>&gt;7 (moderate to severe LUTS)</td>
<td>&lt;7 (mild LUTS)</td>
<td>3×</td>
</tr>
<tr>
<td>PVR (ml)</td>
<td>&gt;50</td>
<td>&lt;50</td>
<td>3×</td>
</tr>
</tbody>
</table>

IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen; PVR, postvoid residual; Qmax, peak flow rate; TRUS, transurethral ultrasound.
the prostate the number of index finger widths, where one finger-breath is said to represent approximately 15g. However, it is easier to estimate the size as small, medium, or large whilst recognising that DRE leads to an underestimation of prostate size [1]. A neurological examination should be undertaken if there is any suspicion that neurological disease that may be contributing to the symptoms (lower extremity neuromuscular function and anal tone).

27.6.3 Objective Assessment of LUTS

IPSS is a validated objective assessment of patients’ LUTS, which has good test–retest reliability and good internal consistency [41, 42]. Completion of the questionnaire yields a total score ranging from 0 to 35 (i.e. 1–7 for minimal symptoms, 8–19 for moderate symptoms, and 20–35 for severe symptoms). The IPSS correlates well with postoperative outcomes from BPH surgery where a high preoperative scores is associated with a good outcome; however, there are weak correlations with prostate volume, flow rate (FR), PVR, and age [43]. The IPSS also incorporates an assessment of the impact of LUTS on the QoL of the patient. Assessment of QoL is important because it helps in making a decision on management for their LUTS [44].

27.6.4 Urinalysis

A urinalysis should be performed to detect blood, glucose, leucocytes, and nitrites. A positive urinalysis for infection should be treated and may well account for the patients LUTS. Haematuria on urinalysis should be investigated with a flexible cystoscopy and upper tract imaging.

The previous four investigations (i.e. history, physical examination, validated questionnaire, and urinalysis) are all recommended by current international guidelines [45].

27.6.5 Frequency or Voiding Volume Chart

A 24- to 72-hour diary of the patients’ fluid intake and voiding history, including approximate volumes voided, should be done. These are simple, cheap, and provide some objective information of voiding and are recommended during initial assessment of male LUTS [4]. Measurements can also elucidate the presence of polyuria and nocturnal polyuria (which may be the cause of symptoms).

27.6.6 Blood Tests

Serum creatinine levels should only be measured if renal impairment as a result of BOO is suspected (i.e. palpable bladder, high PVR and incomplete emptying of the bladder, and rarely signs and symptoms of renal failure) [4]. Routine creatinine measurement is not currently recommended as an analysis of clinical trials involving more than 10,000 patients found the silent rate of renal impairment to be less than 2% [46]. With more recent trials, such as the MTOPS study, showing the risk of developing renal failure in men with LUTS to be less than 1% [47].

Prostate-specific antigen (PSA) testing should be offered to patients after thorough advice and counselling (Table 27.3) and time to decide only if they have LUTS suggestive of BOO secondary to BPE, if their prostate feels abnormal on DRE, or they are concerned about PCa. In patients with LUTS, the PSA is predictive of the likelihood of disease progression due to BPH, with a PSA >1.4 ng ml⁻¹ putting patients at an increased risk of disease progression [48].

Table 27.3 Prostate-specific antigen counselling guidelines.

- Need to highlight potential disadvantages of an abnormal result.
- Need to balance risks and benefits of having clinically significant disease diagnosed.

You must counsel asymptomatic men about the following:
- Cancer will be identified in <5% of men screened.
- Benefits of screening remain controversial.
- Sensitivity is 80%; there is no level of PSA at which prostate cancer can be excluded.
- Specificity is 40–50%; a false-positive is possible (UTI, age ranges, etc.).
- If elevated, diagnostic pathway (DRE, TRUS biopsy & risks: pain, infections, bleeding – each 0.5%)
- TRUS biopsy may miss cancer.
- May need repeat biopsy.
- Treatment may not be necessary.
- Treatment may not be curative.
- Decreased QoL as a result of treatment complications.

DRE, digital rectal examination; PSA, prostate-specific antigen; QoL, quality of life; TRUS, transurethral ultrasound; UTI, urinary tract infection.
(Qmax): <40 years: >21 ml s\(^{-1}\); 40–60 years: >18 ml s\(^{-1}\); and >60 years: >13 ml s\(^{-1}\). The urinary flow test is unable to distinguish between a poorly contractile bladder and BOO. To illustrate this, peak flow rates >15 ml s\(^{-1}\) have been shown to have urodynamic proven BOO in 30% of patients, while those with flows 10–15 ml s\(^{-1}\) have BOO in 60%; however, a FR <10 ml s\(^{-1}\) up to 90% have urodynamic proven BOO [49] (Figure 27.7). This is especially important to establish prior to a surgical intervention as patients whose symptoms are caused by BOO, the likelihood a TURP alleviates their symptoms is >90%, whereas those without BOO will be nearly 60% [50].

PVR is calculated with abdominal ultrasound after the patient has voided by multiplying the length, width, and height of the measured bladder \(\times 0.7\) (i.e. the ellipsoid area calculation). It is, however, not reproducible, and there is a large inter-rater variability. Pretreatment PVR is very weakly associated with treatment outcome. There is inconsistency amongst guidelines with regard to the level at which intervention should be undertaken (200 ml for European Association of Urology, 300 ml for the British Association of Urological Surgeons (BAUS) and 350 ml for American Urological Association (AUA). In all patients with persistently elevated PVR >200 ml bladder dysfunction is likely, and therefore, upper tract imaging (renal ultrasound) should be undertaken to exclude upper tract deterioration (e.g. hydronephrosis).

Urodynamics can categorise the degree of obstruction and can differentiate between patients with a poorly contractile bladder and those with BOO. The purpose of offering urodynamics is to detect those patients without clear BOO who have the lowest benefit from surgery. The Abrams–Griffiths number can also help to determine if the patient has BOO [51].

The routine use of urodynamics for all patients before surgery is unrealistic and expensive; however, it is of value in certain subsets of patients [52]. Therefore, indications for urodynamic test are: (i) patients who are going surgery and have an equivocal FR <150 ml or Qmax >15 ml s\(^{-1}\) (ii) <50 years old or >80 years old, (iii) Patients with a PVR >200–300 ml, (iv) those with a suspicion of neurologic bladder dysfunction (e.g. Parkinson disease, history of spinal injury, multiple sclerosis, etc.) (v) Previous radical pelvic surgery or unsuccessful previous BPH treatment (i.e. medical or surgical).

27.7 Management

The three main treatment aims in patients with BPE and LUTS are [45, 53]:

1) Relief of symptoms.
2) Improvement in QoL.
3) Preventing disease progression.

The treatments offered to patients depend on the balance between the severity of patients’ symptoms and degree of bother and their preferences with regard to outcome and complications.

There has been a large shift in treatment patterns for patients with LUTS in the last one to two decades from one of surgical intervention to medical management [54]. There has been a decrease in the number of TURP being performed as a result of increased use of medical treatment, with up to a 60% reduction in TURP rates in certain parts of the world. [54].

Treatment modalities available:

1) Watchful waiting and conservative treatment
2) Medical management:
   3) Monotherapy
      a) Combination therapy
4) Surgical management

27.7.1 Watchful Waiting

Watchful waiting (WW) [55–57] is a management option where the patient is monitored by their doctor without active intervention for LUTS. The key to this management option is that patients and doctors use conservative interventions until symptoms progress or complications of BPE arise. It has been established that
despite BPH being a progressive disorder, many patients (i.e. more than two-thirds) do not need surgery. Roughly speaking, more than one-third of patients symptoms tend to improve, more than one-third stay the same, and a less than one-third worsen [58].

Conservative interventions [59] include:

- Explaining about postmicturition dribble and how to perform urethral milking.
- Discussing containment products to manage storage LUTS (urinary incontinence).
- Storage LUTS, suggestive of overactive bladder (OAB), can benefit from supervised bladder training, advice on fluid intake, lifestyle advice, and if needed, containment products.
- Discussing external collecting devices (e.g. sheath appliances and pubic pressure urinals) for managing storage LUTS (particularly urinary incontinence) in men before considering indwelling catheterisation.
- Discussing intermittent bladder catheterisation before indwelling urethral or suprapubic catheterisation to men with voiding LUTS that cannot be corrected by less invasive measures.
- Discussing long-term indwelling urethral catheterisation for whom medical management or surgery is not appropriate or unwanted or who are unable to manage intermittent self-catheterisation.

Lifestyle modifications include:

- Reduction of fluid intake in the evening
- Avoidance of irritant substances (e.g. caffeine, alcohol, smoking, etc.)
- Timed or organised toilet scheduling and bladder training
- Altering patient medications or time of delivery (e.g. diuretics, decongestants, antihistamines, and antidepressants)
- Treatment of constipation.

Education about the disease, natural history of it, potential complications and reassurance are also important. Watchful waiting is recommended for patients with mild symptoms (IPSS <7) or moderate to severe symptoms but not reduction is QoL [52].

27.7.2 Medical Management

a) Herbals

In Europe, herbal medications have been used to treat LUTS for many years [60], with most interest in Saw Palmetto (Serenoa repens). Indeed, an early meta-analysis demonstrated improvements in peak FR and nocturia in comparison to placebo [61]. However, an updated meta-analysis with long-term outcome data recently demonstrated that there was no difference in symptom score reduction or peak flow rate improvement between S. repens and placebo [62]; hence, its use has not been recommended [45].

b) Alpha-blockers (α-blocker)

The mode of action of α-blockers is to block the α-receptors located in the prostatic smooth muscle and bladder neck that mediate contraction and thereby reduced flow and the development of LUTS. Blocking these receptors mediates relaxation of the tissues, thereby easing the flow of urine through the lower urinary tract [63]. Some of the α-blockers have also been shown to cause apoptosis of the prostatic epithelium, which may also contribute to their effect [64].

There are two main types of α-receptors (α1 and α2 receptors). The α1 receptors are located mainly in the urinary tract in particular the α1a subtype; however, the α2 receptors are also located elsewhere in the body including blood vessels which accounts for some of the unwanted side-effects of α-blockers, especially the less selective ones such as phenoxypbenzamine [65, 66]. The different types depend on their uroselectivity; uroselective α1a-blockers include Tamsulosin and alfuzosin and nonselective α1-blockers are doxazosin and terazosin [67].

There are many α1-blockers now available, and each have similar efficacy for treatment of LUTS but have differing side-effect profiles. The main side effects of α-blockers are mild, occur in about 15% of patients, and include (more common with non-neuroselective blockers): orthostatic hypotension, headache, dizziness, asthenia, drowsiness, and ejaculatory problems (i.e. retrograde ejaculation, more common with the uroselective blockers) [47]. Tamsulosin has a lower rate of orthostatic hypotension but a higher likelihood of ejaculatory problems (i.e. retrograde ejaculation) than the other α-blockers. Intraoperative floppy iris syndrome during cataract surgery is an important side effect to bear in mind when commencing patients on α-blockers especially tamsulosin which can be seen in up to 86% of patients and about 15% with alfuzosin [68, 69]. There is progressive miosis (i.e. pupil constriction) regardless of dilatory use, billowing of the flaccid iris, and iris prolapse into the incision site that can lead to posterior capsular rupture with vitreous loss and intraocular pressure rise. Though its effects can be prevented with use of atropine, it is best to avoid α-blocker use in all patients contemplating cataract surgery. However, in experienced hands, intraoperative floppy iris syndrome can be anticipated and compensatory techniques employed (such as topical atropine preoperatively, iris retractors, pupil expansion ring, or use of viscoadaptive ophthalmic viscosurgical device with reduced fluidic parameters) to prevent complications leaving excellent visual outcomes [67].
All α1-blockers have a rapid onset of action (48 hours) and a similar efficacy producing an increase in peak flow rate of 2–3 ml s⁻¹ and a 4–6 point improvement in IPSS score. Though they do not alter the natural history and long-term disease progression (i.e. progression to AUR or need for surgery), they can significantly reduce symptoms by at least 30–40% [47, 70].

Alpha-blockers are recommended medical therapy for patients with moderate (8–19 on IPSS) to severe (20–35 on IPSS) LUTS. Patients should be initially be reviewed after 4–6 weeks of therapy and then every 6–12 months [4].

c) 5-alpha reductase inhibitors (5-ARIs):

There are two drugs available in this class, finasteride, which is a type II 5α-reductase inhibitor, and dutasteride, which is a type I & II 5α-reductase inhibitor [71]. These 5-ARIs block the action of the 5α-enzyme and therefore the conversion of testosterone to DHT, the more potent ligand.

Finasteride causes a reduction in DHT by 75%; however, dutasteride causes a reduction of DHT by 95% [22]. This causes atrophy of the prostatic glandular epithelial cells and leads to a 20–30% reduction in prostatic volume; however, 5-ARIs have a slow onset of action varying from 2 to 12 weeks, with peak effect after 6–9 months [72]. Unlike α1-blockers, 5-ARIs prevent BPH disease progression, and in addition, they lead to a 2–3 point improvement in IPSS symptom scores and increase peak flow rate by 1.5–2.5 ml s⁻¹ [22, 47, 73].

5-ARIs reduce the incidence of AUR and the need for surgical intervention by around 50% compared to placebo (i.e. relative-risk reduction 57%) [22, 47, 73]. However as the incidence of AUR is low, translating, the absolute risk reduction to only 4%, or numbers needed to treat to prevent one AUR episode is 25 [22]. Similarly, there was a 55% relative-risk reduction for need for surgical intervention as compared to the placebo groups. Nonetheless, 5-ARIs are recommended for use in patients with LUTS and if patients are at high risk of disease progression but who do not have bothersome symptoms to prevent disease progression [74]. Furthermore, 5-ARIs can lower the microvessel density and VEGF, leading to a reduction in haematuria complications secondary to BPH, in addition to theoretically reducing bleeding during and after TURP [75].

5-ARIs tend to reduce PSA by about 50%, and evidence suggests that it reduces the incidence of PCa by nearly 25% for finasteride and a relative-risk reduction of 40% for dutasteride, albeit both with an observed increase in the risk of high-grade tumours [76]. Theories for these observations include 5-ARIs reduce the size of the prostate and increase the sensitivity of PSA for the detection of PCa, and as a consequence increasing the detection of higher grades of cancer, (i.e. 5-ARIs have a lesser reduction of PSA level in high-grade PCa, leading to more biopsy and increased high-grade detection). Alternatively, others have advocated that 5-ARIs themselves change tissue architecture by inducing histological changes leading to higher-grade cancers. Nonetheless, ongoing trials aim to answer these questions.

Adverse events are usually well tolerated and include erectile dysfunction, altered libido, ejaculatory disorders (low-volume ejaculate), and rarely, gynecomastia and breast tenderness.

d) Combination Therapy (α-blocker and 5-ARIs)

The MTOPS trial, which randomised 3047 men to placebo, doxazosin, finasteride, or combination of doxazosin and finasteride with four to five years follow-up showed a clear advantage for combination therapy in reducing the risk of disease progression (i.e. relative-risk reduction 66%), risk of AUR (relative-risk reduction 81%), and the need for surgery (relative-risk reduction 67%) [47].

Similarly, the CombaAT trial, randomised 4844 men to either dutasteride, tamsulosin, or combination of the two with a four-year follow-up [77]. Combination therapy was significantly better in reducing the risk of disease progression (i.e. relative-risk reduction 44%), risk of AUR (relative-risk reduction 68%), and the need for surgery (relative-risk reduction 71%). Combination therapy also provides greater symptom improvement benefit than either monotherapy regimens alone. Hence, combination therapy may be recommended in patients with bothersome moderate to severe LUTS who are at high risk of disease progression [4].

Combination therapy has similar adverse event profiles to other treatment modalities [44].

e) Anticholinergics

Patients with symptoms suggesting OAB can benefit from combination therapy of a α1-blocker and an anticholinergic if storage symptoms have not improved with monotherapy alone [4, 78].

f) Phosphodiesterase-5 inhibitors:

There has been some benefit in LUTS improvement with the use of phosphodiesterase-5 (PDE-5) inhibitors [79]. However, these are still considered experimental with ongoing trials aimed at establishing an evidence-based practice and a linkage between LUTS and erectile dysfunction.
27.7.2.1 Acute Urinary Retention and Its Management
AUR is the most common urological emergency and is a significant burden on urology services around the world [80]. It affects between 2.2 and 6.8 per 1000 men more commonly in older men with 10% of men older than 80 years of age having an episode of AUR [36]. The impact on QoL is similar to a bout of renal colic [81], and the cost of hospital admission ranges between $2500 and $7500 if a TURP is performed [82]. AUR is also associated with an increased risk of mortality within a year of occurring. In men 74–84 years of age, mortality within the year is between 12.5 and 28.8% depending on comorbidities (Table 27.1) [24].

The management of AUR starts with catheterisation to relieve the patient’s discomfort. The most common route in the UK is urethral catheterisation with 98% of urologists reporting this method [83]. Suprapubic catheterisation (SPC; Figure 27.8) is an alternative method. Advantages of SPC include avoiding damage to the urethra, bladder neck, reduced catheter bypassing, and a lower rate of UTI. However, it has a reported 2.8% risk of bowel injury and 1.8% risk of mortality, consequently in patients with previous abdominal surgery or if the bladder is not palpable blind SPC insertion is not recommended [84, 85].

The next step in the management is to take a thorough history and examination to try to ascertain if the cause of AUR is likely to be secondary to BPE. A DRE allows the urologist to assess for BPE or PCa. Urinalysis should be performed to exclude a UTI or haematuria, whilst blood tests to assess renal function (i.e. urea, creatinine, and estimated glomerular filtration rate) should be performed. If these tests indicate a cause other than BPE to
be the likely cause of the AUR then urodynamics (e.g. functional bladder disorders), cystoscopy (e.g. urethral stricture), or CT or MRI of the nervous system (e.g. neurological disorder) should be performed [86].

Then it should be determined whether hospital admission is required or if an ambulatory care programme is suitable for the patient. Indications for hospital admission include: urosepsis, gross haematuria, residual volume > 11, post-catheterisation diuresis, unusual symptomatology, and those unable to cope with a urethral catheter or ambulatory care programme [82, 87]. Worldwide hospitalisation rates for AUR vary wildly with only 1.7% in Algeria to 100% in France [88].

The timing of the trial without catheter (TWOC) should be at 48–72 hours because it has been shown that after 72 hours of catheterisation the complication rate associated with catheterisation significantly increases, most notably haematuria, urosepsis, and urine bypassing around the catheter [89]. Despite this, internationally and in most instances logistically and practically TWOCs take place after five days of catheterisation [90].

The role of medications in AUR is an important consideration. In 1976, it was first identified by Caine and colleagues that alpha-blockers improve the success rate of TWOC [91]. Since then, five randomised controlled trials and a Cochrane review have been performed. Four randomized controlled trials (RCTs) compared alfuzosin to placebo with one comparing tamsulosin to placebo. Four of the trials favoured the use of alpha-blockers over placebo for success rates of TWOC, corroborated by the Cochrane review, [92].

The largest and landmark RCT was the ALFAUR study where 360 patients were randomised to either placebo or 10 mg of alfuzosin daily [93]. A TWOC was performed at three days, and after a successful TWOC, all patients were randomised to receive a further six months of alfuzosin or placebo. This study showed that at six months, the alfuzosin group had a higher TWOC success rate (i.e. 61.9% vs 47.9%) and a lower rate of surgery requirement (i.e. 17.1% vs 24.1%) compared to placebo. However, a study following patients for a further six years after an episode of AUR managed in this way found that the majority (76%) of those receiving alfuzosin eventually required surgery or had another episode of AUR [23].

These results along with the results of MTOPS and CombAT indicate that alpha-blockers either pre- or post-AUR in patients with BPE merely delay the need for surgery with no real effect on altering disease progression, and therefore, we feel that physicians should always strongly consider the use of 5-ARIs (to prevent disease progression in high-risk patients or those who have had an AUR episode) or alternatively early surgery (TURP) [20]. A management algorithm used locally in our unit is shown in Figure 27.9.

### 27.7.2.2 Chronic Urinary Retention

Is divided largely into two separate groups, high-pressure chronic retention (HPCR), where there is high detrusor pressure at the end of micturition, and low-pressure chronic retention (LPCR) [94, 95]. The constant raised pressure in HPCR leads to back pressure in the kidneys and resultant hydronephrosis and ultimately renal impairment. In LPCR, patients have large-volume bladders, which are compliant and tend to have low detrusor pressures, low FRs, and high residual volumes. In both condition LUTS are uncommon or mild and can be affected by nocturnal enuresis (e.g. drop in urethral resistance during sleep) [96].

Presentation of men with chronic urinary retention is varied and can be asymptomatic or low-volume micturition, increased frequency or hesitancy, nocturnal enuresis, a palpable but painless bladder, or signs of chronic renal impairment [95, 97].

Initial assessment of these men should involve a urinalysis for signs of infection, a renal panel blood test (i.e. urea and electrolytes). In patients with HPCR, renal ultrasound can be performed to demonstrate hydronephrosis. PSA should be avoided because this will be elevated from chronic urinary retention.

Management is somewhat complex and is mainly dictated by the presence of renal impairment (Figure 27.10).

#### 27.7.2.3 Polyuria and Nocturnal Polyuria

Polyuria or nocturnal polyuria is a syndrome where >33% of the total urine output occurs during the night [98]. It is essential to get patients to complete a three-day voiding diary which incorporates the volumes of voided urine; this enables the calculation of ratio of daytime to night-time urine volume voided.

The causes of nocturnal polyuria include congestive heart failure, obstructive sleep apnoea, nephrotic syndrome, autonomic neuropathy, chronic kidney disease, venous insufficiency, neurologic diseases like Parkinson and Alzheimer diseases, and idiopathic [98].

Oedema-forming states lead to nocturnal polyuria due to the mobilisation of the oedema during recumbency which the kidneys process and produce urine at night. Obstructive sleep apnoea is associated with atrial natriuretic peptide (ANP) release. Neurologic conditions cause a change in the diurnal secretion of ANP and antidiuretic hormone (ADH) leading to increased retention of urine and increased production of urine at night. In chronic kidney disease, the kidneys are maximally concentrating the urine and this leads to an increased urine production at night. However, in many cases, there is no definitive cause that can be found.

The mainstay of evaluation is with a three-day voiding diary with volumes voided to be included. This is followed by a thorough history and examination focused to the causes listed previously. If bladder dysfunction is
Figure 27.9 Acute urinary retention management algorithm. BOO, bladder outflow obstruction; BPE, benign prostatic enlargement; DRE, digital rectal examination; HPCR, high-pressure chronic retention; SPC, suprapubic catheterisation; TWOC, trial without catheter; UTI, urinary tract infection.

Figure 27.10 Flow chart of chronic retention management. HPCR, high-pressure chronic retention; ISC, intermittent self-catheterisation; LPCR, low-pressure chronic retention; LTC, long-term catheterisation; LUTS, lower urinary tract symptoms; SPC, suprapubic catheterisation; TURP, transurethral resection of prostate; UTIs, urinary tract infections.
suspected, then this can be treated or further investigation started with urodynamics. Targeted investigations for other causes can be performed also.

The evidence base for the treatment of nocturnal polyuria is limited with only a few RCTs. Conservative measures such as fluid restriction six hours before bedtime has limited affect. Loop diuretics taken 6–10 hours before bedtime have also been shown to have some limited impact.

The medication with the greatest evidence for its use is Desmopressin (a synthetic analogue of vasopressin), which works by mimicking the actions of ADH (reduces urine production). There have been 2 placebo controlled RCTs assessing the effect of Desmopressin on nocturnal polyuria. The largest by Wang et al. [99] was more than 12 months and showed a reduction in the number of times men needed to void at night of 2 less than placebo, with NNT = 2. There were significant improvements in sleep duration and QoL. While Rezakhaniha et al. [100] have shown a reduction in the number of times voiding at night and increased duration of sleep with desmopressin 100 mcg per night compared with placebo.

Important potential side effects include hyponatraemia (14%), headache, nausea, dizziness, and peripheral oedema. This medication is currently not licenced for the treatment of nocturnal polyuria.

27.8 Surgical Management

Surgical management is recommended for patients with BPH or BPE related complications: [45]

1) LUTS refractory to medical therapy
2) Recurrent UTIs
3) BPH or BPE – related visible haematuria refractory to treatment (5-ARIs)
4) Renal insufficiency secondary to BOO
5) Bladder stone(s)
6) Recurrent urinary retention
7) Urinary retention who have failed at least one trial without catheter

Patients who refuse medical therapy or have unacceptable side effects from medications are also candidates for surgery.

The gold standard of surgical management is TURP, except for patients with very small prostates where transurethral incision of the prostate (TUIP) or very large prostates where open (i.e. Millin) prostatectomy remains the gold standard [45]. New techniques such holmium laser enucleation of the prostate (HOLEP) are becoming a more accepted alternatives for both TURP and Millin prostatectomy. Numerous minimally invasive techniques are also being evaluated.

a) Standard Treatments:
   i) TUIP

The bladder neck is divided through a resectoscope, either under general or local anaesthesia, best suited for prostates <30ml. The incision is made with a diathermy electrode or laser which is said to cause neither pain nor bleeding (Figure 27.11).

Just where to cut through the bladder neck is a matter of surgical preference and training. Some surgeons performing only one incision and others two. Wherever the bladder neck is incised, the patient must be warned of retrograde ejaculation.

ii) TURP

Since being pioneered in 1909 and since its use flourished after the invention of the resectoscope in the 1940s, TURP has been the mainstay procedure for urologists [101]. TURP is still considered the benchmark and standard for all treatments for BPH and BOO with prostates >30–< 100ml. The purpose of the operation is to remove enough of the obstructing tissue from the cranial inner zone of the prostate to allow the bladder to empty freely. TURP has been shown to improve symptoms in

Figure 27.11 Bladder neck incision. A 6 o’clock incision avoids damage to the penile neurovascular bundles. The incision goes right through the bladder neck which is seen to gape widely.
more than 90% of patients and improve the mean IPSS score by 62% after 12 months postoperatively and improve peak flow rate by 120% (9.7 ml s\(^{-1}\)) [102]. The requirement for repeat surgical intervention (redo TURP or other procedures) within 10 years is approximately 10–15% (i.e. 2%/year) [103].

27.8.1 Technique
Immediately before prostatectomy, the urethra and bladder are examined to rule out strictures, cancers, diverticula, and stones. There are several different styles of transurethral resection, however, the most commonly used is the technique described first described by Blandy.

27.8.2 Objectives
Transurethral resection removes all the adenoma proximal to the verumontanum and leaves behind a shell of connective tissue and compressed adenoma. Great care is taken to preserve the verumontanum because the intramural sphincter lies so close to it. The neurovascular bundles to the penis are also very close to the membranous urethra and diathermy must be used sparingly in their vicinity. The tissue distal of the verumontanum is left behind (Figure 27.12).

Figure 27.12 The objective of transurethral resection of prostate (TURP) (a) is the same as that of open prostatectomy (b) namely to remove all the tissue from the transitional zone.
27.8.3 Steps of the Operation

Begin by identification of the verumontanum and sphincter. Then the circular fibres of the bladder neck are revealed by resecting the overlying middle lobe tissue (Figure 27.13). Bleeding from the 5 and 7 o’clock arteries of the prostate is controlled by diathermy. The lateral lobe on one side is freed from the bladder neck and capsule by cutting a trench near the midline starting at 1 or 11 o’clock to allow the bulk of the lateral lobe to fall backwards (Figure 27.14). Bleeding from the anterior prostatic arteries is sealed with coagulation. The remainder of the lateral lobe adenoma is then removed with a series of downwardly directed cuts, exposing the capsule (i.e. the thin layer of remaining adenoma which is right up against periprostatic fat and veins). After one lobe has been resected, the same procedure is applied to the other side (Figure 27.15). It only remains to clean away any little tags of tissue that have been overlooked and to obtain perfect haemostasis. Throughout the resection the surgeon must continually refer back to the landmarks of the verumontanum, sphincter and bladder neck.

27.8.4 Postoperative Management

A three-way irrigating catheter is used by most surgeons, and saline is used as the irrigating fluid. The irrigation is stopped when the effluent is reasonably clear and the catheter can usually be removed after 48 hours. Others prefer to use a two-way catheter, and rely on intravenous fluids and a diuretic to keep the bladder irrigated. Patients may go home once successfully passing urine after catheter removal but are advised not to take vigorous exercise for another 10–14 days because of the risk of secondary haemorrhage.

27.8.5 Complications [103, 104–107]

27.8.5.1 Early Complications

Primary haemorrhage on the operating table requiring blood transfusion (10%) is a major complication, but can largely be reduced by a preliminary coagulation of the rim of the prostate at the 2, 10, 5, and 7 o’clock positions where the prostatic arteries are found.

One must bear in mind UTI or sepsis (4–20%) are possible in the postoperative period and that they should be treated promptly to lessen morbidity, although this has decreased in recent years due to the use of prophylactic antibiotics.

Urinary retention occurs (3–9%) postoperatively. This might be due to either an element of poor bladder contractility, failure to resect enough tissue to alleviate the
Figure 27.14 (a) A trench is made between the bladder neck and adenoma at 1 o'clock, allowing the lateral lobe to drop back. (b) The lateral lobe is then resected (c–d) same to the other side.

Figure 27.15 Any little bits of adenoma that have been left are resected especially around the apices and the verumontanum (a–c).
obstruction, or a clot is blocking the exit passage. Catheterisation will be required, and a further TWOC attempted for the first two. If this fails, urodynamics can help diagnose the cause. A bladder washout can clear out clots.

Perforation is also a possible complication. The capsule is thinner than the loop of the resectoscope, so perforations are inevitable. Small perforations do not carry significant risk; however, larger ones may lead to excessive bleeding or fluid extravasation leading to TURP syndrome.

If distilled water is used as an irrigant, there is a risk of haemolysis leading to tubular obstruction by haemoglobin and acute renal failure. Nonelectrolyte solutions that do not haemolys the blood should always be used (e.g. glycine, glucose, or one of the proprietary sorbitol–mannitol mixtures).

TURP syndrome (<1%) is caused by absorption of the irrigant fluid during TURP or rarely transurethral resection of bladder tumour (TURBT) or percutaneous nephrolithotomy (PCNL). Glycine (1.5%), the most commonly used irrigant, is hypotonic (200 mosmol l\(^{-1}\)) compared to plasma; therefore, its absorption will lead to fluid overload, dilutional hyponatraemia, and glycine toxicity.

a) The fluid overload leads early on to hypertension, shortness of breath, pulmonary oedema, and possibly cardiac failure. If left untreated or fluid overload, continues bradycardia and hypotension ensue. The fluid overload also causes the cardiac atria to release atrial natriuretic peptide, which causes an osmotic diuresis and results in loss of salts.

b) Dilutional hyponatraemia, resulting from the excess fluid, shifts water from plasma into the brain. In severe cases leading to cerebral oedema and herniation, which can lead to death if untreated. Symptoms usually start when sodium levels are <130 with restlessness, confusion, or delirium. If sodium drop to <115, seizures ensue and the patient can become unresponsive and comatose.

c) Glycine is metabolised mainly in the liver (90%) and kidneys (10%) into glycolic acid, ammonia, and water (leading to worsening of the fluid overload and hyponatraemia). It is an inhibitory amino acid neurotransmitter, and in the retina, it slows down neurotransmissions to the cerebral cortex, which can manifest as seeing halos or flashing lights or transient blindness. In the face, can cause prickling or numbing sensations. Rarely if left untreated or large amounts absorbed, the inhibition can cause bradycardia and hypotension.

Risk increases if the prostate is >45 ml (1.5%), or the resection time is >60 minutes (2%). Even if solutions are used that cannot cause haemolysis, if a sufficiently large volume enters the vascular space, there will be dilution of the plasma electrolytes, especially sodium, and disturbance of muscle and nerve function.

This syndrome is rare because intravasated fluid is usually rapidly excreted by diuresis, but in very frail old men, this diuresis may be prevented by an inappropriate secretion of the ADH.

Precautions to avoid extravasation of irrigating fluid include (i) keeping the level of the fluid below 20 cm above the operating table; (ii) stopping the resection if large veins are opened or large perforation done; (iii) limiting resection time; and (iv) avoiding TURP in >100-ml prostates.

Recognition is key, if the patient is under a general anaesthetic, hypertension or even hypotension and cardiac arrhythmias with decreased O2 saturation should elude to TURP syndrome; otherwise visual and fascial symptoms, sudden confusion, or irritability if a spinal is used. No treatment is usually needed if the patient is well and is having a good diuresis. Alternatively, a loop diuretic, which induces a diuresis that results in loss of more water than sodium, can be used, such as 40 mg of furosemide. In severe cases of hyponatremia (e.g. uncontrollable epileptic fits), 50 ml of hypertonic solution (29.2% saline) may be given intravenously – preferably through a central venous line in the intensive care unit, with an aim of correcting 1 mmoll l\(^{-1}\) h\(^{-1}\) as to avoid rapid correction that lead to central pontine myelinolysis or demyelination which can results in paralysis.

Late complications include urethral strictures (2–9%), urinary incontinence (0.5%) (Figure 27.16), retrograde ejaculation (50–90%), and bladder neck stenosis (5%).

The risk of impotence after prostatectomy is <10%, and it increases with the age of the patient. Because the neurovascular bundles to the penis are so close to the verumontanum, coagulation in this region may damage them.

Mortality rate is usually low between 0.2 and 0.4%; however, even this figure is decreasing with advancements in equipment and anaesthetic techniques.

Before the national prostatectomy audit was performed in 2004, emergency TURP was being performed at initial AUR presentation. However, this audit identified that surgery immediately following AUR was associated with greater morbidity and mortality than with elective TURP [108]. There were greater intra- and post-operative complications, including bleeding requiring transfusion and 30-day mortality in the patients who underwent emergency TURP. As such careful consideration should be undertaken prior to performing a TURP at initial AUR presentation.

iii) Open prostatectomy

Transvesical open prostatectomy, which carried a low risk of mortality at the time of only 5%, was first popularised by the Irish Urologist Sir Peter Freyer in 1912 [102].
The open retropubic prostatectomy was popularised by Terence Millin in the 1940s, and it provided better exposure, better control of bleeding, and allowed for a lower rate of urinary incontinence than the previous procedures [103]. The mortality rate was less than 1% and was mainly due to haemorrhage, myocardial infarction, or respiratory complications. Other complications include low rates of bladder neck contracture (2%), impotence in 15–20%, and retrograde ejaculation in up to 80% [104]. In the developed world, open prostatectomy is performed in less than 1% of patients; however, in the developing world is up to 55–60% [41]. The recent increase in power of lasers the resultant increase in efficacy for use with large prostates has led to a further reduction in the number of open prostatectomy being performed.

a) Transvesical prostatectomy

This is the classic procedure. Through a cystostomy, the index finger is forced into the internal meatus until it splits to open a plane of cleavage between the adenoma and the so-called ‘surgical capsule’ (Figure 27.17). The finger enucleates the adenoma. Once the adenoma is removed, there may be a torrent of bleeding from the arteries at the neck of the bladder which are difficult to see or suture. Large stitches are placed at the neck of the bladder (Figure 27.18). The difficulty of securing precise haemostasis is the reason why this operation was replaced by that of Millin.

b) Retropubic prostatectomy (Millin operation)

Make a Pfannenstiel incision. Wipe away the fat around the preprostatic veins and divide them between suture ligatures. The layer of areolar tissue and fat is now carefully wiped laterally with a Lahey pledget in the hope of preserving the neurovascular bundles of the penis (Figure 27.19).

Make a transverse incision with a diathermy needle at the junction of the bladder and prostate using the coagulating current to control bleeding (Figure 27.20). As the prostate is thin anteriorly, the incision needs only to be 2 or 3 mm deep before the inner zone adenoma is exposed (Figure 27.21). The plane of cleavage between capsule and adenoma is opened with scissors on each side.
A finger is firmly thrust into the lumen of the prostatic urethra, breaking through the thin anterior commissure. The nipple of the verumontanum can be felt. Pressure down on either side of the verumontanum breaks into the plane between adenoma and capsule (Figure 27.22) and leaves a strip of intact urothelium along the midline.

First one lateral lobe and then the other are enucleated with the finger and brought out into the wound (Figure 27.23). Opening a bladder neck spreader reveals the middle lobe, attached to one or other lateral lobe (Figure 27.24). This is dissected from the bladder neck with the diathermy needle leaving only the strip of intact urothelium along the midline.

Figure 27.17 (a) Freyer transvesical prostatectomy. The salient lobes of the prostate are circumcised with the diathermy, and (b) a finger forced into the internal meatus to split the anterior commissure, and then enucleate the adenoma.

Figure 27.18 After the adenoma has been enucleated sutures at each quadrant help to control bleeding.

Figure 27.19 The fascia is incised on either side of the dorsal veins which are then sutured and divided (a) and the penile neurovascular bundle is displaced laterally and backwards (b).
mucosa leading down to the verumontanum which is cut across well proximal to the sphincter.

The retropubic approach permits perfect haemostasis. First a 2–0 absorbable suture is passed through the bladder, bladder neck, and capsule at each end of the transverse incision to control bleeding from the main prostatic arteries (Figures 27.25 and 27.26). Smaller vessels along the cut edge of the bladder are underrun with fine sutures.

Occasionally an artery continues to spurt from inside the prostatic capsule which is difficult to see. The capsule may be everted by a suture which picks up the lining (Figure 27.27). Traction on the suture reveals the source of the bleeding which is controlled by suture ligature or diathermy.

A three-way irrigating catheter is put in the bladder; the wound is closed and a suitable drain is made. The drain is removed at 48 hours and the catheter on the fourth or fifth day when, if generally well, the patient may go home.

iv) Holmium laser procedures

The holmium aluminium garnet laser has a wavelength of 2140 nm which allows rapid absorption by
water allowing rapid vaporisation of the tissue to a depth of 0.4 mm and a result coagulation depth of 3–4 mm [109]. There are three different techniques that can be utilised by holmium laser. Ablation (HoLAP) which uses the laser to vaporise and create a cavity over the surface of the prostate, resection (HoLRP) which involves removal of pieces of tissue using the cutting action of the laser fibre, and enucleation (HoLEP) which is similar to open prostatectomy in that the laser is used to develop the plane between the adenoma and capsule and the lobes are dissected out before they are morcellated to allow removal.

HoLEP has now superseded the other two techniques and has long-term evidence to support its use. Its clinical efficacy is at least equivalent to TURP with reduced risk of bleeding and blood transfusion requirement and reduced length of hospitalisation and catheterisation time. However, it requires a longer operative time and
has similar complication rates [110]. It has more durable evidence to support its use than photo-vaporisation of the prostate (PVP) although this evidence is also starting to mature [109]. Furthermore, evidence suggest that it can contend with open (i.e. Millin) prostatectomy for >100-ml prostates with less blood loss and shorter hospital stays and catheterisation times, but longer operative time, with no difference in symptom improvements (90% improvements) and complication rates.

The advent of laser prostatectomy has made day-case surgery for BPH now a realistic possibility with more than 90% of cases performed as day cases in some institutes.

c) Minimally invasive therapies

Over the last 20 years there has been an explosion in the number of other possible treatment options, with many focused on treating increasingly elderly and comorbid patients. The introduction of bipolar TURP...
improved the safety profile of the procedure by reducing the risk of TURP syndrome [111]. Many of these are not routinely used in clinical practice in the UK, however, are being used elsewhere and therefore it is important to appreciate them.

i) Transurethral microwave thermotherapy (TUMT)
Delivers heat to the prostate through a transurethral catheter by computer-regulated microwaves (915/1296 MHz). It delivers heat >45°C which destroys prostatic tissue and has a cooling system to protect the urethra during the procedure.

It is the most popular minimally invasive method worldwide because it avoids the need for anaesthesia (i.e. outpatient procedure) and has a short learning curve. Morbidity mainly involves the need for prolonged catheterization and there is a 2–10% failure rate. It is not recommended by NICE but is recommended by the EAU guidelines where no suitable alternative exists [4, 112].

ii) Transurethral needle ablation of the prostate (TUNA)
Delivers low level radiofrequency (460 kHz) to the prostate via needles resulting in temperatures over 100°C, which destroys prostatic tissue. It is simple and safe and can be performed without anaesthesia. Symptom scores improve by 8–10 points and peak flow rate by 3–4 ml s⁻¹, although there has only been one RCT, and there is little long-term data [113, 114]. It is not recommended by NICE but is recommended by the EAU guidelines where no suitable alternative exists [4, 112].

iii) Transurethral electro-vaporization (TUVP)
Delivers uninterrupted high-intensity electrical energy to the prostate using modified transurethral equipment including a rollerball electrode with a larger surface area. It requires continuous bladder irrigation to prevent overheating of urine. Several RCTs have shown similar rates of symptom score improvement and peak FRs to TURP although higher rates of storage symptoms and dysuria. The disadvantage is that the efficacy of the electrode decreases as the tissue desiccates which makes it difficult for larger prostates [102, 115].

iv) Laser prostatectomy:
Four types of laser energies have been used for the treatment of BPE (Nd:YAG, Holmium:YAG, KTP:YAG, and diode).

Greenlight laser prostatectomy (KTP:YAG laser) was an improvement from the earlier Nd:YAG laser by doubling the frequency using a potassium-titanyl-phosphate-KTP crystal which produced a different laser [116]. The resultant KTP:YAG laser (greenlight) beam has a different wavelength to the Nd:YAG laser, and it sits within the visible green region of the electromagnetic spectrum (unlike the Nd:YAG which is in the infrared portion) [117].

The KTP laser is selectively absorbed by haemoglobin in tissue but fully transmitted through aqueous irrigation fluids and therefore is PVP. Absorption of KTP laser leads to instant removal of prostate tissue by photothermal vaporisation of heated intracellular water [118]. The optical penetration of the KTP laser is only 1–2 mm which allows a focused and efficient vaporisation [119]. More advanced KTP systems (e.g. HPS and XPS) have been developed which allow wider beams of increased intensity and enabled larger prostates to be tackled [120].

Efficacy for the greenlight laser prostatectomy has shown similar improvements in IPSS and FR as with TURP with shorter length of stay, reduced blood loss, and better intraoperative safety; however, it is also a slight higher reoperation rate in the long term for it [121].

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**References**


References


28

Prostate Neoplasm

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Abstract

Prostate cancer (PCa) is the most common urological cancer and accounts for nearly a quarter of all new cancers in men. Since the widespread use of prostate-specific antigen (PSA) testing in the 1990s, the incidence of PCa has risen sharply, but overall mortality from PCa has remained static. All areas of PCa from diagnosis through to surgical and medical treatments are rapidly advancing. Besides ongoing evaluation of novel biomarkers and genetic profiling, ground-breaking advances in MRI imaging, biopsy techniques, robotic prostatectomy, imaging-guided radiotherapy, and multiple large-scale clinical trials of new drugs within the last decade make PCa an exciting and ever-expanding field in urology, thus transforming how urologists manage patients with PCa.

Keywords prostate cancer (PCa); magnetic resonance imaging (MRI); prostate-specific antigen (PSA); prostatectomy; radiotherapy

Key Points

- Prostate cancer (PCa) is an extremely common and age-related disease with more than 80% of men older than 80 harbouring detectable disease.
- Only 8% of men diagnosed will develop clinically significant disease and only 3% will die from PCa directly.
- Key to the effective management of this heterogeneous disease is an early risk stratification strategy and active surveillance to avoid overtreatment.
- Androgen-deprivation therapy (ADT) is initially effective in almost all cases of advanced disease, but resistance occurs on average after 30 months with progression to metastatic castration resistant prostate cancer.

28.1 Epidemiology

In the Western world, prostate cancer (PCa) incidence has increased generally since 1970s with a rapid increase in the 1990s and is largely attributable to an aging population and prostate-specific antigen (PSA) testing. Widespread PSA testing has led to the diagnosis of less-aggressive cancers in younger men who are asymptomatic [1]. PCa incidence varies globally, with highest rates in North America and Scandinavia and lowest rates in East Asia [2, 3]. Similarly, PCa mortality varies worldwide, with the highest mortality in the Caribbean and Scandinavia, intermediate rates in US and UK, and lowest rates in China and Japan [4].

PCa has become the most common cancer in men, with more than 41,000 new cancers per annum in the UK, or a lifetime risk of one in eight, accounting for 25%
of all new cancer cases in UK men [1]. More than 10,000 men every year die from PCa. The crude UK incidence rate for 2012 was 134 new PCa cases per 100,000 males [1]. Only 8% of men will get clinically significant PCa and only 3% will die from PCa. This is because PCa commonly has a slow natural history and is predominantly a cancer of elderly men. The majority of men (84%) with PCa are predicted to survive more than 10 years [5].

28.2 Aetiology

The aetiology of PCa is poorly understood. Established nonmodifiable risk factors include age, ethnicity, and family history (genetic susceptibility) have been associated with PCa. Epidemiological migration studies suggest modifiable risk factors such as environmental and lifestyle factors to be important as well, however, have not been conclusively linked to PCa development.

28.2.1 Nonmodifiable Risk Factors

28.2.1.1 Age

PCa has been considered as a cancer of aging as suggested by autopsy studies where nearly 30% of men 50–60 years of age were found to have PCa, nearly 40–50% of men in their 60–70 years of age, >65% in their 70–80 years, more than 80% in their 80s, and all men in their 90s had PCa [6]. Albeit the vast majority of men will die with PCa than of it. Only 1% of PCa cases are diagnosed in men younger than age 50 [1]. The peak age for diagnosis is 75–79 (Figure 28.1). PCa is already a huge health problem in the Western world and its importance on health economics will only increase with an aging population and increasing life expectancy. The population of men aged 65 or older is predicted to increase fourfold between the years 2000 and 2050. By 2030, the older-than-65 population is forecast to make up about one-fifth of the global population demographics [7].

28.2.1.2 Family History and Genetics

Hereditary PCa is defined as having three generations affected or three first-degree relatives or at least two relatives younger than 55 years of age with PCa. First-degree relatives of men with PCa have approximately twice the risk of developing the disease, relative to men without a family history [8]. This is compounded by an early age of onset, in that if the first-degree relative has PCa diagnosed at younger than 60 years of age, the risk is more than fourfold that of men without a family history [9]. In Nordic twin studies, when one of the twins was diagnosed with PCa, identical twins (monozygotic) carried a 50% higher risk of PCa when compared to dizygotic twins [10, 11]. It is estimated that 5–10% of all PCa cases and up to 40% of those occurring in men <55 years of age may be hereditary [12, 13]. When compared to sporadic cases, hereditary PCa tends to be diagnosed on average six to seven years earlier [13]. There have been seven susceptibility gene loci for PCa identified, including HPC-1 (chromosome 1q24–25) and RNase L, but demonstrating linkage has proved to be problematic [14].

Genome wide association studies (GWAS) have identified more than 40 PC-risk genetic variants [15]. Somatic genetic alterations in fatty acid synthase (FASN), Hepsin (HPN), alpha-methylacyl-CoA racemase (AMACR), and

![Figure 28.1 Prostate cancer, average number of new cases per year and age-specific incidence rates, UK males 2009–2011. Source: Taken from UK Cancer Research, 2012 [5].](image-url)
MYC have been fairly consistent and linked to PCa development [16]. Deleterious germ line mutations of BRCA1 and BRCA2 (chrom 13q) are associated with increased PCa risk [14, 17]. Incidentally, family history of breast cancer has been associated with the same mutations of the BRCA genes.

28.2.1.3 Race
Generally, African American men are at a higher risk of PCa, whereas Asians have a lower risk. The highest incidence is seen in people of African American and Jamaican descent and lowest in people native to Japan [18].

28.2.2 Modifiable Risk Factors
Many modifiable risk factors have been studied to find a linkage with development or progression of PCa; however, no strong associated evidence was found for many of these factors with scanty evidence at best.

28.2.2.1 Diet
Migration studies of Japanese men settling in the US showed that their PCa incidence increases and with increased risk correlated with younger age at the time of immigration and longer duration living in the new environment [19]. In a multicentre study of dietary factors, PCa risk was associated with total fat intake in Caucasians, African Americans, and Asian Americans [20]. There is evidence that dietary fat (omega-6 polyunsaturated fatty acids: present in red meats) may play a role in accelerating tumour growth [21]. Conversely, various studies have suggested that cooked and processed tomatoes or tomato products (rich with the lycopene antioxidant), β-carotene, selenium, vitamins E and D, omega-3 unsaturated fatty acids, and other antioxidants may have a weakly protective effect for PCa development [22, 23].

28.2.2.2 Body Mass Index
In a US prospective study of 400,000 men with high body mass index (BMI; 35–39.9) had increased risk of dying from PCa, and it was 34% higher when compared to those with normal BMI [24]. Furthermore, high BMI has been found to be associated with advanced PCa [25, 26]. Possible biological mechanisms include higher levels of androgens, insulin-like growth factor 1 (IGF-1), and serum calcium which are associated with PCa development.

28.2.2.3 Hormonal Factors
Despite the known androgen dependence of PCa, there is little evidence that circulating levels of androgens, estrogens, or 5α-reductase levels are associated with risk of developing the disease [16].

PCa risk does not appear to be affected by other factors such as vasectomy, sexual activity, smoking, alcohol consumption, physical activity, or social class [4, 23].

28.2.2.4 Drugs
5α-reductase inhibitors (5ARI) such as finasteride and dutasteride have been studied for their possible risk reducing effects in PCa [27, 28]. Using 13 years’ of survival data from the Prostate, Lung, Colorectal and Ovarian (PLCO) trial and data from the Reduction by Dutasteride of Prostate Cancer Evens (REDUCE) trial (a clinical research study to reduce the incidence of prostate cancer in men who are at increased risk), both initially showed a reduction of the incidence of PCa, but further analysis showed an increase in the risk of higher-grade disease (i.e. Gleason 8–10), suggesting a worrying slight increase in more aggressive PCa [27, 28]. In the REDUCE trial, which compared 5ARI, dutasteride, and placebo in 6729 men with raised PSA (2.5–10 ng ml⁻¹), showed a 22.8% relative risk (RR) reduction from 25.1% (848 of 3424) to 19.9% (659 of 3305). However, during the last two years, a significantly greater number of patients in the dutasteride group were diagnosed with high-grade Gleason score 8–10 (1 out of 2343 compared to 12 out of 2447). Secondary analysis of Prostate Cancer Prevention Trial (PCPT) data also showed a RR reduction in PCa mortality of 0.87 (95% CI 0.72–1.06). Currently no 5ARIs have been licenced for use in risk reduction in PCa.

Statins have also been implicated in PCa prevention. Epidemiological studies have suggested a reduction in the rate of PCa in patients taking statins; however, the evidence is not clear [29]. The effects of statins in PCa cell culture is to induce apoptotic cell death via reduction of the insulin-like growth factor 1 receptor (IGF-1R) and can also be potentiated by the effects of IGF-1R antagonists [29–31].

28.3 Clinical Features
As the most prevalent male cancer, PCa has become an increasingly pressing clinical problem for urological surgeons worldwide [3]. Despite its prevalence, the disease is poorly understood by the general public, and most men older than the age of 60 will have some experience of PCa through family or friends.

Early or localised PCa (T1–2, N0M0) is typically detected following investigations for concurrent lower urinary tract symptoms (LUTS), haematuria, or after a screening PSA test [32]. Locally advanced PCa (T3–4, N0M0) can cause similar symptoms as the localised disease in addition to obstructive uropathy or lower limb oedema if lymphatics are involved. Nearly 10% of patients present with signs and symptoms of advanced or metastatic PCa with general health decline, weight loss and cachexia, falls and pathological fractures or bone pain from bony metastases, or lower limb weakness from spinal cord compression by vertebral metastases. Bearing in mind metastatic disease can also be asymptomatic and only present with an elevated PSA.
28.4 Prognosis

For many, PCa has an indolent nature, with a prolonged natural history with at least 10 years from initial diagnosis to the first cancer-related mortality [33]. Hence, it is necessary to risk-stratify newly diagnosed PCa into low, intermediate, and high-risk groups. Low-risk PCa confers a disease-specific mortality of <1% over 10 years follow up, thus the option of active surveillance (AS) with deferred treatment is generally used. [33]. This increases dramatically for intermediate- and high-risk PCa groups to around 10% cancer-specific mortality at 10 years without radical treatment [34]. The prognosis of patients with metastatic PCa remains poor, with an average survival of only 42.7 months (3.5 years) from diagnosis, while once castration-resistant PCa (CRPC) has developed, time to death is typically within 22 months [35]. Locally advanced PCa also impacts prognosis, increasing the risk of cancer-specific death by seven times with an overall 10 years cancer-specific mortality rate of 23.9% [36]. Therefore, the understanding of the natural history of PCa is vital to ensure patients are managed appropriately.

28.5 Investigations

28.5.1 Prostate-Specific Antigen

PSA is a 34 kDa serine protease, also known as Kallikrein Related Peptidase-3 encoded by the KLK3 gene on chromosome 19. Its physiological function is the hydrolysis of semenogelin-1, causing liquefaction of the seminal ejaculate to aid spermatozoa mobility [37]. It has a half life of 2.2 days with 75% of circulating PSA bound to alpha-1 antichymotrypsin and alpha-2 macroglobulin and is metabolised in the liver. The remaining 25% is free and is excreted in the urine. It is found in high quantities in seminal fluid and its discovery as a PCa serum biomarker occurred concurrently with its discovery and use in forensic analysis of seminal fluid leading to many pseudonyms such as γ-seminoprotein. In 1979 T. Ming Chu purified and characterised PSA from serum and was the first to appreciate its clinical relevance as a biomarker for PCa [38].

Prior to PSA, prostatic acid phosphatase (PAP) was widely used; however, it was only raised in metastatic disease and was not useful in early detection or screening. In 1987, Stamey et al. showed that PSA was superior to PAP as a clinical biomarker for detecting early PCa [39]. Today, PSA is the most widely used clinical biomarker. The major limitation of PSA as a biomarker for PCa is that it is produced by both normal and malignant prostatic epithelium, and its detection in serum is proportional to the amount of prostate tissue (both healthy and diseased, benign and malignant), with variable normal range amongst men, increasing with age (Table 28.1). PCa cells produce less PSA than non-PCa cells; however because of the disruption of the basement membrane architecture of the gland in cancer, more PSA ‘leaks’ into the circulation.

A number of conditions that irritate the prostate can cause the serum PSA to elevate such as, urinary tract infections (UTIs), prostatitis, benign prostatic hyperplasia (BPH), acute urinary retention, catheterizations, prostatic biopsy or operations such as transurethral resection of prostate (TURP). Prostatic massage, digital rectal examination (DRE), and anything causing pressure on the perineum may also transiently increase the PSA levels. Avid cyclists have been known to have an intermittently raised PSA due to pressure from the bike saddle and strenuous exercise [42].

The PSA kinetics, rather than the absolute values, are more important in identifying men harbouring an early tumour [43]. Ultimately, to decide whether to proceed to prostatic biopsy requires a fully informed patient on the risks and benefits of the procedure and should not be based on PSA alone, taking into account an individual’s risk of PCa and comorbidity factors as well as any co-existing UTI or prostatitis and findings on DRE [40].

A number of PSA kinetics exist, but only PSA doubling time and velocity are regularly used in clinical practice for monitoring in AS and during biochemical relapse following treatment [44]. They are a measure of increasing volume of disease and the rate of progression and can predict PCa specific survival [45].

28.5.2 PSA Density

PSA density is the serum PSA level per ml of prostate tissue. PSA levels are higher in men with larger prostate glands. The PSA density is sometimes used for men with large prostate to try to adjust for this. The volume of the prostate gland can be measured using transurethral ultrasound (TRUS) or computed tomography (CT) scans. A PSA density of >0.15 ng ml⁻¹ per ml of prostate tissue is highly indicative of PCa [46].

Table 28.1 Age-specific reference ranges used to trigger referral for prostate biopsy adapted from NICE guidelines [40, 41].

<table>
<thead>
<tr>
<th>Age</th>
<th>PSA (ng ml⁻¹) triggering referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49</td>
<td>&gt;2.0</td>
</tr>
<tr>
<td>50–59</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>60–69</td>
<td>&gt;4.0</td>
</tr>
<tr>
<td>&gt;70</td>
<td>&gt;5.0</td>
</tr>
</tbody>
</table>

NICE, National Institute for Health and Care Excellence.
28.5.3 PSA Doubling Time

Doubling time is the length in months or years in which the PSA doubles. The doubling time is used more for follow-up of patients’ progress after treatment or during AS. Clinical examples of the doubling time use: a doubling time of five years is highly suggestive of PC, while three years in patients undergoing AS indicates disease progression, and a doubling time of three months after radical treatment might trigger need for hormonal therapy. Multiple online calculators can aid in the doubling time calculations (e.g. https://www.mskcc.org/nomograms/prostate).

28.5.4 PSA Velocity

PSA velocity is the rise in PSA per year, with a rise of more than 0.75 ng ml\(^{-1}\) per year being associated with a higher risk of PCa [47]. The velocity can be calculated by using the following formula: \( \text{PSA Velocity} = 0.5 \times \left( \frac{[\text{PSA2} - \text{PSA1}/\text{time1}]}{\text{time1}} + \frac{[\text{PSA3}-\text{PSA2}/\text{time2}]}{\text{time2}} \right) \); time being in years.

28.5.5 Digital Rectal Examination

As the majority of PCa arises in the peripheral zone of the prostate, PCa can be easily palpated during DRE and used for staging purposes as well. A DRE can give you an estimation of the size of the prostate, symmetry, firmness, presence of nodules, and in advanced disease, a craggy solid fixed feeling prostate. Although an abnormal feeling prostate would raise the suspicion of PC, the risk increases if the PSA was also raised (Table 28.2) [48, 49]. DRE alone can detect only 18% of PC, irrespective of the PSA. Abnormal DRE with an elevated PSA level of >3 ng ml\(^{-1}\) gives a positive predictive value of just under 50% [50]. A number of risk calculators are available online [51].

28.5.6 Diagnostic Investigations

28.5.6.1 Transrectal Ultrasound Imaging

Prostate biopsies remain the clinical standard and the most reliable means to diagnose PCa (Figure 28.2).

On grey scale TRUS, the normal central part of the prostate has a lower echogenity (darker) compared with the peripheral part (Figure 28.3). About 60–75% of the tumours have a lower echogenicity compared with the surrounding prostate tissue. Many nonmalignant conditions such as prostatitis, infarction, and adenoma may give similar hypoechoic appearance. Approximately 12–30% of prostate tumours are isoechoic and not visible with the usual grey scale ultrasonography. A small proportion of tumours are hyperechoic [53]. The sensitivity and specificity of TRUS are therefore too low for PCa screening, and its main role is to provide guidance for prostate biopsy.

Table 28.2 Predicted value for prostate cancer based on digital rectal examination (DRE) and prostate-specific antigen (PSA).

<table>
<thead>
<tr>
<th>PSA (ng ml(^{-1}))</th>
<th>&lt;4</th>
<th>4–10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal DRE</td>
<td>&lt;20%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Abnormal DRE</td>
<td>&lt;30%</td>
<td>50%</td>
<td>&gt;75%</td>
</tr>
</tbody>
</table>

Figure 28.2 Imaging algorithm in patients with elevated prostate-specific antigen (PSA), abnormal rectal examination, or family history of prostate cancer. mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; TRUS, transrectal ultrasound. Source: Modified from ESUR prostate MR guidelines [52].
Compared with normal prostate tissue, malignant focus has increased cell density and therefore a change in tissue elasticity. When manual compression is applied, this change in tissue elasticity causes a change in reflection of applied sound waves, and this can be detected by a technique known as ‘elastography’. Elastography is able to increase PCa detection compared to the standard grey scale TRUS [54]. Early results are promising, with one study showing a PCa detection rate of about 93%, compared with 59% by grey scale TRUS [55]. Shear wave elastography is an alternative technique using acoustic impulse to produce a shear wave. This technique is less operator-dependent and is easier to perform because it does not require the operator to apply pressure. Early published results are favourable [56], but large prospective trials are needed to fully evaluate their value as imaging tools to diagnose PCa.

TRUS also allows the measurement of the prostate size, which is the equation for area of an ellipsoid: prostate volume (cm³) = anteroposterior diameter (cm) × width (cm) × sagittal (cm) × (π/6).

28.5.6.2 TRUS-Guided Biopsy
Each patient should be informed of how the procedure is carried out (no enema is required) and the potential complications; written informed consent should be obtained. Anticoagulation therapy, warfarin and anti-platelet agents, should be stopped before biopsy, and antibiotic prophylaxis must be given to all patients. General anaesthesia is rarely necessary and local periprostatic anaesthesia should be given.

The diagnostic yield of systemic sextant biopsies varies between patient population studied, but in general, between 20 and 35% of patients are confirmed to have cancer using the original technique described by Hodge et al. [57]. Increasing the number of biopsy cores and biopsy areas will increase the yield of the procedure. Most studies had demonstrated that extended biopsy is superior to the sextant protocol without incurring significant complications [58]. The addition of laterally directed biopsies has shown to increase the PCa detection rate by 5–35% [59, 60]. This is explained by the simple fact that PCa mainly arises in the outer zone of the prostate (Figure 28.4). The base and the apex of the peripheral gland are the sites where most tumours are located and where biopsies should be directed. Biopsies of the transitional zone add little to cancer detection and should therefore not be sampled during initial biopsy [61].
Recommendations are for 10–12 core samples taken during systematic biopsy from as far posterior and lateral in the peripheral gland as possible. These can be supplemented with cores from suspected areas detected by either DRE or TRUS [32]. TRUS-guided biopsy is in general a safe procedure. Complications are minor and self-limiting. These include vasovagal episode, pain, mild haematuria, transient rectal bleeding, haematuria, and haematospermia. Major complications are rare; however, they can lead to significant morbidity and include severe rectal or urinary bleeding, acute or clot urinary retention and infection, and severe sepsis.

28.5.6.3 Repeat and Saturation Biopsy
Because a negative biopsy does not rule out PCa, a continued suspicion of malignancy on the basis of rising or persistently raised PSA level, suspicious DRE, or abnormal histology such as atypical small acinar proliferation (ASAP) [32], a repeat biopsy is usually indicated. It has been shown that more than 90% of PCa can be detected by two successive sextant biopsies [60] and is unlikely to miss any clinically significant disease. However, the more biopsies obtained, the less the probability of finding PCa is, with 22% on the first biopsy, 10% on the second, 5% on the third, and 4% on the fourth [62]. Furthermore, the more biopsies taken, the more likely a lower-grade disease will be detected, therefore, more likely a clinically insignificant disease.

In saturation biopsy, 20 or more cores of tissue are obtained in a systemic fashion. The theory behind the saturation biopsy is that the more biopsies one takes, the higher is the chance of detecting PCa [63, 64]. However saturation biopsy is recommended only for patients with an initial negative biopsy because this technique does not offer any benefit as a routine initial biopsy protocol [65]. The approach of transperineal template prostatic biopsies can also be considered.

If clinical suspicion for PCa persists despite repeated negative prostate biopsies, magnetic resonance imaging (MRI) may be used to investigate the possibility of an anterior located tumour, which can then be targeted for biopsy [32].

28.5.6.4 Incidental Finding in Positron Emission Tomography–Computed Tomography
18F-fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET–CT) is now widely used for staging, restaging, and monitoring of treatment response of an increasing number of cancers. The rising number of incidental prostate 18FDG uptake has created a dilemma for clinicians. A retrospective review of more than 11000 men who underwent 18FDG PET–CT showed the prevalence of incidental prostate uptake to be 1.8%. Within this group, there was a one-in-five chance of finding PCa in the older patient with uptake within the peripheral zone; in such incidental cases, referral and further evaluation is suggested [66]. However, as a primary imaging modality, 18FDG PET–CT does not reliably detect primary PCa due to low metabolic activity within PCa tumours and also signals being obscured by contrast accumulation in the urine [40].

28.5.7 Staging Investigations
Classification is by the tumour, node, and metastasis (TNM) staging system (Table 28.3 and Figure 28.5) [67].

28.5.7.1 Local Staging
28.5.7.1.1 Spread of Prostatic Cancer
PCa spreads by direct invasion, lymphatics, veins, and along the perineural spaces, and adequate staging should precede treatment.

Direct invasion occurs into seminal vesicles, urethra, base of the bladder, and around the rectum. Cancer never penetrates Denonvilliers’ fascia unless it has been perforated by a biopsy needle.

Capsule The notion of the ‘capsule’ in the context of carcinoma is misleading. The only anatomical capsule is a thin layer of connective tissue continuous with that of the veins and fat around the gland. This layer of connective tissue is thinner than the loop of the resectoscope and extends alongside the small nerves, arteries, veins, and lymphatics which enter the prostate at many places. In addition to the lymphatics each nerve is surrounded by a perineural space in which cancer readily spreads.

Lymph Nodes Lymph nodes may be invaded in many apparently localised cancers.

Bone Invasion In addition to the involvement of lymph nodes by prostatic cancer, there is a direct route from the prostate through its veins and lymphatics to the marrow of the vertebrae, pelvis, and upper third of the femur.

CT defines the intraprostatic features poorly and is not reliable for local tumour staging. If MRI is contraindicated, CT can be offered, if knowledge of staging could affect management.

Recent technical improvement and the availability of functional parameters such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced, and spectroscopic imaging have greatly improved the accuracy of MRI in local tumour staging. Multiplanar T2-weighted (T2W) imaging is the foundation of multiparametric examination and provides high-resolution images of the prostate’s zonal anatomy and capsule (Figure 28.6a). T2W imaging alone is estimated to have a sensitivity of
Table 28.3 TNM staging.

<table>
<thead>
<tr>
<th>T (Primary tumour)</th>
<th>TX</th>
<th>T0</th>
<th>T1</th>
<th>T1a</th>
<th>T1b</th>
<th>T1c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary tumour cannot be assessed</td>
<td>There is no evidence of a tumour in the prostate</td>
<td>Tumours are too small to be seen on scans or felt during examination of the prostate; they may have been discovered by needle biopsy, after finding a raised PSA level</td>
<td>Cancer is seen in &lt;5% of prostatic tissue removed by TURP.</td>
<td>Cancer is an incidental histological finding from TURP, with &gt;5% of the tissue involved.</td>
<td>Cancer is found by needle biopsy performed because of elevated PSA.</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>T2a</td>
<td>T2b</td>
<td>T2c</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumours are completely inside the prostate</td>
<td>Tumour is in one-half of one of the lobes of the prostate gland</td>
<td>Tumour is in more than half of one of the lobes</td>
<td>Tumour is in both lobes but is still confined within the prostate gland</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>T3a</td>
<td>T3b</td>
<td>T4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumours have broken through the prostate gland but not involving adjacent organs</td>
<td>Tumour has broken through the prostate capsule either on one side or on both sides of the prostate, or it has spread to the neck of the bladder</td>
<td>Tumour has spread into the seminal vesicles</td>
<td>Tumours have spread into other pelvic organs.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N (Regional lymph nodes)

NX | Regional lymph nodes cannot be assessed
N0 | No regional lymph node metastasis
N1 | The tumour has spread to one or more lymph nodes in the pelvis

M (Distant metastasis)

Mx | Distant metastasis cannot be assessed
M0 | No distant metastasis
M1 | Tumour has spread outside the pelvis
M1a | To non-regional lymph node(s)
M1b | Tumour has spread to the bones
M1c | Tumour has spread to other part parts of the body, with or without spread to the bone

PSA, prostate-specific antigen; TNM, tumour, node, metastasis; TURP, transurethral resection of prostate.

Figure 28.5 Diagrams representing tumour, node, metastasis (TNM) staging system for prostate cancer.
Investigations

Criteria for extracapsular extension includes capsular irregularity, localised bulge, measurable extracapsular disease, and obliteration of the rectoprostatic angle (Figure 28.6b). Biopsy can cause haemorrhage, inflammation, and infarction. This causes abnormalities that can mimic tumour and reduces the accuracy of the staging MRI. Most radiologists therefore recommend an interval of at least six to eight weeks between biopsy and MRI to minimise this artefact.

DWI measures the movement of water molecules through the soft tissues under the influence of strong magnetic field and radiofrequency pulses (Figure 28.6c–e). Cancer tissue exhibits a reduced diffusion compared to normal tissue. Apparent diffusion coefficient (ADC) maps of the prostate are then derived which demonstrate the tumour as a low signal focus relative to surrounding normal prostate. DWI, therefore, provides an easily visible contrast between normal and cancerous tissue. Combination of DWI with the more anatomical T2W imaging improved the overall diagnostic accuracy with an estimated sensitivity and specificity of 80–90% [69, 70].

In dynamic contrast-enhanced MRI (DCE-MRI), multiple rapid sequential images of the prostate are obtained following the intravenous administration of a gadolinium-based contrast medium. The increased perfusion and permeability of the new vessels in PCa will cause an early, fast, and intense enhancement of the tumour with early wash-out of the contrast agent. By comparison, normal peripheral zone tissue usually shows a less intense, slower, and progressive wash-in. The DCE-MRI data and the resultant enhancement curves can be assessed qualitatively (visually), semi-quantitatively, or quantitatively with appropriate imaging software.

As there is considerable overlap between the contrast enhancement rate for the tumour, normal tissue in the transitional zone, and hypervascular benign prostatic hypertrophy, DCE-MR is not recommended to be used as a stand-alone study [71]. It is a helpful tool for detecting, localising, and staging PCa but should be used in combination with T2W imaging, DWI, and possibly spectroscopic imaging as part of a multiparametric approach to prostate imaging [52].

Prostate Imaging Reporting and Data System Version 2 (PI-RADS v2) To improve consensus on the diagnosis and management of patients with localised PC, the American College of Radiology, the European Association of Urology Section of Urological Research (ESUR), and the
AdMeTech Foundation formed a joint committee to develop essential standards for a Prostate Imaging Reporting and Data System (PI-RADS). The goal was to facilitate the application of high-quality MRI by radiologists, urologists, and oncologists in a user-friendly diagnostic scoring format. In 2015, PI-RADS v2 (updated PI-RADS system as version 2) [72] was introduced, providing a simplified numerical score from one (most probably benign) to five (most likely malignant) for each intraprostatic lesion on MRI. The score is based on T2W images, a DCE study, and DWI sequence. Each study provides useful information on the lesion scored. T2W images are scored from one to five for the peripheral zone and transitional zone separately providing anatomical localization and lesion size. DWI is scored from one to five, confirming the lesion on T2W imaging is likely malignant. DCE is either positive or negative and may be omitted in the latest scoring system depending on the quality of the study. The updated system also ensures that an index lesion is identified as the most clinically significant intraprostatic lesion.

28.5.7.2 Lymph Node Staging

Local pelvic nodal disease can be estimated as part of the overall MRI examination. About 70% of the involved lymph nodes are too small (<8 mm) to be evaluated using MRI, so conventional size criteria tends to underestimate the extent of nodal involvement [73].

28.5.7.2.1 Distinct Metastases

In an autopsy study, haematogenous spread was found in 35% of the 1589 patients with a history of PCa. The most frequent involved sites were bone (90%), lung (46%), liver (25%), pleura (21%), and adrenals (13%) [74]. It was also noted that the burden of bone disease correlates directly with survival [75]. In patient where distant extraskeletal metastasis is suspected, a whole body CT is often indicated.

Skeletal metastasis is currently routinely assessed by radionuclide imaging using technetium methylene diphosphonate (99mTc-MDP; Figure 28.6f). Radioisotope bone scan is not indicated in asymptomatic patients if the serum PSA level is <10 ng ml\(^{-1}\) in the presence of well-differentiated or moderately differentiated tumours [32]. If PSA is <20 ng ml\(^{-1}\), <5% of patients will have lymph node involvement and <1% will have skeletal metastasis.

Radioisotope bone scan has an acceptable false-negative rate but a high false-positive rate mainly as a result of other coexisting hyper-metabolic lesions such as degenerative disease, fractures, healing metastasis, or Paget disease. Metastatic involvement is usually demonstrated by increased activity and is more commonly seen in bone with a greater percentage of red marrow such as pelvis, spine, ribs, and skull. Although the predictive value of radioisotope bone scans increases with the number of metastatic sites, the ability to ascertain the exact nature of individual lesions is limited without further diagnostic tests. Traditionally, plain radiograph of the abnormal area is taken to detect the presence of possible sclerotic metastasis, but advances in other imaging techniques have rendered this almost obsolete.

Single photon emission computed tomography–computed tomography (SPECT–CT), utilising a scanner that can obtain planar and cross-sectional isotope images as well as selected CT images of the affected area during the same examination, increases the specificity and number of lesions identified compared with the traditional planar radioisotope bone scan. For example, increased tracer activity in the vertebral-pedicle combination has a predictive value of 73–82% for metastatic disease, while the demonstration of activity only in the facet was 100% predictive of benign degenerative changes [76]. SPECT scanning alone could detect lesion down to 2 mm in diameter [77].

Diffuse metastatic deposits involving most of the skeletal system (super-scan) will produce generalised increased activity of most bones and may be difficult to be recognised. The hypermetabolic response as a result of healing metastasis (i.e. flare response) can lead to a false-positive diagnosis of disease progression. It usually takes between three to six months for this flare response to subside completely. If the radioisotope bone scan is taken three months after introduction of therapy shows worsening of disease, there is a high probability that this represents metastatic disease. If, however, the patients’ clinical parameters indicate a response, then flare response should be considered. A follow up scan at six months will usually resolve the issue [78].

If the result of the radioisotope bone scan or SPECT–CT remains uncertain, other imaging modality such as MRI has been recommended to differentiate active metastases from benign or healing disease [32]. MRI, which can demonstrates early bone marrow infiltration, is more sensitive than radioisotope bone scan with sensitivities and specificities of 100 and 88% for MRI and 46 and 32% for radioisotope bone scan, respectively [79].

28.5.7.2.2 Imaging Possible Disease Relapse

Rising PSA after radical prostatectomy or radiotherapy signifies biochemical recurrence. Although the patient’s symptomatology and pathology may be helpful, further imaging is often needed to identify possible local, nodal, or distant disease. TRUS biopsy is effective in about 50% of post radiotherapy relapse.

MRI and CT are the two most frequent imaging modalities used currently to evaluate such patients, but results remain poor largely because of low-volume disease [73]. Radioisotope bone scan is useful for possible bone metastasis, but its lack of specificity often requires further imaging evaluation.
PET–CT already has an established role in the management of a large number of cancers. Unfortunately, most PCa cells have a low avidity towards the most commonly used radiotracer, FDG. In addition, this tracer is excreted by the kidneys, and the presence of bladder activity limits pelvic evaluation unless bladder catheterisation and diuresis are used. Altered choline metabolism has been noted as a characteristic of PCa and novel radiotracers such as $^{18}$F-Choline and $^{11}$C-Choline have been investigated as a single non-invasive modality in staging patients with biochemical recurrence after primary treatment with a sensitivity between 43 and 93% [80, 81].

28.6 Pathology, Histopathology, and Molecular Pathology

28.6.1 Histopathology

28.6.1.1 Prostatic Intraepithelial Neoplasia
Prostatic intraepithelial neoplasia (PIN) consists of an abnormal proliferation of cytologically atypical epithelial cells within the prostatic glands without stromal invasion. It does not secrete PSA. Glands involved by PIN retain a layer of basal cells. It constitutes the preinvasive stage of prostatic acinar adenocarcinoma [82]. The incidence of isolated PIN in prostate biopsies is on average 9% [83]. Both the incidence as well as the extent of PIN increases with age [6, 84]. Based on the nucleoli prominence, PIN can be either low grade or high grade. PIN carries a predictive value for cancer in repeated biopsies ranging from 18 to 58% [85, 86]. The predictive value is especially high if PIN is of high grade, multifocal, and present in multiple (>4) core biopsies [87]. The recent use of extended biopsy techniques and more thorough prostate sampling is leading to a reduced positive predictive value of PIN as more cancers are picked up on initial biopsy [88, 89].

28.6.1.2 Atypical Small Acinar Proliferation
Atypical small acinar proliferation (ASAP) is a term used for small foci of atypical prostatic acini in prostate core biopsies that are suspicious for cancer but fall below the diagnostic threshold. ASAP often represents undersampled cancer, with about 60% positive for cancer on repeat biopsies [41, 90, 91]. Repeat biopsies are required if high-grade, multifocal PIN or ASAP are detected.

28.6.1.3 Adenocarcinoma
The majority of cancers arising within the prostate are adenocarcinomas, most displaying acinar histologic features (Figure 28.7). These acinar adenocarcinomas comprise an extremely heterogeneous group of malignancies and can range from well-differentiated cancers, with appearances very similar to benign prostatic glands, to poorly differentiated tumours with no resemblance to prostatic tissue [92].

Other variants of adenocarcinoma include ductal, foamy, mucinous, atrophic, pseudohyperplastic, oncocytic, signet ring cell, and lymphoepithelioma-like adenocarcinoma; the latter two are associated with a poor clinical prognosis. The recognition of histologic variants of PCa is important. Some types are cytologically very bland and may be mistaken for benign changes, while other types are associated with a distinct clinical outcome [92, 93].

Some adenocarcinomas show focal neuroendocrine differentiation. This transformation to a neuroendocrine phenotype is one possible mechanism of resistance to androgen receptor–targeted treatments because neuroendocrine cells lack androgen receptors and secrete various neuroendocrine peptides that stimulate androgen-independent proliferation [1, 94–96].

28.6.1.4 Other PCa
Squamous cell and adeno-squamous carcinomas are rare, aggressive tumours that can arise after radiation or hormonal therapy [92, 97]. Neuroendocrine tumours comprise small cell carcinomas and extremely rare large cell neuroendocrine carcinomas and carcinoids. These neuroendocrine carcinomas can be pure or mixed with adenocarcinomas [98, 99].

Small cell carcinomas (Figure 28.8) are poorly differentiated neuroendocrine carcinomas. They are rare and extremely aggressive tumours. They have often already metastasised at presentation but show low PSA. They can also arise after radiation or hormonal therapy [41, 92].

Carcinosarcoma or sarcomatoid carcinomas are rare biphasic tumours that consist of a malignant glandular and stromal component and carry a poor prognosis [93, 97]. Prostatic stromal sarcomas are rare tumours and can arise in patients of all ages with prognosis depending on grade and stage [92, 100]. Other sarcomas (e.g. leiomyosarcoma, rhabdomyosarcoma, and synovial sarcoma) are exceedingly rare [87, 96]. Lymphomas in the prostate can be either primary or secondary [92, 101, 102].

28.6.2 Grading

28.6.2.1 Gleason Grading
The histologic tumour grade is an important prognostic factor, with impact on treatment choices and patient outcome. Most tumour grading systems assess features of the tumour cells (cytology) or the growth pattern of the tumour (architecture). The Gleason grading system is used in prostatic adenocarcinoma (Figure 28.9). It is primarily based on the tumour architecture. This method was devised in the 1960s and 1970s by Dr. Donald F Gleason [102].
Prostatic adenocarcinoma is often multifocal and different tumour grades may be present in the same patient [103–105]. As a result, the tumour is assigned a primary pattern for the dominant grade and a secondary pattern for the non dominant grade. The Gleason score is derived by adding these together. The Gleason grades range from 1 to 5, with 5 being very poorly differentiated. Gleason grades 1 and 2 (well-differentiated cancer which requires nodular circumscription as a diagnostic criterion) cannot be easily diagnosed in the limited tissue of core biopsies. For practical purposes, Gleason grades 1 and 2 (Gleason scores 2–5) are not reported in core-biopsy specimens but only in prostatectomy specimens [106]. In prostatectomy specimens, the Gleason score is the sum of the most prevalent grade and the less prevalent grade.

28.6.2.2 Translating to an Updated Grading System

In 2014, the International Society of Urologic Pathology (ISUP) endorsed modifications to the Gleason grading system by defining grade groups 1–5 based on the Gleason score described previously. This new grading system was initially described in 2013 by Johns Hopkins Hospital and subsequently validated in a multi-institutional study of 20845 patients who underwent radical prostatectomy with a mean follow-up period of three years [107].
Gleason 3
Gleason’s pattern
1. Small, uniform glands
2. More stroma between glands
3. Distinctly infiltrative margins
4. Irregular masses of neoplastic glands
5. Only occasional gland formation

Figure 28.8 Histopathology of prostatic small cell neuroendocrine Carcinoma. (a) H&E, (b) Chromogranin, (c) Synaptophysin, (d) CD56. H&E, Haemotoxylin and eosin.

Figure 28.9 Gleason’s grading pattern. Source: Adapted from National Institute of Cancer (http://training.seer.cancer.gov/prostate/abstract-code-stage/morphology.html) public domain licence.
The new system includes five distinct grade groups based on the Gleason scoring system described previously. Gleason sum scores of 3 + 3, 3 + 4, 4 + 3, 8, and 9/10 directly translate to Grades 1, 2, 3, 4, and 5, respectively. These grade groups correspond to a five-year biochemical risk-free survival based on radical prostatectomy grade of 96% (grade 1), 88% (grade 2), 63% (grade 3), 48% (grade 4), and 26% (grade 5) (Table 28.4). The new grade groups are more accurate at predicting biochemical relapse than Gleason risk stratification groups (≤6, 7, 8–10), aligned with contemporary management strategies including AS. The new system also simplifies explanation to patients. For instance, grade 1 is the lowest grade and >95% of patients will have no detectable recurrence up to five years after radical prostatectomy. In 2016, this new system was adopted by the World Health Organisation (WHO) and will be phased in via side by side reporting to eventually replace the Gleason scoring system [108].

### 28.6.3 Immunostains

The use of immunohistochemical staining has increased rapidly in all areas of pathology, and there are many indications in prostate pathology where different antibodies are used to reach a diagnosis (Figure 28.10) [41, 113–115].

#### 28.6.3.1 Basal Cell–Associated Markers

In the presence of small amount of atypical glands, markers for basal cell are used to diagnose invasive malignancy in which the basal cell layer is missing (Figure 28.10c–e). Antibodies that demonstrate a complete absence of basal cells can help diagnose invasion. Basal cell antibodies include p63 (a member of the p53 gene family), 34betaE12 (a high molecular weight cytokeratin), and CK5/6 (another high molecular weight cytokeratin).

#### 28.6.3.2 Prostate Cancer–Associated Markers

The use of immunohistochemical staining has increased rapidly in all areas of pathology, and there are many indications in prostate pathology where different antibodies are used to reach a diagnosis (Figure 28.10) [41, 113–115].

#### 28.6.3.3 Prostate Lineage–Specific Markers

PSA and prostate-specific acid phosphatase (PSAP) are used to confirm a prostatic acinar cell origin. Both stains are used to determine the origin of metastatic disease (e.g. in pleural fluids or lymph nodes biopsies) or to rule out the presence of secondary tumours within the prostate when the tumour has an unusual morphology.

#### 28.6.4 Molecular Pathology

Prostate cancer is a complex heterogeneous malignancy with a wide range of histopathological features and clinical outcomes. Further histological or molecular markers are needed to better risk-stratify patients in selecting appropriate treatment [119–121]. In contrast to other tumours where genetic testing or immunohistochemistry is performed routinely to plan the appropriate treatment, molecular tests are currently not available for PCa in a routine clinical setting [122].

In the absence of routinely used molecular markers, the following histological markers are currently included
in pathology reports of prostatic core biopsies to predict tumour behaviour:
- Gleason grading
- Tumour quantification (percentage of tumour in biopsies)
- Perineural invasion (presence or absence)
- Extraprostatic extension (presence or absence)

### 28.6.4.1 Potential Molecular Markers

#### 28.6.4.1.1 Ki67/Mib1
Ki67 is a marker of cell proliferation and is expressed by cells in late G1, S, G2, and M phases, but not in resting cells in G0. It is used to estimate the proliferation index of a tumour. Studies have shown that measuring of the proliferation index can predict PCa outcome. It also appears predictive for biochemical relapse following radical prostatectomy and radiotherapy [123–127].

#### 28.6.4.1.2 p27
p27 is a cyclin dependent kinase inhibitor. Loss of p27 has been associated with progression for many carcinomas. Many studies have evaluated the role of p27 in PCa and found that a loss correlates with more aggressive disease [127–129].

#### 28.6.4.1.3 c-MYC
The oncogene c-MYC encodes a transcription factor and is amplified in approximately 70% of PCa. Gain of c-MYC was found predictive for tumour recurrence after radiotherapy [130, 131].

#### 28.6.4.1.4 Epigenetic Alterations
Epigenetic alterations include gene methylation, microRNA (miR) expression, and histone modification. Gene promoter hyper-methylation is a molecular mechanism of gene silencing, commonly observed in many cancers. Several genes are known to be methylated in PCa. One of them, PITX2, was shown to be a prognostic marker following radical prostatectomies [132–134]. MicroRNAs (miRs) are small, noncoding RNAs that interfere with gene expression. Studies have shown that higher levels of a specific microRNA (miR-96) were predictive of earlier biochemical relapse [41, 135–137].

### 28.7 Management, Treatments, and Patient Selection

Risk stratification is essential to guide the management of PCa. All men with newly diagnosed PCa are assigned a risk category, and treatment algorithms (Figure 28.11) are based on this classification (Table 28.5) [40]. However,
nothing creates more debate amongst clinicians (i.e. urologists and oncologists) than the optimal therapy for localised PCa (T1–2). This is due to the uncertainty of the relative efficacies of the various management options, namely deferred treatment [AS], radical prostatectomy [RP], and radical radiotherapy [RRT]). Treatment is currently based on age (i.e. life expectancy), tumour characteristics (grade and stage), patient performance status, and associated morbidity of the treatment as well as patient and physician preferences (or biases).

In general, PCa which is localised can be of low risk to the patient and managed with AS until disease progression at which point definitive treatment can be commenced, thus reducing the period of treatment and side effects. Localised but high-risk PCa requires definitive management with surgery or radiotherapy therapy because of its higher risk of invasion and metastasis. Locally advanced PCa has already spread beyond the prostate capsule but without evidence of detectable macroscopic metastasis; however, it may be managed either with local radiotherapy, surgery or systemic hormone manipulation as with overt metastatic disease depending on the patient and tumour factors.

Table 28.5 Risk stratification for men with localised prostate cancer. (Please refer to ongoing adoption of a new system of tumour grade grouping described in text.)

<table>
<thead>
<tr>
<th>Level of risk</th>
<th>PSA</th>
<th>Gleason score</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt;10 ng ml⁻¹ and ≤6</td>
<td>and T1–T2a</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>10–20 ng ml⁻¹ or 7</td>
<td>or T2b</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;20 ng ml⁻¹ or 8–10</td>
<td>or ≥T2c</td>
<td></td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen.

28.7.1 Low-Risk Localised Prostate Cancer

28.7.1.1 Active Surveillance and Watchful Waiting

There is a big difference between the incidence of PCa and death rate attributed to this disease. The incidence of small, localised, well-differentiated PCa is increasing, mainly as a result of PSA screening and multicore prostatic biopsies [138]. Evidence suggests that up to 45% of men with PSA-detected PCa are candidates for conservative management [139]. Furthermore, in men with comorbidities and a limited life expectancy, treatment of localised PCa may be deferred to avoid loss of quality of life from treatment, especially because the PCa will not affect their life expectancy.

Watchful waiting (WW) (Table 28.6), also known as symptom-guided treatment, is typically considered for individuals not indicated for radical intervention.

Table 28.6 Definitions of Active Surveillance and Watchful Waiting.

<table>
<thead>
<tr>
<th></th>
<th>Active Surveillance</th>
<th>Watchful Waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent</td>
<td>Curative</td>
<td>Palliative</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Predefined schedule</td>
<td>Patient-specific</td>
</tr>
<tr>
<td>Assessment/markers used</td>
<td>DRE, PSA, Re-biopsy, (MRI)</td>
<td>Not determined</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>&gt;10 years</td>
<td>&lt;10 years</td>
</tr>
<tr>
<td>Aim</td>
<td>Minimise treatment-related toxicity without compromising survival</td>
<td>Minimise treatment-related toxicity</td>
</tr>
<tr>
<td>Stage</td>
<td>Low and subset of patients with intermediate risk only</td>
<td>Can apply to patients of all stages</td>
</tr>
</tbody>
</table>

Source: Adapted for EAU Guidelines on Prostate Cancer.
DRE, digital rectal examination; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.
This concept was popularised in the pre-PSA era (pre-1990) and refers to a conservative approach of PCa until the development of local or systemic (symptomatic) progression. At this stage the patient would be treated symptomatically (TURP for obstruction and hormonal or radiotherapy for palliation of metastasis).

AS or monitoring (Table 28.7) is a recent concept in deferring treatment with a curative intent. Men with early stage, low- to intermediate-risk disease are followed up with serial PSA measurements, DRE, and TRUS-guided biopsies to ensure stability of the tumour. A variety of AS regimes exist [33]. Popularised in the last decade, it includes an active decision not to treat the patient immediately; instead the patient is kept under close follow-up. In young patients, it might mean delaying treatment by years. Cancers are usually treated on the first signs of subclinical progression (Table 28.7) [140, 141], with 20–41% of men on such regimes requiring treatment at three to five years of follow-up. Importantly, treatment at progression appears to be as effective as if it were delivered at the time of diagnosis for most men. Several patient and tumour characteristics were found to be predictive of later biopsy progression and deferred treatment. Men with positive confirmatory biopsies, a higher PSA density, and a higher number of positive cores were at increased risk of progression [142, 143].

### 28.7.2 High-Risk Localised PCa

#### 28.7.2.1 Radical Prostatectomy

The first prostatectomy was first performed via the perineal route by Hugh Hampton Young in 1904 and via the retropubic route by Terence Millin in 1945 [144]. However, the procedure remained unpopular because of frequent complications of incontinence and impotence. The popularity of RP followed radical improvements in our understanding of the surgical anatomy of the pelvis [145], including the dorsal venous complex, urethral sphincter, and the course of cavernous nerves, which collectively helped minimise surgical complication rates and improve functional outcomes with reduced blood loss, improved continence rates, and preservation of erectile function via nerve-sparing techniques.

More recently, minimally invasive laparoscopic radical prostatectomy (LRP) and robot-assisted laparoscopic prostatectomy (RALP) have been developed, with RALP now displacing radical retropubic prostatectomy (RRP) as the gold standard in the US and increasingly worldwide. This has occurred despite the lack of evidence demonstrating superiority of RALP over RRP in terms of critical outcomes of cancer control, preservation of continence, and erectile function [146, 147]. Currently, RRP is the only treatment for localised PCa to show a benefit in overall survival (OS) and cancer-specific survival (CSS) compared with conservative management at follow-up of 15 years [34]. The number need to treat (NNT) to avert one death was 15 for all men and 7 for men <65 years of age [34]. Subsequently the Prostate Cancer Intervention Versus Observation Trial (PIVOT) study demonstrated that RP did not reduce all-cause mortality or significantly reduce PCa mortality [148]. But in subgroup analysis of intermediate (significant) and high risk (non-significant), there was a reduction in all-cause mortality. Similarly there was also a significant reduction in all-cause mortality in men with PSA >10 [148].

Patients with localised cancer undergoing radical surgery have 10-year disease-free survival (DFS) ranging from 70 to 85%. High-grade tumours (Gleason sum >7) have a higher risk of progression. At 10 years, the DFS rates for patients with Gleason 2–6, 7, and >8 tumours are >70, 50, and 15%, respectively. The impact of positive surgical margins remains controversial. Neoadjuvant ADT reduces the risk of positive surgical margins, but it does not impact on long-term biochemical relapse-free survival [149], in addition makes surgical dissection more difficult.

#### 28.7.2.1.1 Technique of Radical Prostatectomy

With the patient head-down the bladder is catheterized. A long lower midline incision is made and a node dissection is now performed for patients with intermediate- and high-risk disease.

The bladder is retracted upwards and the fat cleaned from the retropubic veins. The pelvic fascia is incised on either side of the puboprostatic ligament which contains the dorsal vein (Figure 28.12). The leash of veins is...
carefully suture ligated, and the layer of pelvic fascia containing the neurovascular bundles are displaced laterally (Figure 28.13). A sling is passed around the urethra and pulled up. The urethra is opened just distal to the apex of the prostate and just cephalad to the membranous urethra and its intramural sphincter (Figure 28.14). The catheter is now used to pull up the prostate, and the tissue behind the prostate – the rectourethralis muscle – is divided in the midline and again displaced laterally and backwards away from the prostate on either side to preserve the penile neurovascular bundles (Figure 28.15). Medial to this bundle, there is a stout leash of inferior vesical vessels which must be suture ligated (Figure 28.16).

The bladder is opened at the bladder neck (Figure 28.17). Deflating the balloon of the catheter, and using the catheter as a sling, the prostate is lifted up and the bladder is dissected away from the prostate. When the bladder is finally cut across, its calibre is similar to
that of the cut edge of the urethra. As the back of the trigone is dissected from the prostate, the seminal vesicles and vasa efferentia are displayed (Figure 28.18). Their arterial bundles are ligated and divided well medial to the penile neurovascular bundles (Figure 28.19).

The bladder neck may have to be narrowed with one or two sutures before it is anastomosed over a 20-Ch silicone catheter to the stump of the urethra. Great care is taken in making this anastomosis to get a precise urothelial junction and not to injure the intramural sphincter mechanism immediately distal to the site of division (Figure 28.20). It helps to place all the sutures before tying them.
28.7.2.1.2 Complications

Morbidity associated with RP may be significant and is related to surgical experience.

Intraoperative complications include blood loss requiring blood transfusion, rectal injury, and ureteral injury. Laparoscopic approaches decrease bleeding rates, but carry the additional risks of laparoscopic access and insufflation, as well as patient positioning (e.g. lower limb compartment syndrome).

Perioperative complications include anastomotic leak, deep vein thrombosis, pulmonary embolus, and wound infection.

Late complications include urinary incontinence, impotence or erectile dysfunction, and bladder neck stenosis.

- Urinary incontinence, usually stress incontinence as a result of damage to the external urethral sphincter.

De novo urgency incontinence and incontinence due to bladder neck stenosis (overflow) are the other types that can occur. The return of continence after surgery may be gradual, with many men regaining continence by two to three months, but recovery continues up to one year. Most academic series report long-term continence rates of 80–95% by one year; however, continence rates from population-based studies are often much less. Pelvic floor exercises pre- and postoperatively can help regain continence; however, if lasting more than one year, the insertion of an artificial urinary sphincter will be required.

- Impotence or erectile dysfunction can affect 60–90% of patients. Like continence, reported rates of potency preservation vary widely, ranging from 40 to 82% in men younger than 60 years when both nerves are preserved and drops to 20–60% when only one nerve is preserved. Recovery of sexual function generally occurs gradually within 6–24 months following surgery. Potency may be improved with early use of phosphodiesterase-5 (PDE-5) inhibitors.

- Bladder neck stenosis, noticed when the flow becomes weaker or poor flow with worsening storage symptoms (e.g. frequency and urgency) is treated with a bladder neck incision or resection of the scarred tissue.

28.7.3 Role of (Pelvic) Lymph Node Dissection

Extended lymph node dissection (eLND) provides important prognostic information, which surpasses any current imaging modality (Figure 28.21). There is, however, no consensus about when it is indicated and to what extent. According to nomograms, patients with PSA <10 ng ml\(^{-1}\) and biopsy Gleason <7 have a low risk of lymph node metastasis, and therefore, eLND may not be beneficial. However, it should be noted that most nomograms are based on limited eLND (i.e. obturator fossa and external iliac vein), resulting in an underestimation in the incidence of patients with positive lymph nodes [150]. The removal a greater number of nodes results in improved staging. Greater than two nodes involved is an independent predictor of poorer PC-specific survival with a 1.9-fold relative increase in risk of PC-specific death [151].

eLND includes removal of nodes overlying the external iliac artery and vein, nodes within the obturator fossa, and nodes medial and lateral to the internal iliac artery. Some templates include clearing the common iliac nodes to the ureteric crossing, suggesting 75% of all anatomical landing sites are cleared with this approach [152]. Some studies suggest a therapeutic impact of eLND in a subset of patients with limited lymph node metastases, with improvements in

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*Figure 28.20* After narrowing the bladder neck, a precise mucosa-to-mucosa anastomosis is made between the bladder neck and the urethra over a 20 F catheter. Place all sutures prior to tying them.
biochemical disease-free survival (BDFS) in patients with intermediate- and high-risk disease [153–155]. When comparing eLND to limited LND, threefold higher complication rates have been reported in some studies [156]. Complications include lymphocele, lymphedema (scrotal and or lower limb), deep vein thrombosis, and pulmonary embolism.

28.7.4 Radical Radiotherapy

Radiation treatment for PCa goes back for nearly a century. Two types of radiotherapy are used for PC: (i) external beam radiotherapy (EBRT) or (ii) interstitial irradiation (brachytherapy). With no high-quality head-to-head comparative trials, radiotherapy is an important alternative to surgery for curative therapy.

28.7.4.1 External Beam Radiotherapy

Standard EBRT regimes allow the delivery of 65–70 Gy to the prostate, in rectangular fields (as determined by bony landmarks from CT), with minimal to no blocking and small boost fields. Unsurprisingly up to 41% of patients may have inadequate coverage of the target volume. Improvements in imaging and treatment planning (three-dimensional, conformal radiation therapy [3D-CRT] and intensity-modulated radiation therapy [IMRT]) has allowed for better targeting and conforming of the treatment to the prostate, facilitating the use of increased doses, whilst limiting the toxicity secondary to an excessive dosage to surrounding normal tissues. These innovations have resulted in dramatic improvements in both acute and late toxicity of radiotherapy and improved cancer control compared with standard EBRT.

The use of dose escalation, whole pelvic radiation (including regional lymph nodes) and androgen deprivation (i.e. neoadjuvant, concurrent, and adjuvant) has improved the results of radiotherapy in intermediate and high-risk locally advanced PCa. Short-term (three to six months) neoadjuvant (three months prior) and concurrent (three month after) androgen deprivation is recommended for those with intermediate-risk disease, whereas those with high-risk disease should receive neoadjuvant (three months prior), concurrent, and long-term adjuvant (24 months after) androgen deprivation [157–159].

Side effects of radiotherapy are related to urinary (e.g. urgency, frequency, and haematuria), bowel (e.g. diarrhoea, rectal bleeding, and tenesmus), and gradual onset sexual dysfunction. The impact on sexual function may not be apparent for up to two years and are often exacerbated with the concurrent use of androgen deprivation [160]. Long-term risks include urethral stricture, recto-urinary fistula, and radiation cystitis, which although uncommon can be severely debilitating for the patient and offer complex management challenges for the physician.

As with all radiotherapy, there is an increase in secondary cancers (1 in 300); with prostate EBRT, there is a doubling of the risk of rectal cancer and bladder cancer starting 10 years after prostate radiotherapy [161]. Therefore, pelvic radiotherapy is contraindicated in patients who have had previous pelvic radiotherapy, severe LUTS, and inflammatory bowel disease.

28.7.4.2 Stereotactic Ablative Radiotherapy

Standard radiotherapy delivers treatment for PCa over seven to eight weeks using 2 Gy per fraction. This is considered as conventional fractionation. The radiobiology of PCa clearly suggests that higher doses per fraction can potentially be more effective and improves on local control rates due to increased sensitivity to fraction size.

Stereotactic ablative radiotherapy (SABR) refers to the use of higher dose per fraction over a much shorter period of time (hypofractionation), which enhances
tumour control and is certainly more convenient to patients as well. This technique delivers highly conformal radiotherapy over shorter period, which can now be achieved safely with the use of better on-treatment imaging and image-guided radiotherapy [41, 162, 163].

### 28.7.4.3 Brachytherapy

In the past, free-hand seed placement techniques were associated with high rates of treatment failure, resulting in this technique falling out of favour. The accurate placement of the radioactive seeds under TRUS guidance has coincided with an increase in the popularity of the procedure. Radioactive implants are either permanently placed in the prostate (I\(^{125}\) half-life 60 days, or Pd\(^{103}\) half-life 17 days [164]) or radiation can be delivered via hollow-core catheters (Ir\(^{192}\)) attached to temporary implants for the duration of hospitalisation. Permanent implants have a lower dose rate (LDR), but a higher total dose delivered, compared to temporary implants which have high dose rates (HDR) and lower total doses.

Eligibility criteria for permanent seed implantation [165]:

- Stage cT1b-T2a, N0, M0
- Gleason score <=6
- Initial PSA <=10 ng ml\(^{-1}\)
- <=50% biopsy cores involved with cancer
- Prostate volume <50 cm\(^3\)
- International Prostate Symptom Score (IPSS) <=12

Some patients experience significant urinary complications, such as urinary retention (1.5–22%), with post implantation TURP required in up to 8.7%, and urinary incontinence (0–19%) (increased risk with previous TURP) [166]. The incidence of grade III toxicity is less than 5%. Erectile dysfunction develops in about 40% of patients after three to five years. Therefore, contraindications include moderate (IPSS 8–19) to severe (IPSS >20) LUTS (due to increased risk of retention), previous TURP, and >50 cm\(^3\) prostate volume due to difficulty in seed placement.

Patients with low-risk PCAs are the most suitable candidates for lower-dose rate brachytherapy. EBRT is often given to those with intermediate- and high-risk cancers. As opposed to EBRT, androgen deprivation does not appear to improve the outcomes of men with low- and intermediate-risk disease being treated with brachytherapy [167]. Androgen deprivation can be used to shrink the prostate prior to brachytherapy to facilitate seed placement, with the caveat of additional side effects (Table 28.8) [168]. For nonsurgical intervention, patients with high-risk PCa tend to be managed by EBRT and adjuvant androgen-deprivation therapy (ADT).

A word of caution on monitoring patients after radiotherapy: while checking the PSA, one might notice a rise in PSA after the NADIR. This is not recurrence, but coined ‘PSA bounce’ which occurs around nine months post-RT, but can occur anytime for the first two years. The PSA level is usually <1.5 ng ml\(^{-1}\).

### 28.7.5 Locally Advanced PCa

Men with PCa that is clinically staged as T3a (locally advanced), Gleason score 8–10, or PSA level greater than 20 ng ml\(^{-1}\) are considered at high risk of recurrent disease despite definitive radical treatment. Treatment for patients with locally advanced PCa should take into consideration patients’ comorbidities, general health, and life expectancy. After careful staging with pelvic MRI and bone scintigraphy, patients may be considered for the following treatment options.

#### 28.7.5.1 Radical External Beam Radiotherapy

The preferred treatment option is 3D-CRT (or IMRT) with daily image-guided RT (IGRT) in conjunction with long-term ADT for two to three years. Combining ADT with RT has been comprehensively demonstrated to improve disease-specific survival and OS compared to single-modality treatment: (i) Two randomised phase III trials evaluated long-term ADT with or without radiation in mostly T3 patients [1, 36]; (ii) 415 patients were randomised to either EBRT alone or EBRT plus three-year ADT [160]; (iii) In the RTOG 8531 study, 977 patients with T3 disease were treated with RT with either immediate adjuvant ADT or delayed ADT at disease relapse [161]. Furthermore, increasing evidence favours long-term over short-term adjuvant (following neoadjuvant or concurrent) ADT in patients with high-risk disease. The European Organisation for Research and Treatment of Cancer (EORTC) 22961 trial showed superior survival when 2.5 years of ADT were added to RT given with sixmonths of ADT in 970 patients, mostly with T2c-T3, N0 disease [173].

There are emerging data that associate lower biochemical failure rates with the addition of HDR brachytherapy boost to EBRT in patients at high risk [174, 175]. The practical principles for radiation therapy using IMRT and image-guided RT techniques allow safer delivery of higher doses of radiation (74 Gy in 37 fractions most commonly used in the UK). For those with high risk of lymph node involvement (predicted risk of >15% using the Roach formula: 2/3 PSA + (10× [Gleason score-6])), pelvic nodal irradiation using IMRT technique should be considered. Prostate RT accuracy is enhanced with the use of fiducial markers (such as implanted gold seeds) and tracking devices that facilitate image-guided treatment to minimise radiation-induced toxicity.

Patients with high-risk locally advanced PCa (cT3b–T4 N0 or any T, N1) have a significant risk of disease...
progression and cancer-related death. The optimal treatment approach, therefore, often necessitates multiple modalities to achieve local control as well as controlling the highly likely microscopic disease. Neoadjuvant and adjuvant ADT with radiotherapy is commonly used in this setting but risk of recurrence is very high (>20% over approximately 10 years). Both ETORC [158, 169] and RTOG 92–02 studies evaluated long-term OS and progression-free survival (PFS) in such high-risk localised disease with median follow up of 9.1 and 11.3 years, respectively. Both showed a benefit of combined ADT and radiotherapy with an increase in OS and PFS at follow up (40–58% increase in OS and 23–48% PFS for EORTC) [169]. ADT or RT of the primary tumour plus neoadjuvant, concomitant, or adjuvant ADT (of two to three years) are available options for patients with N1 disease on presentation [36, 41]. ADT as single modality (bicalutamide 150 mg

<table>
<thead>
<tr>
<th>Timing</th>
<th>Side effects</th>
<th>Prevalence if known</th>
<th>Possible monitoring and treatment of side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>Flare Phenomenon – Bony pain, spinal cord compression</td>
<td>Unknown</td>
<td>Analgesia, steroids</td>
</tr>
<tr>
<td>Acute (Few weeks)</td>
<td>Hot flushes (vasomotor flushing) – low testosterone interrupts negative feedback on hypothalamic noradrenaline production which resets hypothalamic thermoregulatory centre.</td>
<td>up to 80%</td>
<td>Progesterone agents - medroxyprogesterone (20mg OD), megestrol acetate (20mg BD for 4 weeks)</td>
</tr>
<tr>
<td></td>
<td>Sexual dysfunction – Loss of libido, shrinkage of genitalia</td>
<td>80–90%</td>
<td>Anti-androgen cyproterone acetate</td>
</tr>
<tr>
<td></td>
<td>● Erectile dysfunction</td>
<td></td>
<td>SSRI paroxetine</td>
</tr>
<tr>
<td></td>
<td>● Breast tenderness and or growth</td>
<td></td>
<td>SSNRIs venlafaxine, gabapentin</td>
</tr>
<tr>
<td>Chronic (months – years)</td>
<td>Skeletal related events – loss of BMD is associated with length of ADT</td>
<td>20%</td>
<td>Education, counselling and sexual therapy, Parenteral oestrogen, sperm storage.</td>
</tr>
<tr>
<td></td>
<td>● Fractures</td>
<td></td>
<td>Referral to specialist erectile dysfunction services, PDE5 inhibitors, vacuum erection devices, intrarethral inserts, intracorporal injections or prostheses.</td>
</tr>
<tr>
<td></td>
<td>● Osteoporosis</td>
<td></td>
<td>Radiotherapy to breast buds</td>
</tr>
<tr>
<td></td>
<td>Decreased cognitive function – decline in memory and executive functioning</td>
<td>Unknown</td>
<td>Combined resistance and aerobic exercise programs.</td>
</tr>
<tr>
<td></td>
<td>Low mood and depression</td>
<td>Unknown</td>
<td>Counselling and regular exercise, antidepressants.</td>
</tr>
<tr>
<td></td>
<td>Metabolic / cardiovascular dysfunction – obesity, insulin</td>
<td>14–70%</td>
<td>Annual lipid profile, lifestyle modifications stop smoking, weight loss, exercise program.</td>
</tr>
<tr>
<td></td>
<td>insensitivity and alters lipid profiles (increase cholesterol)</td>
<td></td>
<td>Hypoglycaemics metformin, antihypertensives, statins, aspirin, toremifene (improves lipid profile).</td>
</tr>
<tr>
<td></td>
<td>Anaemia – reduced erythrogenesis</td>
<td>90%</td>
<td>Iron and vitamin B12 or folate supplements when appropriate.</td>
</tr>
<tr>
<td></td>
<td>Fatigue &amp; lean muscle wasting</td>
<td>40%</td>
<td>If severe, blood transfusion or darbepoetin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Supervised resistance and aerobic exercises ≥ twice a week for 12 weeks.</td>
</tr>
</tbody>
</table>

ADT, androgen-deprivation therapy; BMD, bone mineral density; DEXA, Dual X-ray absorptiometry; PC, prostate cancer; PDE5, Phosphodiesterase type 5; SERT, Selective oestrogen receptor modulator; SSRI, selective serotonin reuptake inhibitors; SSNRI, serotonin-norepinephrine reuptake inhibitors.
daily) is considered to be an inferior and noncurative treatment option when compared to combination therapy (i.e. ADT and radiotherapy) and best suited for patients who are elderly and symptomatic or those unwilling to undergo EBRT [36, 41].

28.7.5.2 Radical Prostatectomy
Surgical resection of locally advanced PCa is an option depending on the health status of the patient. There is no gold standard for locally advanced PCa because it requires multimodal therapy with either a curative aim or to improve local control, stay metastasis free, and for PC-specific survival. RP for locally advanced PCa should ideally be combined with extended lymph node dissection in patients with a life expectancy of >10 years and with minimal comorbidities [170]. RRP for locally advanced PCa has recently shown promise and has reported equivalent outcomes to open surgery [171].

28.7.6 Recurrence after Curative Intent Treatment

28.7.6.1 Adjuvant versus Salvage Treatment
Relapse after radical therapy either radiation or surgery is a salvage treatment modality. Combined treatment at the time of radical therapy (usually within six months) is considered an adjuvant treatment modality. Despite the earlier nature of adjuvant radiotherapy compared to salvage radiotherapy after radical prostatectomy biochemical relapse-free survival (BCR) is not significantly changed. Briganti et al. performed a randomised trial of adjuvant versus early salvage radiotherapy (eSRT) (SRT for PSA rising but ≤2 ng ml⁻¹) and showed no significant difference between patients treated with observation and eSRT versus adjuvant RT (>6 months post surgery) [172]. Therefore, eSRT for biochemical recurrence following surgery given before the PSA rises above 2 ng ml⁻¹ is as effective as adjuvant radiotherapy in patients undergoing RP for locally advanced high-risk PCa. However, current European Association of Urology (EAU) recommendations define a rising PSA cut-off of ≤0.5 ng ml⁻¹ to initiate eSRT post surgery for high-risk locally advanced disease to provide approximately 80% chance of being progression free at five years [173].

28.7.6.2 Salvage Radiotherapy Post-Radical Prostatectomy
There currently is no imaging modality that can effectively detect recurrence or relapse, post-RP. Furthermore, biopsy of the pelvic prostatic bed is not common practice. Therefore, recurrence or relapse is considered as any rise in PSA >0.2 ng ml⁻¹. Subsequent treatment options include observation, radiotherapy, or ADT.

Good response to salvage radiotherapy is seen in patients with a low-grade or low-stage disease from the start, PSA rise >1 year after prostatectomy, doubling time >12 months, and PSA is <1 ng ml⁻¹. Generally, a period of surveillance is offered, and radiotherapy is given when the PSA is rising but <0.5 ng ml⁻¹. For a positive surgical margin, radiotherapy is given once PSA is between 0.5 and 1 ng ml⁻¹ after a period of surveillance.

If lymph node dissection yielded nodal involvement, options are either early or delayed hormonal therapy.

28.7.6.3 Salvage Therapy Postradical Radiotherapy (Androgen-Deprivation Therapy or Salvage Prostatectomy)
Treatment failure is defined as a rise in PSA by 2 ng ml⁻¹ from the nadir (the lowest recorded PSA after treatment). ADT is the mainstay of salvage therapy post-RP, either immediate or delayed until symptomatic. However in selected patients, salvage radical prostatectomy can be considered. Alternatively, brachytherapy can be offered; however, repeat biopsies will be required to demonstrate viable cancer cells.

28.7.6.4 Metastatic Prostate Cancer
Metastatic PC (mPC) currently has an incidence of approximately 10% at diagnosis from European Randomised Study of Screening for Prostate Cancer (ERSPC) data [174]; this depends on the level of PSA screening which is discussed further in Section 28.11.1. An autopsy study in the year 2000 of 19,316 routine autopsies in men older than 40 years detected PCa in 8.2% (1589). This study showed that 35% of PCa detected was metastatic at autopsy and in most (90%) cases in bone. The next most common sites were lung (46%) followed by liver (25%), pleura (21%), and adrenal glands (13%). Interestingly, an inverse relationship was seen between lung and bone metastasis, suggesting independent mechanisms of metastatic spread. More recently phylogenetic mapping of mPC has revealed the complexity of the evolution of mPC using deep genome sequencing, which is also discussed further in Section 28.11.5.7 [175].

As with normal prostate epithelium, mPC depends on dihydrotestosterone (DHT), the active form of testosterone. Testosterone is made in the Leydig cells of the testicles, but the adrenal glands secrete an additional amount of steroid precursors, which are converted to testosterone by the enzyme 5-alpha reductase expressed in prostate cells (Figure 28.22). The active DHT interacts with the androgen receptor (AR) present in normal and PCa cells. The AR translocates to the nucleus after binding DHT and dimerises to act as a potent transcription factor directly binding to DNA at many androgen-response elements (AREs) and driving the transcription of essential genes for growth and survival in normal and mPC cells.
In 1941, Huggins and Hodges reported the ‘dramatic clinical effects of suppressing serum testosterone levels’ by surgical (bilateral orchiectomy) or pharmacological castration (diethylstilboestrol [DES], which suppresses luteinising hormone-releasing hormone [LHRH] production at the hypothalamus) (Figure 28.22) in men with advanced PCa [176]. They were awarded the Noble Prize in 1967 for establishing the concept of ADT, which remains universally accepted as the first-line treatment for symptomatic mPC. National Institute for Health and Care Excellence (NICE) and the European Society for Medical Oncology (ESMO) guidelines also recommend ADT to be used as a neoadjuvant therapy for four to six months in patients receiving radical radiotherapy for high-risk disease and should also be considered for intermediate-risk disease. This should be followed with two to three years of adjuvant ADT in patients having EBRT for high-risk disease. Neoadjuvant and adjuvant ADT is not routinely recommended for patients undergoing RP.

In the 1970s, ADT was delivered as LHRH agonists, chronic use of which decreases luteinising hormone (LH) by desensitising pituitary LHRH receptors. The monthly depot of leuprolide was the first LHRH agonist shown to be as clinically effective as DES but with a lower incidence of cardiovascular toxicity. LHRH agonists are still the most commonly used method of ADT. Different preparations differ in their route of administration (i.e. intramuscular injection, subcutaneous injection, or implant) and frequency of administration (1–12 months). There is little difference in the side effect profiles between different LHRH agonists, with minimal survival differences between compounds [177].

ADT has numerous well-recognised adverse effects, and it is essential that clinicians understand these side effects to limit treatment-related morbidity (Table 28.8). Acrutely, LHRH agonists stimulate the anterior pituitary gland to promote testosterone secretion from the testes (and to a lesser extent the adrenal glands), thus potentially resulting in initial ‘flare’ symptoms [178]. These symptoms may manifest, depending on the tumour burden of the individual patient. For example, if patient has spinal metastases, even a short-term increase in tumour growth could have disastrous consequence of spinal cord compression. Anti-androgens are, therefore,
Prostate Neoplasm

routinely given for a few weeks when starting LHRH analogues to prevent flare symptoms. Less acutely, side effects due to castration levels of testosterone include hot flushes, loss of libido, and erectile dysfunction. ADT decreases lean body mass and increases subcutaneous fat mass. Observational studies associate ADT with increased insulin resistance, cardiovascular disease, and development of the metabolic syndrome [179, 180]. Several studies show increased cardiovascular risk unrelated to the duration of ADT therapy [181, 182], yet a recent meta-analysis found no increased risk of cardiovascular death [183]. Cardiac disease need not preclude the use of ADT; however, appropriate secondary preventative measures to lower cardiac risk should be considered [184].

Increased bone loss following ADT results from impaired bone remodelling. ADT causes up to 3–5% in the annual decrease of bone mineral density (BMD) [185], in a time-dependent manner, resulting in sixfold increase in fracture rate associated with ADT-induced osteoporosis. Supplementation of calcium and vitamin D should be utilised, as well as quantifying BMD before commencing ADT. In patients with PCa and osteoporosis, bisphosphonates should be used to decrease osteoclast activity, with a recognised improvement in BMD of 7% in oneyear [186]. Denosumab, a human monoclonal antibody directed to RANK ligand (a mediator of osteoclasts), reduces vertebral fractures by half, when compared to placebo [187], and has been found to delay skeletal-related events (SREs) for longer than zoledronic acid. However, neither agent has been shown to prolong survival. Side effects include hypocalcaemia and osteonecrosis of the jaw [188].

Newer ADT drugs, such as LHRH antagonists (e.g. degarelix) bind competitively to the pituitary LHRH receptors, thereby reducing LH and testosterone levels without the risk of an initial testosterone flare. Degarelix is equally effective in maintaining testosterone suppression than LHRH agonist over a 12-month period [189] and has a role in patients with metastatic PCa and impending spinal cord compression. It is administered as a monthly subcutaneous injection, and side effects include local injection site redness, pain and swelling, and liver enzyme abnormalities.

28.8.1 Anti-Androgens

Nonsteroidal anti-androgens (e.g. flutamide, bicalutamide) block the effects of adrenal androgens dehydroepiandrosterone (DHEA) and androstenedione at the androgen receptor by competitive ligand binding in PCA cells. Their main side effects are gynaecomastia, diarrhoea, nausea, and fatigue. Bicalutamide monotherapy is not as effective as LHRH treatment for mPC; however, it is equivalent to no-metastatic disease. NICE and ESMO guidelines support the use of bicalutamide (150 mg daily) in metastatic PCa if a patient wishes to maintain sexual function and understands that there is limited data on survival and progression outcomes. This is because nonsteroidal anti-androgens do not inhibit at the pituitary level; therefore, serum testosterone is normal or higher. However, if sexual function is not maintained on bicalutamide, individual patients should be changed to LHRH-based ADT. There is peripheral conversion of testosterone to oestrogen with their use which can lead to gynaecomastia with or without breast pain. Therefore, patients should be offered prophylactic radiotherapy to breast buds to prevent gynaecomastia within the first month of starting bicalutamide monotherapy. If this is unsuccessful, weekly tamoxifen should be considered.

Steroidal anti-androgens also inhibit pituitary via negative feedback. Cyproterone acetate can also be used to prevent LHRH-associated flares, but also help with side effects such as the hot flushes associated with castration. However, are associated with cardiovascular side effects.

Scheduling of ADT has also been considered. Due to the adverse effects of ADT and the onset of castration resistance, intermittent therapy is believed to allow hormonal balancing during alternating androgen blockade and treatment ‘holiday’ (or recovery). Although there is no evidence of a survival inferiority in intermittent ADT compared to continuous ADT (mainly in metastatic cases), additional longer-term outcome data is required [190]. In accordance with NICE guidelines, men considering intermittent ADT need to be counselled about the limited evidence for reduction in side effects and possible effect on progression of PCa. PSA should be measured every three months and ADT should be restarted if PSA ≥10 nmol/L or if symptomatic progression. The timing of commencing ADT remains unresolved. In locally advanced disease not amenable to local therapy, immediate ADT is justifiable in those with a high initial PSA (>50 ng ml⁻¹) or a PSA doubling time of <12 months to delay progression complications [191]. After BCR following radical treatment, ADT should only be commenced with symptomatic local disease progression, any proven metastases, or PSA doubling time of less than three months (NICE guidelines) [40].

28.8.2 Dual and Combined Androgen Blockade

LHRH agonists (or antagonists) and AR antagonists can be combined to provide what used to be referred to as ‘maximal androgen blockade’ (MAB). Given the advent of the new drugs enzalutamide and abiraterone, it seemed unlikely that bicalutamide plus LHRH is ‘maximum’.
Hence the terms ‘dual androgen blockade’ (DAB) and ‘combined androgen blockade’ (CAB) are considered more accurate descriptions of the practice. Nearly 25% of men will benefit from adding bicalutamide 50mg to the LHRH injections for CAB. NICE guidelines do not recommend combined ADT as first-line treatment for men with mPC. However, as a second-line treatment, CAB improves survival at five years by 5% compared to LHRH agonist therapy alone in men with advanced disease [192]. The additional treatment is not without side effects, and patients may experience decreased quality of life due to impaired cognitive function, thermoregulation disruption, and sexual function [193]. It has been reported that in up to 25% men when their PCa stops responding to CAB, stopping the anti-androgen drug, stops the tumour growth for a short time. This has been called anti-androgen withdrawal effect for which the mechanism is not fully understood but is likely related to mutations in the ligand binding domain of the AR, thus switching the AR antagonists (such as bicalutamide) from inhibiting to activating the AR [194]. Corticosteroid such as dexamethasone (0.5 mg daily) can be offered as third-line hormonal therapy after combination ADT.

28.8.3 Second-Generation Anti-Androgens: Enzalutamide and Abiraterone

After a variable period of ADT, patients eventually progress to CRPC. The main driver for cancer progression in CRPC is persistent activation of the AR signalling axis. ADT should be continued in CRPC, and these patients should be offered further hormone therapies or if a poor response to initial hormone therapy, chemotherapy or clinical trials can be considered. A new generation of AR-targeting agents has been developed, including abiraterone acetate (which inhibits CYP17, the rate-limiting enzyme involved in androgen biosynthesis) and enzalutamide (which inhibits AR translocation into the nucleus).

Abiraterone, in combination with prednisolone, was approved for treatment of asymptomatic and mildly symptomatic metastatic CRPC [184]. It has to be taken with prednisolone to avoid serious side effects associated with reactive mineralocorticoid excess (e.g. hypokalaemia, hypertension, and cardiac failure), and in combination with LHRH analogues. Alone abiraterone does not stop the testicular production of testosterone. Abiraterone treatment increased patient OS by 8.6 months following disease progression despite previous docetaxel treatment [195]. Enzalutamide (ENZ) acts as an AR inhibitor, with greater affinity to AR than bicalutamide [196]. For patients with mPC, ENZ improved the OS by 5.8 months, with additional improvements in time to PSA rise (biochemical progression) and skeletal events compared to placebo. Side effect profiles for ENZ and abiraterone are similar, with hot flushes, back pain, fatigue, nausea, and diarrhoea the most common complaints. Abiraterone also causes hypertension and peripheral oedema, whereas ENZ can cause dizziness and rarely, seizures. Both abiraterone and enzalutamide are oral medications.

28.8.4 Androgen-Deprivation Therapy Options

28.8.4.1 First-Line Androgen-Deprivation Therapy

28.8.4.1.1 Luteinizing Hormone-Releasing Hormone Analogues

Compounds which imitate the action of LHRH agonists boost the output of LH by the pituitary until it is exhausted. For about a week the testicles and adrenals are in overdrive, and there is a surge in the level of testosterone in the blood which produces a flare of symptoms which can sometimes be serious (e.g. paraplegia) [41, 197]. The results of treatment with LHRH agonists are equivalent to orchedectomy. During the first week of treatment with LHRH agonists, the side effects of the surge in testosterone level may be prevented by androgen receptor blockers [41, 197].

28.8.4.1.2 Luteinizing Hormone-Releasing Hormone Antagonist

LHRH antagonist (i.e. degarelix) [189] therapy is a new generation of hormonal therapies, which avoids the flare phenomena and does not require short-term anti-androgen cover. Orchietomy is an equally effective option and should be considered as an option in metastatic disease, provided it is acceptable to patient. In a population-based study, ADT with a LHRH agonist was associated with an increased risk for individuals to develop diabetes (hazard ratio [HR], 1.44; P < 0.001), coronary artery disease (HR, 1.16; P < 0.001), and myocardial infarction (HR, 1.11; P = 0.03) [183, 198, 199]. Compared to LHRH agonists, treatment with LHRH antagonist halved the number of cardiac events experienced by men with pre-existing cardiovascular disease during the first year of ADT [200].

28.8.4.1.3 Bilateral Subcapsular Orchiectomy

This is an irreversible and, compared with the other options, cheap form of ADT. Through a transverse scrotal incision one testis is delivered, the tunicae are incised, the testicular tubules are wiped away, and haemostasis is obtained by suture and diathermy (Figure 28.23). The same is done on the other side. Great care must be taken in regard to haemostasis to prevent a haematoma. It can
be done under local anaesthesia using bilateral inguinal blocks and infiltration of the scrotal skin.

28.8.4.1.4 Androgen Receptor-Blockers
These compounds are known as anti-androgens outlined previously. There are two main types. The first are the steroids cyproterone acetate and megestrol acetate. These prevent flare in the first couple of weeks of treatment with LHRH agonists and also subsequently prevent the tiresome side effect of hot flushes, seen either with orchiectomy or LHRH treatment. The second are non-steroidal compounds such as flutamide, nilutamide, and bicalutamide. Used on their own, the anti-androgens can have a therapeutic benefit that compares reasonably with orchiectomy, but when given to the patient whose metastases have escaped from the effect of orchiectomy or LHRH agonists, they have little effect.

28.8.5 Second-Line Androgen-Deprivation Therapy

28.8.5.1 Dual and Combined Androgen Blockade
Orchiectomy lowers the plasma testosterone by more than 90%, but it only reduces the level of testosterone in the prostate by about 75%. The residual testosterone is derived from adrenal precursors dehydroepiandrosterone and androstenedione which are converted in the cell to testosterone. (For a time in the 1960s, adrenalectomy was widely used for clinical relapse after orchiectomy, but the results did not justify the morbidity of the operation.)

DAB and CAB refer to the use of medical or surgical castration together with anti-androgen. No survival advantage of this approach has been shown by any prospective randomised trials. However, meta-analysis suggested that non-cyproterone acetate anti-androgens such as bicalutamide may provide an additional OS [201, 202].

28.8.6 Third-Line Androgen-Deprivation Therapy

28.8.6.1 Oestrogenic Therapy
Oral oestrogen (e.g. DES) was used previously as a method of ADT and is as effective as orchiectomy or LHRH agonists in producing castration levels of testosterone. It also avoids some of the side effects associated with other hormonal therapies such as osteoporosis, osteoporotic fractures, and hot flushes, but it is not used routinely as first-line therapy because of the increased incidence of cardiovascular complications [203]. The Scandinavian Prostatic Cancer Group-5 trial, involved slightly more than 900 patients randomised to either polyestradiol phosphate (PEP) intramuscular injection or ADT (orchiectomy or triptorelin + flutamide) [204–206]. Most recent analysis shows no difference in OS or disease-specific survival and no difference in cardiovascular-symptom mortality. This approach is currently been explored using oestradiol transcutaneous patches (PATCH trial MRC PR09 trial) [207].

28.8.6.2 Combined and Upfront Chemohormonal Therapy
Combined use of new agents like Abiraterone or ENZ in patients with hormone-sensitive disease has recently been evaluated within the context of clinical trials (CHAARTED, USA and STAMPEDE, UK) [208, 209]. These studies assessed the role of chemotherapy (Docetaxel) in conjunction with ADT in hormone-sensitive disease and have shown that upfront treatment with Docetaxel provides an OS over standard of care (ADT alone) of 13.6 months further increased to 17 months in a subgroup analysis of patients with high volume mPC. Such a significant increase in survival prompted recommendations that upfront Docetaxel with ADT has now becomes the new standard of care for high volume mPC.
28.9 Castration-Resistant Prostate Cancer

CRPC occurs in response to ADT with castrate serum levels of testosterone (i.e. testosterone <50 ng dl\(^{-1}\) or <1.7 nmol l\(^{-1}\)). It can be defined as three consecutive increases in PSA, at least one week apart, resulting in two 50% increases over the lowest PSA. As PSA is an androgen-responsive gene, this clinical definition of CRPC relies on reactivation of AR signalling.

Anti-androgens such as bicalutamide can activate AR signalling in the case of mutant AR expression [194]. The initial response in DAB is withdrawal of the anti-androgen for at least four weeks for flutamide and for at least six weeks for bicalutamide. PSA progression, despite consecutive hormonal manipulations or progressive metastatic lesions on bone scan or soft-tissue lesions (nodes >2 cm in diameter), are all indicators of progression to CRPC.

28.9.1 Castration-Resistant Nonmetastatic Prostate Cancer

There are no clear prospective data from randomised trials to guide treatment for the group of patients with castration-resistant nonmetastatic PCa (n-mCRPC). The only randomised controlled trial in this setting evaluated the role of Denosumab. In a phase III randomised trial involving 1432 patients with n-mCRPC, Denosumab was reported to delay bone metastasis by four months compared to placebo [210]. However, OS did not improve.

28.9.2 Metastatic Castration-Resistant Prostate Cancer

The group with metastatic castration-resistant PC (mCRPC) is more prevalent than the n-mCRPC group with more than 85% of men who die of PCa having mCRPC to the bone [211]. The management of this group of patients has changed quite significantly over the last few years with a number of new agents demonstrated to positively impact OS (Table 28.9).

These options include:

1) **Androgen synthesis inhibitor**: Abiraterone acetate (a CYP450c17 enzyme inhibitor, blocking androgen biosynthesis within cells), in combination with low-dose prednisone, for the treatment of men with mCRPC following prior chemotherapy containing Docetaxel. The median survival were 15.8 vs. 11.2 months in the Abiraterone and placebo arms, respectively [195, 223, 224]. Furthermore, in another randomised phase III trial of Abiraterone acetate and prednisone versus prednisone alone in men with asymptomatic or minimally symptomatic (chemo-therapy naïve) mCRPC, the OS was also improved, providing evidence for use of Abiraterone prior to Docetaxel chemotherapy [225].

2) **Chemotherapy (Docetaxel)**: Two randomised phase III studies have evaluated Docetaxel-based regimens in symptomatic or rapidly progressive disease (TAX 327 and SWOG 9916). TAX 327 compared docetaxel (every three weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1006 men. Thrice weekly Docetaxel resulted in higher median OS than mitoxantrone (18.9 vs. 16.5 months; P = 0.009) [200, 226, 227].

3) **ENZ** is a novel anti-androgen agent (AR antagonist, inhibits the process of receptor-hormone complex transporting into the cell nucleus) and is recently approved for use in mCRPC based on the results from the AFFIRM study, whereby 1199 men were randomised to ENZ or placebo. Median survival was improved with enzalutamide from 13.6 to 18.4 months (HR, 0.63; P < 0.001) [228].

4) **Sipuleucel-T** became the first in a new class of cancer immunotherapeutic agents to be approved for minimally symptomatic or asymptomatic mCRPC. This autologous cancer vaccine involves collection of the white blood cell fraction containing antigen-presenting cells from individual patients, and exposure of these cells to the PAP-granulocyte macrophage (GM)-colony-stimulating factor (CSF) (PAP-GM-CSF recombinant fusion protein), followed by reinfusion of the cells into the patient. Sipuleucel-T treatment resulted in a 22% relative-risk reduction in mortality (HR, 0.78). This represented a 4.1 months increase in median survival compared to placebo (25.8 vs. 21.7 months). Over a follow-up period of 36 months, the survival probability was 31.7% in the group treated with sipuleucel-T versus 23.0% in the placebo group [219].

5) **Cabazitaxel** is semi-synthetic taxane derivative for men with mCRPC previously treated with a Docetaxel-containing regimen. Cabazitaxel is effective in mCRPC as a second-line chemotherapy following Docetaxel. Randomised controlled phase III trial revealed a 2.4 months benefit in OS with cabazitaxel compared to mitoxantrone in patients who had relapsed following previous Docetaxel treatment (HR, 0.72; P < 0.0001) [218].

6) **Radium 223** is an alpha emitting radiopharmaceutical shown to extend survival in men with mCRPC and symptomatic bone metastases without visceral metastases; median survival at 14.9 months (compared to 11.3 months for placebo) as well as prolonged time to first SRE (median 15.6 months vs. 9.8 months for placebo) [204].

7) **Zoledronic acid** is an intravenous bisphosphonate for patients with mCRPC and asymptomatic or
Prostate Neoplasm
minimally symptomatic bone disease. It inhibits osteoclastic activity and prevents bone resorption. At 15 months, fewer men in the zoledronic acid treatment group developed SREs, 33 vs. 44% in the placebo group; P = 0.02) [229]. On the other hand, Denosumab is a subcutaneously administered, fully human monoclonal antibody that binds to and inhibits RANK ligand, thereby blunting osteoclast function and delaying generalised bone resorption and local bone destruction. Denosumab was compared to zoledronic acid in a randomised controlled study in men with mCRPC [188]. The absolute incidence of SREs was similar in the two groups; however, the median time to first SRE was delayed by 3.6 months by Denosumab compared to zoledronic acid (20.7 vs. 17.1 months).

### 28.9.3 Palliative Management of Metastatic Castration Resistant Prostate Cancer

#### 28.9.3.1 Palliative Radiotherapy

Radiation is an effective means of palliation for bone metastases. A short course consisting of a single 8 Gy is as effective as and less toxic than 30 Gy in 10 fractions [230], providing adequate therapy for most patients.

Beta-emitting radiopharmaceuticals are an effective and appropriate option for patients with widespread metastatic disease, particularly if they are no longer candidates for effective chemotherapy [231]. Because many patients have multifocal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Unlike the alpha-emitting agent radium-223, beta

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### Table 28.9 Timeline of clinical trials of therapy in advanced prostate cancer. Clinical trials of therapy in advanced metastatic prostate cancer showing how this area of clinical research has progressed rapidly in the last 10 years.

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
<th>Types</th>
<th>Overall survival benefit (months)</th>
<th>Clinical trial major outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941</td>
<td>Bilateral orchidectomy</td>
<td>Surgical</td>
<td>–</td>
<td>Reduced PAP for mean 180 days in metastatic PCa [176, 212]</td>
</tr>
<tr>
<td>1967</td>
<td>Veterans Administration Cooperative Urological Research Group (VACURG) DES vs Orchidectomy</td>
<td>Surgical Castration vs Oestrogens</td>
<td>–</td>
<td>DES (1 mg or 5 mg) vs orchidectomy – 3 mg DES recommended to achieve castrate levels of testosterone and reduce cardiotoxicity Reduced cardiovascular death with 1 mg DES [213].</td>
</tr>
<tr>
<td>1984</td>
<td>Leuprolide Study Group first monthly depot</td>
<td>LHRH analogue</td>
<td>–</td>
<td>Leuprolide vs DES 3 mg – equal efficacy for reducing serum testosterone to castrate levels but less cardiotoxicity [214].</td>
</tr>
<tr>
<td>1989</td>
<td>Goserelin (Zoladex) + Flutamide (EORTC 30853)</td>
<td>Maximum androgen blockade</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>Bicalutamide vs Castration</td>
<td>AR antagonist</td>
<td>–</td>
<td>50 mg Bicalutamide OD vs castration – monotherapy improved QoL outcomes [215].</td>
</tr>
<tr>
<td>2003</td>
<td>Triptorelin vs Leuprolide</td>
<td>2nd-generation LHRH analogue</td>
<td>–</td>
<td>Triptorelin 97% vs Leuprolide 90.5% survival at 9 months [177].</td>
</tr>
<tr>
<td>1999</td>
<td>Mitoxanthrone + HC vs HC alone for CRPC (cancer and leukaemia group B 9182 study)</td>
<td>Chemotherapy and palliation</td>
<td>–</td>
<td>Mitoxanthrone with or without HC for CRPC showed improvement in palliative end points but no survival benefit [216].</td>
</tr>
<tr>
<td>2004</td>
<td>Docetaxel (TAX 327)</td>
<td>Chemotherapy</td>
<td>2.9 m</td>
<td>Docetaxel + Prednisone vs Mitoxanthrone + Prednisone [217].</td>
</tr>
<tr>
<td>2010</td>
<td>Cabazitaxel (TROPIC)</td>
<td>Chemotherapy</td>
<td>2.4 m</td>
<td>Cabazitaxel + Prednisone vs Mitoxanthrone + Prednisone [218]</td>
</tr>
<tr>
<td>2010</td>
<td>Sipuleucel-T (IMPACT)</td>
<td>Immunotherapy</td>
<td>4.1 m</td>
<td>Leucopheresis of antigen presenting cells and in vitro immunisation with recombinant PAP [219].</td>
</tr>
<tr>
<td>2013</td>
<td>Abiraterone (COU-AA-302)</td>
<td>Androgen synthesis blockade</td>
<td>4.4 m</td>
<td>Abiraterone + Prednisone vs Prednisone alone [220].</td>
</tr>
<tr>
<td>2013</td>
<td>Radium-223 (ALSYMPCA)</td>
<td>Alpha emitter</td>
<td>3.6 m</td>
<td>Radium-223 injection vs placebo for men who had received, were not eligible for or declined docetaxel [221].</td>
</tr>
<tr>
<td>2014</td>
<td>Enzalutamide (AFFIRM)</td>
<td>2nd-generation AR antagonist</td>
<td>4.8 m</td>
<td>For docetaxel-resistant CRPC enzalutamide treatment vs placebo, delayed time to first skeletal event by 3.4 m [222].</td>
</tr>
<tr>
<td>2015</td>
<td>ARN-509 (SPARTAN) – recruiting</td>
<td>2nd-generation AR antagonist</td>
<td>–</td>
<td>ARN-509 (non-ligand binding domain AR antagonist) vs placebo.</td>
</tr>
</tbody>
</table>

AR, androgen receptor; CRPC, castration-resistant prostate cancer; DES, Diethylstilbestrol; HC, hydrocortisone; LHRH, luteinising hormone-releasing hormone; OD, once daily; PAP, prostatic acid phosphatase; QoL, quality of life.
emitters confer no survival advantage and are palliative. Radiopharmaceuticals agent that are available for the treatment of painful bone metastases are strontium-89 (89Sr) and samarium-153 (153Sm) [232].

28.9.3.2 Emergency Management
Advanced disease can present with an obstructive uropathy which might require stent insertion. Nephrostomy of the resultant hydronephrosis, followed by antegrade stenting is the usual treatment path. Renal function should be checked and consideration for dialysis where applicable. Of course, taking into consideration whether invasive treatment is the best option for the patient (i.e. frailty and multiple comorbidities with or without dementia) as it might be best for complete supportive care with the understanding that the patient will die of their renal failure.

Spinal cord compression, on the other hand, will need urgent treatment. Initial treatment includes analgesics and high-dose steroids: dexamethasone 16 mg followed by 4 mg every six hours is given, while a more definitive treatment is organised. Spinal MRI is the investigation of choice. Either radiotherapy or surgical decompression should be performed within the first 24 hours of presentation. Treatment of PCa in this situation is in line with that of metastatic disease; however, urgent subcapsular orchectomy or degarelix can be used to ensure castration levels of testosterone are reached sooner rather than later. Invariably signs of cord compression or imminent compression are the first presentation of PCa. These include, new onset back pain, which can worsen by straining or coughing, alteration of sensation below the compression root with lower limb muscle weakness affecting mobility, incontinence of stool or urine or both, or acute urinary retention.

28.9.3.3 Supportive Care
Supportive care is an essential part in managing metastatic and treatment-resistant PCa. With improving treatment options and better survival for these patients, more and more patients are living longer with PCa and the delayed or long-term side effects of the treatment they have received. The most common needs are fatigue, pain, nausea, vomiting, nutritional issues, and breathlessness. Palliative radiotherapy and radiopharmaceuticals are good options for pain control. Bisphosphonate, as indicated previously, can provide further improvement in quality of life through prevention of SREs. Other therapeutic options should be considered including physiotherapy and social and psychological supports are all an important part of a comprehensive package of care that is often required. A limited or ‘channel’ TURP can be offered for bothersome LUTS.

28.10 The Role of TURP for Voiding Symptoms Associated with PCa

Many patients have severe outflow obstruction, and even though there is evidence of widespread metastases, TURP is needed to give symptomatic relief. In such cases, the technique is somewhat different from that used in BPH. When there are widespread metastases, there may be abnormal circulating fibrinolysins, leading to clotting disorders, and if there is any suggestion of spontaneous bruising, it is wise to obtain expert haematological advice. Tranexamic acid may be required.

The prostatic urethra may be so stiff and rigid that passing the resectoscope risks creating a false passage. A useful trick is to pass a filiform guide first to guide the resectoscope sheath through the rigid cancer. Once the first few chips have been removed, the resectoscope becomes mobile.

The aim of the operation is not to take out all the tumour down to the capsule because most cancers originate in the peripheral part of the prostate. The aim is to cut out a generous cone of tissue with its apex at the verumontanum (Figure 28.24). Keep well away from the region of the sphincter, which may already be invaded by cancer. Resecting in its vicinity may bring on incontinence, which is more commonly seen after TURP in patients with PCa.

Figure 28.24 The aim of transurethral resection of prostate (TURP) in prostate cancer is to cut out an even cone.
28.11 Controversies, Cutting-Edge Developments, and Hot Topics

28.11.1 PSA Screening

Screening for a disease is only worthwhile if the benefit outweighs the risk of harm associated with diagnosis and proposed intervention. PSA screening for PCa diagnosis remains highly controversial. The natural history of PCa is also highly variable, ranging from an indolent nature to an aggressive life-shortening disease. In 1968, Wilson and Junger developed 10 guiding principles for WHO for overseeing a national screening programme (Table 28.10).

PCa only meets one of these principles: The condition is an important health problem. In the UK, as in many countries worldwide, PSA screening is not routinely offered to men. However, early detection through the primary care-based Prostate Cancer Risk Management programme is considered beneficial. Introduced in 2002, it provides patients with clear information regarding investigations, treatment, and the long-term implications of a diagnosis to allow patients to make an informed choice [234]. The 2014 EAU guidelines advise an individualised strategy for early testing of those who are at risk (i.e. increasing age, family history, Afro-Caribbean ethnicity) [173].

The European Randomised Study of Screening of Prostate Cancer studied 160,000 men and found at 11 years screening reduced mortality by 21%. Screening was particularly useful in men ages 55–69. However, there was a high level of overtreatment of cancer. The number needed to screen to prevent one death from PCa at 11 years of follow-up was 1055 men. An additional 37 cancers would need to be detected to prevent one death from PCa [235]. In 2012, the Prostate, Colon, Lung and Ovarian (PLCO) study published their results into randomised screening or standard review of over 76,000 men. At 13 years, there was no evidence of mortality benefit from screening PC; however, the results were potentially flawed as many of the nonscreened arm had their PSA checked out with the study [236].

One reason screening has not been introduced is that we do not know which treatment modality is best suited for individual patients. The Prostate Testing for Cancer and Treatment (ProtecT) study was set up to evaluate treatment options for early PCa. Its primary aim is to assess the clinical effectiveness, cost-effectiveness and acceptability of active monitoring, radiotherapy or radical prostatectomy in men with localised PCa identified through population-based PSA testing [237]. Furthermore, Research Plan CAP (Comparison Arm for ProtecT) is a current Cancer Research UK randomised controlled trial evaluating population-based screening for localised PCa in the United Kingdom; 587 general practice providers in eight centres in England and Wales have been allocated to either population-based PSA testing (screened) or standard practice (unscreened) and the results are awaited [238].

A 2013 Cochrane review of screening showed that PSA testing increased diagnosis and identification of localised PCa with an unknown impact on quality of life. The review was first undertaken in 2006, but there was insufficient evidence to either support or refute screening. A 2010 update of the review looked at five randomised controlled trials, totalling 321,342 men between 45 and 80 years old, all of whom received a PSA test with or without DRE and were followed up for between 7 and 20 years. Meta-analysis showed no statistically significant difference in disease-specific mortality between the screened and control groups. It concluded that the diagnosis of PCa was greater in the screened group and that screening overall does not significantly reduce disease-specific death [239]. In 2014, the findings of a Swedish population-based cohort study was published which showed men with a PSA >2 ng ml⁻¹ at 60 years old benefited from ongoing PSA screening, whereas men with PSA <1 ng ml⁻¹ had no benefit from screening [240]. In summary, PSA screening continues to be a controversial topic within urology with ongoing research needed to fully assess the risks versus benefits.

28.11.2 Biopsy Approach: Transrectal versus Transperineal

Prostate biopsies are required to obtain tissue for historical diagnosis. They are usually performed with local anaesthetic but can also be performed under general

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Table 28.10 Wilson & Junger WHO criteria for disease screening [233].

<table>
<thead>
<tr>
<th>Criteria for disease screening (Wilson &amp; Junger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) The condition should be an important health problem.</td>
</tr>
<tr>
<td>2) There should be an accepted treatment for patients with recognised disease.</td>
</tr>
<tr>
<td>3) Facilities for diagnosis and treatment should be available.</td>
</tr>
<tr>
<td>4) There should be a recognised latent or early symptomatic stage.</td>
</tr>
<tr>
<td>5) There should be a suitable test or examination.</td>
</tr>
<tr>
<td>6) The test should be acceptable to the population.</td>
</tr>
<tr>
<td>7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.</td>
</tr>
<tr>
<td>8) There should be an agreed policy on when to treat patients.</td>
</tr>
<tr>
<td>9) The cost of case finding should be economically balanced in relation to possible expenditure on medical care as a whole.</td>
</tr>
<tr>
<td>Case finding should be a continuous process and not a once and for all project.</td>
</tr>
</tbody>
</table>
anaesthesia (Figure 28.25). Since the 1980s, TRUS-guided prostate biopsy has been widely accepted in clinic practice and is recommended as first-line biopsy technique by NICE [40]. Controversy arises around the low diagnostic yield of the initial biopsy (35% maximum) and significant yet low 1 in 500 risk of death post-TRUS biopsy from associated sepsis. Increasing requirement for biopsies due to PSA testing has made this side effect a necessary consideration to be discussed with patients prior to their consent [173].

To avoid false-negative biopsy results, there has previously been a trend to repeat TRUS biopsies if earlier biopsies were negative. Such repeat biopsies often have reduced detection rates [62]. The 2014 PCa NICE guidelines advise the consideration of multiparametric MRI (T2W and DWI) for men with a negative TRUS biopsy to determine if another is needed [40]. Further biopsies should only be performed if the MRI is positive or if there is still a risk that cancer is present; for instance, if there has been previous high-grade PIN (HGPIN), ASAP, or an abnormal DRE.

If subsequent biopsies are warranted, then transperineal template biopsies can obtain a greater number of cores in a systematic manner, sampling the anterior prostate easily. The transperineal route predates the transrectal route for prostate biopsy, but in the late 1990s, it was combined with the template technique for insertion of brachytherapy seeds and found to be a precise technique to systematically sample the whole gland. The biopsies are performed under general anaesthetic with antibiotic cover via a template guide on the perineum that correlates to an ultrasound image (Figure 28.10). Up to 50 systematic biopsies can be taken of the prostate via the template grid at 5-mm intervals. This can aid diagnosis of PCA, or offer reassurance to patients if histology remains negative. The drawback of such a large number of biopsies is the subsequent inflammation or swelling with risk of acute urinary retention (1.9%) and significant fibrosis, making future RP difficult. On the other hand, the transperineal route has a lower risk of sepsis than the transrectal route [241].

28.11.3 Role of Multiparametric MRI and MRI Fusion Biopsy

Functional MRI parameters such as DWI are increasingly incorporated as part of the routine MRI staging protocol, leading to increased diagnostic accuracy [52]. Multiparametric MRI (mpMRI) appears to be able to exclude clinically significant cancer with a high negative predictive value and specificity of more than 90% [242–244]. This has led to recent recommendation by NICE that it can be used to determine whether repeat biopsy is necessary in patients with an initial negative prostate sampling [40]. mpMRI has also been suggested as the method of AS [245, 246] with the potential of minimising overtreatment and facilitating cost-effective management of these patients [247, 248]. The validity of these assumptions still has to be assessed by ongoing studies. Whatever the outcome, the addition of a large number of MRI examinations will have important financial impact.

28.11.4 MRI-Guided Biopsy

The accepted standard 10- to 12-core TRUS-guided biopsy has a good negative predictive value for cancer but can also lead to the detection of a number of low-volume low-risk disease. In addition, the standard biopsy approach is poor at sampling tumours at the anterior, midline, and apex of the prostate, leading to underdiagnosis of clinically significant disease. MRI, as the best imaging modality for demonstrating the prostate anatomy, is most suited method for image-guided biopsy. This can be done as MRI-guided TRUS biopsy, in-gantry real-time MRI-guided biopsy, or MRI-TRUS fusion-guided biopsy. The advantage of the first method is that it does not require any specialised equipment except access to an MRI machine or change in biopsy technique. The disadvantage is the uncertainty of obtaining the biopsy from the suspicious region. The in-gantry method is the most accurate, but it is time consuming and resource intensive. The MRI-TRUS fusion technique is a hybrid of the two previous methods. A designated software is used to co-register the MRIs onto the corresponding ultrasound images which are then used to guide a real-time TRUS biopsy. This technique produces fairly accurate sampling, although error can be introduced as a result of deformation of the prostate during TRUS imaging. A recent systematic review has shown that MRI-guided TRUS biopsy does not just increase the cancer detection rate, it also reduces the number of cores required to make
the final diagnosis and at the same time, favours the detection of clinically significant cancer [249].

28.11.5 Emerging Biomarkers

A biomarker (or biological marker) is broadly a measurable response to a biological process [250]. For PCa, this is the progression to adenocarcinoma from normal prostate epithelium. Since the advent of PSA, a number of biomarkers have been proposed as clinically relevant for various stages of PCa.

28.11.5.1 Serum Biomarkers

PSA has been the major clinical biomarker used in early PCa since the 1990s. The abundance of various forms of PSA becomes easier to understand with knowledge of the normal physiology of PSA. PSA can be bound to serum proteins (complexed) or in its free form (fPSA). PSA or KLK3 is part of the Kalikrein family of proteins which cleave peptide bonds. PSA exists in an inactive proPSA form with additional amino acids that prevent its folding into active PSA. When cleaved by KLK2, PSA becomes active. Forms of proPSA are denoted by the number of extra amino acids (i.e. [−2]proPSA). This name was later shortened to p2PSA as it was the isoform found in high amounts in peripheral zone PCa and was also inactive (iPSA). p2PSA measurement provides the basis of the prostate health index (PHI) which is a formula including fPSA, tPSA, and p2PSA (PHI = p2PSA/fPSA × √tPSA). The PHI value has been suggested to outperform the standard tPSA in detecting PCa (Table 28.11) [251].

C-reactive protein (CRP) has been recognised as a marker of poor prognosis in high-risk and locally advanced disease treated with radiotherapy independent of Gleason grade and PSA [253]. Interleukin-6 (IL-6) levels have also been suggested as a biomarker in later high-grade disease as a marker of cancer associated inflammation and the anti-IL6 monoclonal antibody siltuximab is in phase II trials [254].

28.11.5.2 Urine Biomarkers

Prostate cancer antigen 3 (PCA3) is a long noncoding RNA gene found to be specific for PCa. Urine detection tests have shown some promise in predicting biopsy result [252]. The detection of the TMPRSS2:ERG fusion gene (a common translocation event in PC) in urine has also been suggested as a potentially additive biomarker in early PCa [255].

28.11.5.3 Whole Blood Biomarkers

Neutrophil-to-leucocyte ratio (NLR) rises in late mCRPC and can predict outcome along with a number of standard clinical tests [256]. The presence of liver metastasis, Hb <12 g dL−1, ALP >2 ¥ upper limit of normal (ULN), LDH >1.2 ¥ ULN and NLR >3 have been combined into a prognostic score for mCRPC [195]. Combining standard parameters such as lactate dehydrogenase (LDH) with the presence of circulating tumour cells (CTCs) has been shown as a surrogate marker for survival for mCRPC in the COU-AA-301 Abiraterone trial [257].

28.11.5.4 Circulating Tumour DNA

Circulating tumour-specific DNA (i.e. genetic materials released by tumour cell into the peripheral circulation) can be used as a potential biomarker in later stage disease. DNA hypermethylation is commonly seen in PCa (and all cancers) as a mechanism of epigenetic silencing of tumour suppressors [134]. Methylated glutathione S-transferase 1 DNA (mGSTP1) levels have shown promise as a prognostic biomarker for mCRPC [258]. Mechanistically, mGSTP1 can result in hypermethylation of CpG islands (targets for methylation) within gene promoters, occurring in most PCa [259].

28.11.5.5 Exosomes

These are phospholipid encapsulated vesicles released from tumour cells into blood and urine and contain a

<table>
<thead>
<tr>
<th>Name</th>
<th>Site</th>
<th>Stage</th>
<th>Description</th>
<th>ROC (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPSA</td>
<td>Serum</td>
<td>Early</td>
<td>Standard total PSA</td>
<td>0.55 [251]</td>
</tr>
<tr>
<td>%fPSA</td>
<td>Serum</td>
<td>Early</td>
<td>&gt;25% fPSA less likely to have positive biopsy</td>
<td>0.65 [251]</td>
</tr>
<tr>
<td>p2PSA</td>
<td>Serum</td>
<td>Early</td>
<td>Splice variant of PSA</td>
<td>0.55 [251]</td>
</tr>
<tr>
<td>PHI</td>
<td>Serum</td>
<td>Early</td>
<td>Calculated Index</td>
<td>0.70 [251]</td>
</tr>
<tr>
<td>PCA3</td>
<td>Urine</td>
<td>Early</td>
<td>Non coding mRNA</td>
<td>0.74 [252]</td>
</tr>
<tr>
<td>TMPRSS2:ERG</td>
<td>Urine</td>
<td>Early</td>
<td>Fusion gene</td>
<td>0.68 [252]</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen.
variety of lipids, proteins, and miRNA. Their detection can be exploited as potential prognostic markers in PCa [260].

28.11.5.6 Tissue Biomarkers
Immunohistochemistry (IHC) staining of biopsy samples has become increasingly used in routine clinical practice (see Section 28.6.3). There have also been a huge number of proposed prognostic biomarkers published, but none have significantly added to clinical practice as yet.

A recent study identified 2900 PubMed hits for ‘prostate cancer prognostic marker’, amongst which 28 IHC markers were further evaluated in a retrospective cohort of 238 RP samples with median follow up of 72 months. Out of the 28 markers, only 4 were verified to be statistically independent predictors of PSA relapse (AKT1, Stromal AR, EZH2 and PSMA) [122]. AKT1 also known as Protein Kinase B is a serine/threonine kinase constitutively active in many human cancers which plays a key role in PCa growth and survival [261, 262]. The loss of stromal AR along with high nuclear AR in tumour epithelium portends a poorer prognosis with increased relapse in early stage PCa [263]. EZH2 (also known as lysine N-methyltransferase, a protein involved in histone methylation and gene silencing) is upregulated in PCa. Prostate specific membrane antigen (PSMA) is a membrane glycoprotein with high prostate specificity [264]. Except for AR staining, none of these biomarkers are currently incorporated into routine clinical practice.

28.11.5.7 Genetic Mutations and Gene Expression Profiling
The genetics of PCa has been extensively examined with the advent of next-generation sequencing (NGS) techniques. This has given us a deeper understanding of this complex and heterogeneous disease and more recently has allowed us to follow its natural progression through metastasis as never before [265, 266]. The PCa genome has surprisingly few mutations compared to other cancers at approximately 1 mb⁻¹ [267].

The genetic landscape of PCa is that of genomic instability resulting in significant chromopexy (e.g. the abnormal joining of chromatin from one or more chromosomes), resulting in some cases in a ‘gain of function’ fusion gene product, which provides survival advantage for certain cell clone(s). The most common fusion event in PCa is the TMPRSS2:ERG fusion resulting in ERG (an ETS family transcription factor) overexpression mediated by the androgen-responsive element of TMPRSS2 [268]. ERG in this context is thought to mediate the invasive phenotype of PCa distinguishing it from high-grade PIN (HGPIN) and may also play a role in activating biosynthetic pathways leading to CRPC [269]. Activation of the WNT/beta-catenin pathway along with mTOR may also drive growth and metastasis in PCa [270].

Alongside gain of function alterations, ‘loss-of-function’ alterations in PCa include deletion of PTEN (a common tumour suppressor involved in most human cancers) and loss of P53 function evading apoptosis. Loss of regulators of the tyrosine kinase P13K/AKT growth and survival pathway have also been shown to be lost in a large proportion of localised disease and to a greater extent in metastatic disease [271].

NKPX3.1 is a homeodomain transcription factor and androgen-responsive element which has been shown to oppose the TMPRSS2:ERG fusion, which occurs in most PCa and its tumour suppressor role is also lost in most PCa [272].

The upstream cause of the genomic instability in PCa is thought to be a collection of epigenetic modifications including aberrant DNA hyper- and hypomethylation, histone remodelling, and miRNA expression, over time leading to the genetic alterations characteristic of PCa [273]. To date, the most common point mutation occurring in up to 15% of all PCa is in the substrate binding site of SPOP, a ubiquitin ligase which interacts with histone associated proteins [274].

Phylogenetic mapping of PCa has recently shown that the heterogeneity in localised tumour and metastasis is greater than previously hypothesised. In the case of localised multifocal disease, it has been shown that separate tumours arise spontaneously and regions surrounding the tumours may also bear characteristic driver mutations despite histologically appearing normal. Such field effects may have a profound impact on the use of focal therapy for PCa [175]. Metastatic lesions also have been shown to arise from parental metastatic lesions in a stepwise fashion rather than originating from the primary site [265].

28.11.5.7.1 Gene Expression Profiling
There are multiple gene expression panels for risk stratification in PCa. These genetic tools have the potential to predict future outcome based on the retrospective transcriptional profiling of thousands of prostate samples using NGS techniques. Candidate genes, which correlate with outcome in such retrospective studies, have been incorporated into a number of screening panels which can be applied to initial prostate biopsies. Depending on the expression profile of the tumour, a theoretical risk of progression can be used to guide future management. These powerful tools, though expensive, provide a pathway to personalised management of PCa from the initial biopsy [275].

At the time of writing this chapter, examples of the commercially available gene expression profiling tests include Prolaris, Oncotype DX, and Decipher. Prolaris uses an RNA expression profile, whereas the others use a genomic DNA profile to risk-stratify PCa. ConfirmMDX is another commercial test that assesses
gene methylation patterns to look for PCa in a histologically negative biopsy [276]. The use of specific groups of genetic mutations to predict outcome of patients with early disease is a powerful tool, which may have a greater role in the future but requires careful validation in a heterogeneous disease such as PCa.

28.11.5.8 Focal Therapies

28.11.5.8.1 High-Dose Rate Brachytherapy

HDR brachytherapy involves temporary insertion of a radiation source into the prostate and provides a boost dose in addition to EBRT for patients at high risk of recurrence. Combining EBRT (40–50 Gy) and HDR brachytherapy allows dose escalation while minimising acute or late toxicity in patients with high-risk localised or locally advanced cancer [277–279]. Studies have demonstrated reduced risk of recurrence with the addition of brachytherapy to EBRT [280–282]. Common boost doses include 9.5–11.5 Gy in two fractions, 5.5–7.5 Gy in 3 fractions, or 4.0–6.0 Gy in four fractions.

28.11.5.8.2 Cryotherapy

Cryotherapy is an evolving minimally invasive therapy for PCa through local or focal freezing. The role of cryotherapy as a primary modality is still not well established and is currently not recommended as a routine primary therapy due to limited long-term data and lack of randomised trials [283]. Salvage cryotherapy may be considered as an option in patients who have local disease relapse following primary radiation therapy.

The current standard of care for patients with radiation recurrent PCa is deferred ADT, an essentially palliative treatment option, making randomisation between an active and deferred treatment challenging [284]. The Cryo On-Line Data (COLD) registry is a registry of prostate cryotherapy cases which aims to address the questions plagued by the ongoing difficulties around performing a randomised controlled trial in the focal therapy arena [285]. Therefore, current treatment needs to be individualised and patients have to be carefully selected including those with positive biopsy and low suspicion of metastatic disease [286].

28.11.5.8.3 High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is another evolving technique for treatment of localised PCa. HIFU therapy is usually targeted at the part of the prostate containing the cancer inducing tumour necrosis and cavitation by its thermal effect. This treatment is currently not recommended as a primary therapy due also to lack of randomised controlled trials and long-term data [287, 288].

<table>
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<th>Expert Opinion</th>
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<td>Initial suspicion of PCa commonly begins with a raised PSA. The current method of detection is opportunistic screening of men presenting with lower urinary tract symptoms (LUTS) or requesting a prostate-specific antigen (PSA) test from their general practitioner. After biopsy confirmed diagnosis, risk stratification into low-, intermediate-, and high-risk groups allows for optimum management. Complete resection of localised disease with open, laparoscopic, or robotic radical prostatectomy is the only curative option providing the best long-term survival. Such a radical approach has significant side effects; patients should be adequately counselled, and alternative treatment options such as radical radiotherapy should be discussed. The multidisciplinary approach to the management of advanced PCa is paramount and encompasses expertise from oncology, radiology, pathology and urology. This provides patients with access to adjuvant, neoadjuvant, and combination multimodality treatments which are rapidly changing as the evidence behind complex clinical problems matures in the light of new drugs and technology shown to be effective in randomised trials.</td>
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Part V
29

Penis and Urethra Structure and Penis

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Abstract

The male urethra extends from the bladder neck to the external urethral meatus at the tip of the penis. It conveys the urine and semen. In females, the urethra is shorter than men and terminates in the external urethral meatus, which is just above the vaginal introitus.

The penis is composed of three cylinders of specialised erectile tissue, namely corpus spongiosum that engulfs the urethra and a couple of corpus cavernosa superiorly. The scrotum is divided into two compartments where each of the testicles lies.

This chapter describes the anatomy and physiology of the urethra and external male genitalia. Also, there will be a brief discussion of the process of penile erection.

Keywords urethra; penis; scrotum; erection

Key Points

1) Understanding of the penile fascial fusions helps in the recognition of penile and urethral anatomy.
2) The arterial supply of the penis is from the internal pudendal artery, a branch of the internal iliac artery.
3) Scrotal blood vessels do not cross the midline, which makes the scrotal central raphe an ideal place for scrotal surgical incisions.
4) Erection is a complex neurovascular process-mediated neurotransmitters.

29.1 Anatomy and Physiology

29.1.1 Comparative Anatomy

There is a wide variation in the anatomy of the penis and scrotum in mammals. In elephants, whales, and hedgehogs, the testes are abdominal – respectively just caudal to the kidneys, in the pelvis, or at the internal ring. In pigs, they are in the superficial inguinal pouch; in sheep and man, they lie at the bottom of a pendulous scrotum.

The rich blood supply of the testicle and the scrotum has been seen both as a heat-exchanging mechanism and a sexual signal. In many monkeys, the brightly coloured scrotum is important in the mating season. The penis varies considerably in size and shape amongst mammals.

In some monkeys, it is equipped with sharp recurved spines of unknown function [1].

29.1.2 Topographical Anatomy

29.2 The Penis

The penis has three elements: the two corpora cavernosa and the corpus spongiosum, which expands distally to form the glans penis (Figure 29.1). Each corpus consists of a sponge of intercommunicating venous sinuses. Each corpus cavernosum is attached to the medial aspect of the ischiopubic ramus (Figure 29.2). They join under the symphysis pubis to form the hilum of the penis, which is attached by the suspensory ligament.
Each corpus is enclosed in the specialised tunica albuginea made of strong fibroelastic tissue and is predominantly collagenous (Figure 29.3). Between the corpora, the tunicae fuse to form the pectinate septum that is perforated by endothelium lined cavernous sinuses that form the spongy-like appearance of the tissue on macroscopic examination. These sinuses allow intracorporeal communication between the two erectile bodies; hence, one corpus instantly fills the other. The corpus spongiosum runs ventral to the corpus cavernosa and is traversed by the anterior urethra throughout its entire length. The urethra opens at the external urethral meatus at the tip of the glans penis, which is an expansion of the corpus spongiosum capping all three corpora.

Buck fascia surrounds both corpus cavernosa and splits at the ventral aspect to enclose to encircle the corpus spongiosum. Proximally, Buck fascia fuses with tunica albuginea and distally fuses with the base of the glans at the corona [2]. As a result of this fascial fusion, bleeding within Buck fascia is limited to the penile shaft. In Buck fascia run the deep dorsal vein and the sensory nerves supplying the glans penis. Between Buck fascia and the skin is a loose layer of vascular connective tissue. The skin continues over the glans as the prepuce [3].

29.2.1 Blood Supply and Lymphatic Drainage

29.2.1.1 Arterial Supply

The arteries of the penis are terminal branches of the internal pudendal artery – last branch of the internal iliac artery. Each internal pudendal artery splits into three (Figure 29.4):

1) A dorsal artery enters between the crus of the penis and the pubis and runs in Buck fascia on either side of the deep dorsal vein of the penis. It gives off circumferential branches, supplying the corpus spongiosum and urethra.

2) A second larger cavernous artery runs in the middle of each corpus cavernosum and is the main artery responsible for erection.

3) A pair of bulbourethral arteries run in the corpus spongiosum on either side of the urethra [4, 5], supplying the urethra and the glans.

The corpus spongiosum and its contained urethra receive dual blood supply from bulbourethral and circumferential branches of the dorsal arteries.

The cavernous arteries supply blood for tumescence of the corpora cavernosa in the first and second stages of erection: the dorsal and bulbar arteries are responsible for distension of the glans penis in the third stage.

The arteries of the corpora cavernosa and spongiosum give off short branches, which open directly into the venous sinuses. In the flaccid state, these arteries
are constricted; in the first and second phases of erection they dilate (Figure 29.5).

29.2.1.2 Venous Drainage
The venous sinuses of the spongy tissue drain into efferent veins. Those of the glans enter a coronal plexus, which flows into the deep dorsal vein. Emissary veins that run obliquely through the tunica albuginea drain the middle part of the penis into the deep dorsal vein directly or via circumflex veins (Figure 29.6).

The veins of the bulb and proximal corpora cavernosa join up to form large cavernosal veins which flow into the deep dorsal vein which itself runs under the symphysis into the pre-prostatic plexus of Santorini.

A superficial venous system drains the subcutaneous tissues of the penis via the superficial dorsal vein of the penis into the saphenous vein. There are many communications between these two venous systems [4, 5].

29.2.1.3 Lymphatics
Most of the lymphatics of the penis join dorsally and then drain into the medial group of superficial inguinal lymph nodes, superficial to the deep fascia of the thigh (i.e. fascia lata) in both sides; some flow through the ‘sentinel’ node lying over the fossa ovalis, and others accompany the deep dorsal vein under the pubis into the lymphatics of the pelvis [6].
Figure 29.5 Blood supply to the penis (a) arterial, (b) venous.

Figure 29.6 Venous drainage of the penis.
29.2.2 Nerve Supply

29.2.2.1 Autonomic
A rich autonomic plexus forms a sleeve around the cavernous and bulbar arteries. This is linked to primitive centres in the brain – the hippocampus, cingulate gyrus, and thalamus [7, 8]. There are two spinal centres concerned with erection, one at T12–L3, the other at S2–S4 [9].

The main neurovascular bundle lies posterolateral to the prostate gland and can sometimes be preserved during prostatectomy or cystectomy by displacing the bundle laterally in its layer of pelvic fascia [10].

29.2.2.2 Somatic Afferent and Efferent Nerves
The pudendal nerve (i.e. S2, S3) terminates with two branches, the dorsal nerve of the penis and the perineal nerve. Sensory branches run with the two dorsal nerves of the penis in Buck fascia to the skin and glans penis and branches to the corpus cavernosum. Care must be taken to safeguard these nerves when operating for Peyronie disease. The perineal nerve supplies the perineal muscles, urethral sphincter, ischiocavernous and bulbospongious, penile urethra sensation, and posterior scrotal branches. Small branches of the perineal nerve supply the ventral surface of the penis nearing the urethra and glans.

Efferent fibres supply the bulbospongious and ischiocavernous muscles to raise the blood pressure within the corpora above the systolic pressure during the third phase of erection.

29.3 The Scrotum

The skin of the scrotum is hairy and rich in sebaceous glands. There is a distinct plane of cleavage between the scrotal skin and the dartos that has a rich vascular supply and is innervated by sympathetic fibres of S4. The midline raphe defines the line of fusion of the genital tubercle, and it runs from the external urinary meatus to the anus. The scrotum has two compartments separated by a septum and contains a testicle in each compartment.

The dartos is part of the panniculus carnosus of the body and continues as a distinct layer over the penis. It has a profuse blood supply and is sensitive to temperature; when cold it contracts, converting the scrotum into a compact lump. When warm, the scrotum becomes a loose dependent bag.

29.3.1 Fascia
The fascia of Colles is attached behind to the perineal membrane, each side to the pubis and continues upwards as the fascia of Scarpa onto the abdominal wall. Blood and extravasated urine will collect in this space and sharply define its limits (Figure 29.7).

29.3.2 Blood Supply and Lymphatic Drainage

29.3.2.1 Arterial Supply
The anterior scrotal wall derives its arterial supply from the external pudendal artery branch of the femoral artery. Posterior branches of the perineal arteries supply the posterior aspect of the scrotum. Arteries normally course parallel to the scrotal rugae and do not cross the median scrotal raphe.

29.3.2.2 Venous Drainage
The venous drainage of the scrotum is via the saphenous to the femoral vein. The scrotal veins anastomose freely with those of the penis.

29.3.2.3 Lymphatic Drainage
The scrotal lymphatics drain into the ipsilateral superficial group of the inguinal lymph nodes, and from there, along the course of the external iliac artery.

29.3.2.4 Nerves
The anterior third of the scrotum is innervated by the ilio‐inguinal nerve (L1): the posterior two‐thirds by the scrotal branches of the perineal (S3) and posterior cutaneous nerve of the thigh (S2) (Figure 29.8) [11].

29.4 The Urethra

29.4.1 Male Urethra
The male urethra is an elastic tube capable of doubling in length during erection. It is lined with transitional epithelium as far as the bulb where it is squamous for the next 5 cm and cuboidal for the remainder of its length. Paraurethral glands enter the urethra along its length, being most numerous in the bulb and near the external meatus (Figure 29.9). Cowper’s glands lie within the levator ani muscle and send their ducts down beside the bulbar urethra to open into it. Paired glands of Littré open on either side of the external urinary meatus.

A sleeve of spongy tissue – the corpus spongiosum – with a structure similar to that of the corpora cavernosa, surrounds the urethra and is continuous with the glans penis. Like the corpora cavernosa, the nerves of the corpus spongiosum and urethra come from the neurovascular bundles just posterolateral to the prostate.

In small boys, the urethra is extremely narrow and does not enlarge until puberty. The calibre of the adult
Figure 29.7 Attachments of the fasciae of Colles and Scarpa which (a) limit the spread of extravasated blood and urine in the perineum, but (b) allow it to diffuse up in the fat of the abdominal wall.

Figure 29.8 Cutaneous nerves of the scrotum.
The female urethra measures about 4 cm in length and is lined with transitional epithelium above and squamous epithelium below; the junction between the two types of epithelia is variable, and it is normal for the squamous epithelium to extend up onto the trigone [12] (Figure 29.10).

The urethra is surrounded by erectile spongy tissue that is anatomically continuous with the glans of the clitoris [11] (Figure 29.11).

Surrounding the spongy tissue is a sleeve of smooth and striated muscle fibres, entirely distinct from the levator ani sheet. These muscles contain fast- and slow-twitch fibres, similar to those of the intramural sphincter of the male membranous urethra.

The lumen of the female urethra forms a crescent, with a marked crest on the posterior wall (Figure 29.12). Numerous paraurethral glands of unknown function open into the urethra.

29.5 Erection

Erection is a complex neurovascular process involving relaxation of endothelial smooth muscle in the corpus cavernosa resulting in increased intracavernosal arterial blood volume and pressure and restricted venous drainage. This process is mediated through neurotransmitters.

When the penis is flaccid its arterioles are constricted, and there is a very low blood flow. Parasympathetic activity from conscious erotic stimulation or local contact, releases neurotransmitter substances, which relax the branches of the deep artery of the corpora cavernosa.

Acetylcholine (Ach) and nitric oxide (NO) play a critical role in the physiology of penile erection. L-arginine, an amino acid, is converted to NO. NO synthase (NOS) cleaves nitrogen for the amino acid and combines it with oxygen to form NO. Ach stimulates endothelial cells and neuronal endings to produce NO. Three types of NOS exist depending on the tissue producing them, neuronal NOS, endothelial NOS, and cytokine-inducible NOS.
Increase in NO causes activates guanylate cyclase, which causes an influx of intracellular calcium into the endoplasmic reticulum ergo reducing intracellular calcium, leading to smooth muscle relaxation. Phosphodiesterase (PDE) catalyse the conversion of cGMP to its inactive form GMP leading to the termination of this process. Other mediators may release a factor from endothelium causing the smooth muscle to relax, or may act with vas- 

![Figure 29.11](image1.png) Surrounding the corpus spongiosum of the female urethra is a sleeve of smooth and striated muscle, similar to the supramembranous intramural sphincter of the male. Outside this is the striated external sphincter, part of the levator ani sheet.

![Figure 29.12](image2.png) The lumen of the female urethra is crescentic in shape. The bladder neck is seen in the distance.
There are five phases in erection:

**Phase 1 (Tumescence):** As the first stimuli reach the penis, there is an increased blood flow. The spaces of the corpora fill with blood. At first there is no increase in pressure whereby the penis remains soft (Phase 1A) and then there will be a progressive increase in pressure causing some increase in length and girth (Phase 1B).

**Phase 2 (Erection):** When the vascular sinusoids are filled, there is an increase in pressure inside the corpora, which makes the penis stiff. At the end of this phase, the blood flow into the penis slows down.

**Phase 3 (Full erection):** Intracavernosal pressure rises, causing occlusion of the venous flow through the emissary veins caused by impediment against the noncompliant tunica albuginea, but the pressure inside the corpora is still only 10 mm Hg below the systolic pressure. The inflow of blood has almost stopped.

**Phase 4 (Rigid erection):** The intracavernous pressure rises to several times that of the systolic blood pressure. The change from ‘full’ to ‘rigid’ erection requires closure of the emissary veins, which are still under the effect of the ‘veno-occlusive mechanism’ (Figure 29.13). In addition, the bulbospongious muscles contract and blood ceases to flow in or out of the penis.

**Phase 5 (Detumescence):** Here, the venous outflow starts again, the arterial inflow remaining very small; the penis shrinks and gradually returns to its flaccid state [3].
29.6 Function of the Scrotum

The marked alterations in the size and shape of the scrotum with temperature and the pampiniform plexus of the spermatic cord have been interpreted as a temperature-regulating system designed to keep the testicles cool – a concept which has been disputed in view of the intra-abdominal position of the testes in so many other mammals [11].

29.6.1 Physiology of the Urethra

The urethra serves as a conduit for the passage of urine but more importantly contains the main sphincter mechanism that maintains urinary continence. Additional mechanisms for continence also exist. The role of the muscles of the urethra in females is essential for continence at all times because in women the bladder neck appears to be open at rest. The function of the paraurethral glands in either sex is not known.

References

30

Penis and Urethra and Prostate Congenital Anomalies

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Abstract

There are many conditions that affect the genital organs, varying from minor conditions treated conservatively to those that cause significant long-term functional, psychological, and emotional problems. A sound knowledge of the wide ranges conditions would ensure the essential counselling and initiation of treatment starts on the correct path.

Keywords hypospadias; epispadias; urethral valves; posterior urethral valve (PUV); syringocele; urethral duplication; disorders of sex development (DSD)

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Key Points \\
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This chapter covers the following: \\
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- foreskin anomalies \\
- hypospadias \\
- primary epispadias \\
- posterior urethral valves \\
- prostatic utricle \\
\hline
- syringocele \\
- anterior urethral valves and diverticula \\
- urethral duplication \\
- urethral anomalies in anorectal malformations: disorder of sex development (DSD) \\
- interesting terminologies \\
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30.1 Foreskin

30.1.1 Embryology and Function Review

The prepuce develops at the same time as the urethra and is dependent on normal urethral development. At about eight weeks of gestation, low preputial folds appear on both sides of the penile shaft, which join dorsally to form a flat ridge at the proximal edge of the corona. The ridge does not entirely encircle the glans because it is blocked ventrally by incomplete development of the glanular urethra. Thus, the preputial fold is transported distally by active growth of the mesenchyme between it and the glanular lamella. The process continues until the preputial fold (foreskin) covers all of the glans. If the genital folds fail to fuse, the preputial tissues do not form ventrally; consequently, in hypospadias, preputial tissue is absent ventrally and is excessive dorsally [1, 2].

30.1.2 Phimosis

Phimosis is the most common urological presentation in children. It is either primary or physiological or secondary or pathological (e.g. Lichen sclerosis also commonly known as balanitis xerotica obliterans ([BXO])).

The foreskin is physiologically non-retractile beyond the glandular sulcus, in almost 100% of neonates, 50% by one year, and in most of the cases becomes retractile spontaneously [3–5]. The incidence drops to <10% at 7 years and around 1% of 18 year old have nonretractile foreskin [3–5].

In all neonates the inner foreskin skin is fused to the glans, and the separation occurs gradually due to accumulation of smegma. The smegma is the sebaceous secretion from the inner foreskin that accumulates between the skin and glans and causes its separation. The accumulating smegma can form pearl like cyst (i.e. smegmal cyst) under the foreskin, or some time mimics
purulent discharge when expelled out of foreskin meatus and often prompts urological consultation, needing only reassurance (Figure 30.1).

Given the natural history of phimosis in children, only symptomatic patients, particularly those with recurrent local infections or scarring should undergo surgery before puberty in the absence of foreskin abnormalities on physical examination [5].

In symptomatic patients, nonsurgical treatment can still be offered in the form of a course of four to eight weeks with one to two applications per day of topical steroids, with a success rate of >90%; however, there is a recurrence rate of 15–20% [4, 6–8]. Of note, it is controversial whether local steroids are more effective than preputial manipulation and stretching alone [5, 6].

### 30.1.3 Circumcision

In patients experiencing recurrent symptoms despite local steroids, circumcision is the standard treatment. If the patient or the parents wish the prepuce to be preserved, preputioplasty techniques (Figure 30.2), involving one or more dorsal incisions and transverse suturing resulting in widening the preputial ring, are an option, although many surgeons consider the cosmetic results of these procedures unacceptable [9, 10].

#### 30.1.3.1 Medical Indications of Circumcision

The only absolute indications for a circumcisions are secondary phimosis (i.e. BXO), paraphimosis, recurrent infections with scarring, other indications include primary phimosis (i.e. patient preference usually cultural or religious reasons), recurrent balanoposthitis, and recurrent urinary tract infections (UTIs) in patients with urinary tract abnormalities (as this significantly reduces the bacterial colonisation of the glans) [4].

Circumcision is contraindicated in patients with an acute local infection and congenital penile anomalies where the foreskin will be needed for reconstruction (e.g. hypospadias or buried penis) [4].

Different treatment options like preputial stretching, preputioplasty, or topical corticosteroid creams have been proposed as alternative therapy as well.

#### 30.1.3.2 Alternatives to Circumcision

1) Gentle retraction of the prepuce. Many circumcisions can be avoided by counselling the mother. Gentle retraction of the prepuce maybe at bath time could stretch the foreskin orifice and help with maintaining...
the hygiene. Forceful preputial retractions should be avoided because it could cause tear and hence scarring.

2) Dorsal slit. A short vertical incision in the prepuce – the dorsal slit – just enough to allow the prepuce to be retracted fully, serves the same purpose, but the result is somewhat unsightly. Closing the incision transversely may be the answer (Figure 30.2).

30.1.3.3 Technique of Circumcision

Circumcision may be performed with local or general anaesthesia. If local anaesthetic is used, it must not contain adrenaline because arterial spasm caused by adrenaline may lead to necrosis of the penis. Care must be taken in using the diathermy to avoid coagulation of the vessels of the penis. The bipolar diathermy is safe, but if this is not available, the penis should be surrounded by swabs soaked in saline to provide a wide pathway for the current to return to earth (Figure 30.3), however, the wide availability of bipolar diathermy as leads to the this risk is almost nonexistent.

Draw the foreskin forwards. Make a clean incision with a knife level with the corona of the glans (Figure 30.4). Then draw the foreskin backwards, if necessary making a small slit in the prepuce. Make a second clean incision with the knife 3–4 mm proximal to the sulcus of the
glands. Join the two incisions and dissect the sleeve of skin off the shaft of the penis. Seal every small vessel with the bipolar diathermy or very fine catgut.

If the frenulum is prominent and short then it could be divided with bipolar forceps. Use only very fine absorbable sutures and or tissue glue as per the preference.

Circumcision can be associated with severe complications, such as glanular amputation or urethral fistula formation, if the procedure is performed by physicians not properly trained [11]. In hospital setting, complications after elective circumcision are reportedly less than 1%. Acute complications are usually minor and most commonly involve bleeding, infection, or an imperfect cosmetic outcome. Late complications include trapped penis, skin bridges, and meatal stenosis [12].

30.1.4 Paraphimosis

Paraphimosis is defined by acute swelling and inflammation of the distal penis and glans caused by a constriction ring of tight foreskin. Paraphimosis is a medical emergency because delay in treatment can cause maceration of foreskin and even glanular ischemia [4, 13]. Most cases are amenable to reduction in accidents and emergencies with the use of topic anaesthetics, oral morphine, or intravenous injection sedation depending on the age of the patient. The manoeuvre used for reduction of an uncomplicated paraphimosis is performed by first squeezing the glans gently to reduce its volume and then, with the help of the index and middle fingers, the thumb is used to slowly push the glans proximally through the phimotic ring. Other substances or manoeuvres that have been used to help reduce glans swelling include sugar [14], mannitol soaked gauze [15], hyaluronidase [16], puncture of the prepuce with a small gauge needle [17], and an ice pack [18]. If conservative manoeuvres are not successful, dorsal slit or circumcision may be required; however, it might lead to unsatisfactory cosmetic outcomes, needing revision surgery later on [4].

30.1.5 Infections and Inflammation of the Foreskin

Normal penile skin is susceptible to infections and inflammation. Nonspecific infections are most commonly caused by gram-positive organisms (i.e. Staphylococcus pyogenes and Staphylococcus aureus), which are saprophytes of the skin. However, the causative organism is seldom identified, as swab cultures are generally not obtained [5].

The infection causes a collection of debris or pus under the foreskin that presents with swelling, erythema and inflammation. This is called balanitis (i.e. inflammation of glans) or balanoposthitis (i.e. inflammation of glans and foreskin). Balanoposthitis is seen in approximately 4% of uncircumcised boys, mostly between two and five years of age after potty training [19]. The aetiology is unclear, and no cause can be identified in many cases, although infection, mechanical trauma, contact irritation, and contact allergy are cited [20]. When the bacteria find skin or mucosal breakdown, they gain access to the subcutaneous tissue, resulting in diffuse cellulitis of the whole penis, which is sometimes quite dramatic. This may be associated with discharge, and patients may also complain of dysuria, bleeding from the foreskin, and glans ulceration [19]. In more severe cases, skin erythema can be accompanied by pain and fever.

Treatment of balanoposthitis generally includes sitz baths and local antibiotic creams [21]. In cases of penile
cellulitis or systemic symptoms, oral broad-spectrum antibiotics should be administered. Short-term bladder catheterization can be required in cases of acute urinary retention. Surgical procedures, such as incision and drainage, are almost never required, but recurrent infections can cause local scarring and phimosis requiring eventual circumcision [5].

The other possible diagnosis to be considered while assessing patients presenting with penile swelling, erythema, and inflammation caused by trauma, hair coil penile strangulation syndrome, animal attack, insect bite, bicycle accident, zipper injury, and electrical injury [22–27].

30.1.5.1 Lichen Sclerosis or Balanitis Xerotica Obliterans
BXO is cause of pathological phimosis in paediatric population (Figure 30.5). BXO is a chronic progressive dermatitis of unknown aetiology, a variant of lichen sclerosus et. atrophicus confined to the male genitalia. In most cases, only the prepuce, but in some, the glans, external urethral meatus, and urethra may be involved as well.

The incidence of the condition is unknown, but most authors agree it is increasing and many cases of phimosis undergoing nonelective circumcision in childhood might be in fact have undiagnosed BXO [5, 28]. However, BXO can be found in about 20% of cases with phimosis at <10 years of age [4]. It is diagnosed by histological features, including hyperkeratosis and hyperplasia of the squamous mucosa along with homogenous collagen deposition in the upper dermis [28].

Clinically, the condition can be suspected in the presence of a white, sclerotic, scared, nonretractile preputial ring. If the inflammatory process involves the external urethral meatus or urethra, mental stenosis or urethral strictures can ensue. Most of the patients are asymptomatic. Progressive preputial tightening is the most common complaint [5]. Nonspecific voiding symptoms can be present, particularly if there is involvement of the external meatus or urethra [29].

In terms of treatment, circumcision alone is generally curative.

Meatotomy or meatoplasty might be required in cases of mental stenosis, whereas rare cases of urethral stricture make the condition very difficult to treat, requiring multiple urethral dilatation and might require substitution urethroplasty with oral mucosa [29, 30]. Adjuvant treatments with corticosteroids have also been proposed preoperatively, intraoperatively, or postoperatively, but the actual role of such an adjunctive treatment is unknown [29]. Surgery for BXO can be associated with quite a high complication rate. Mental stenosis can recur after circumcision and the disease can progress leading to mental stenosis or urethral stricture [5].

30.1.5.2 Buried Penis and Congenital Megaprepuce
A buried penis refers to a normal-sized penis buried in prepubic tissue. A normal penis can be buried by large scrotal masses, such as hernias or hydroceles or by the presence of excessive suprapubic fat. The prepubic fat can reduce in volume dramatically as the child learns to walk along with appropriate dietary advice and physical activity [5]. Some surgeons recommend that any surgery is deferred at least until the child is three years old [31]. The prepubic fat is sensitive to androgens, penile appearance can improve spontaneously as the child approaches puberty [32, 33].

Megaprepuce is indeed a variant of buried penis where there is a large redundancy of the inner preputial layer, characterised by a penis with a wide dome-shaped base that exhibits hemispheric ballooning during micturition. There is an enormously capacious preputial sac, engulfing the whole penile shaft and upper scrotum (Figures 30.6 and 30.7). Urine collects in this preputial

Figure 30.5 Balanitis xerotica obliterans.
sac and dribbles more or less continuously. The sac can be readily emptied by compression [34]; this prompted the term ‘preputial bladder’. It has been widely debated whether such skin excess is congenital or acquired because of progressive stretching of the inner preputial mucosa during micturition in a phimotic prepuce [35]. Surgery is usually undertaken because of functional and cosmetic concerns and poses significant technical challenges. The limiting factors are the deficiency of penile shaft skin, an absence of defined penopubic and penoscrotal angles and a marked excess of inner preputial ‘mucosa’. Different surgical techniques have been described. Essentially, the excess inner preputial skin is excised. The penile skin is refashioned resulting in a circumcised penis. Postoperatively, redundant penile skin or recurrence of the buried appearance is not uncommon and revision surgery may be required [36, 37].

30.2 Hypospadias

Hypospadias, by definition, implies that the urethral meatus is placed ventrally, short of its normal terminal location. It can be located anywhere from the under surface of the glans to the perineum.

30.2.1 Embryology

Embryologically, most of the urethra is formed by inrolling of the urethral folds of the developing phallus (which involves fusion of the medial edges of the endodermal urethral folds along with the ectodermal edges of the urethral groove that fuse to form the median raphe), but the last part – the channel through the glans – starts as a solid rod and then canalises. This process takes place between 8 to 12 weeks of gestation. The glanular urethra forms after the 16th week of gestation either by endodermal cellular differentiation or by primary intrusion of ectodermal tissue from the glans pit [38–40]. Any part of this complex process may go wrong. Its most severe forms are often associated with undescended testes and should raise the suspicion of disorder of sexual development (DSD).

If the solid cord that burrows through the glans fails to canalise, the urethra opens on its ventral aspect – glandular hypospadias. This is common, and apart from looking slightly unusual, never causes any functional trouble (Figure 30.8).

Failure of enrolling of the urethral folds is accompanied by errors in development of the corpora cavernosa and spongiosum. The distal part of the corpus spongiosum may be a thin strand of fibrous tissue which acts like the cord of a bow causing the penis to bend over during erection – chordee.

30.2.2 Incidence, Risk Factors, and Associations

The incidence of hypospadias is 1 in 300–500 live male births [4, 41]. However, there is considerable regional variations worldwide.

A variety of genetic, hormonal, enzymatic, and environmental factors have been implicated as possible etiological factors. Low birth weight and higher maternal age may also play a role (possibly mediated by placental insufficiency).
Hypospadias is more common in monozygotic twins and in the offspring of fathers who have hypospadias, indicating that there may be a polygenic inheritance. Recently, hypospadias is associated with specific gene \((\text{Ins} \, \text{i3})\) knockout mice. The overall incidence of hypospadias in first-degree male relatives of affected boys is 7–10%, rising to 10–20% in brothers of boys with severe forms of the condition [41].

Hypospadias is associated with high incidence of undescended testes. The average incidence is 5–10% but can rise as high as 50% is severe cases [41, 42]. There can be associated inguinal hernias or hydroceles. Abnormalities of the urinary tract are unusual and occur in approximately 2% of patients; thus, routine ultrasound of these children is unnecessary. Severe forms of hypospadias are also associated with a persistent prostatic utricle in 14–20% of cases, which on occasions can make urethral catheterisation of the bladder difficult [41, 42]. Routine investigations to identify a utricle are not recommended as most cases are asymptomatic. It is essential to exclude disorders of sexual development early on in patients with hypospadias with undescended testicles.

The use of oral contraceptive pills during pregnancy increase the risk of hypospadias [4].

### 30.2.3 Classification [41, 42]

Commonly used anatomical classification of hypospadias (Figures 30.8–30.10):

- **a)** Distal or anterior (glandular, subcoronal, distal penile)
- **b)** Penile or middle (midshaft, proximal penile)
- **c)** Proximal or posterior (penoscrotal, scrotal and perineal)

It has three major components in various combinations:

- **a)** abnormal ventral opening of the urethral meatus
- **b)** ventral curvature (chordee) of the penis
- **c)** hooded foreskin, with ventral deficiency

Overall there is hypoplasia of the ventral skin and spongiosum with resultant deficiency of tissues that give rise to a spectrum of presentations. Not all three of these features may be present in every case; hence, the management needs to be individualised. Therefore, can be grouped into: mild (i.e. distal or penile without chordee,
micropenis, or scrotal anomalies) or severe (i.e. proximal and associated chordee and scrotal anomalies) [4].

30.2.4 Diagnosis

Usually diagnosed at birth or when foreskin is retracted. Examination should include presence of other features of hypospadias, as well as presence of cryptorchidism and other congenital anomalies.

Severe hypospadias with cryptorchidism or ambiguous genitalia will require a complete genetic and endocrine work-up to exclude DSD.

30.2.5 Management

Indications for surgery include functional and cosmetic. Functional reasons include voiding (straight in standing position), sex, and reproduction. However, not all cases need treatment and management needs to be individualised rather than protocol driven. It is crucial to ensure appropriate parental counselling.

Current practice is to aim for surgical correction in the preschool age preferably while the child is in nappies (6–18 months) [4, 43, 44].

More than 300 types of operations have been described in literature. It is beyond the scope of this book to go through the technical aspects in depth. However, the general principles are [45, 46]:

a) correction of chordee
b) reconstruction of the urethra (urethroplasty)
c) skin cover

Preoperative testosterone, dihydrotestosterone, or beta-chorionic gonadotropin locally or parenterally can
Hypospadias lead to a significant enlargement of the glans and shaft of the penis and is especially helpful with proximal hypospadias, small penises, small glans, or poor urethral plates [4].

Surgical tips include keeping the use of diathermy or tourniquet time to the minimum, attention to symmetry, tension free and wide calibre urethroplasty, adequate size meatus, and use of additional water-proofing layer (Figure 30.11).

### 30.2.5.1 Penile Curvature

In the majority of cases (>70%), excision of the chordee connective tissue will straighten the curvature. However, if there is residual curvature, it will be due to corporeal disproportion and will require straightening with dorsal midline plications or a Nesbit plication [4]. In severe curvatures (>45°), which is also associated with a short urethral plate, a more extensive reconstructive operation will be required, but in essence, is comprised of ventral lengthening procedures and plications with and without flaps or grafts.

### 30.2.5.2 Urethral Reconstruction

Many procedures have been described; however, the type of operation depends mainly on the type of hypospadias:

For distal hypospadias with minimal or no chordee and a good size glans tubularised incised plate urethroplasty [47] with or without a graft [48] is the most commonly performed procedure (i.e. Snodgrass-Orkiszewski). In this operation the native urethral plate is tubularised by making two parallel incisions at the edge of urethral plate and a midline incision in the urethral plate is made (with or without free foreskin graft) to facilitate the tension-free repair. The lateral edges of the parallel incisions are mobilised to raise glans wings and glansplasty is performed. Use of fine instruments, fine sutures, inversion of epithelium, using dartos flap as barrier layer over the urethroplasty, and a tension-free repair is key to the good outcome (Figure 30.12).

The main complication of this type of hypospadias repair is breakdown of part of the suture line, resulting in a fistula. Several months should be allowed to pass before attempting to repair it.

A meatal advancement and glansplasty (MAGPI) has also been described for selected cases of very distal hypospadias. Cut the little fold at the distal end of the pit which represents the true meatus in the midline and close it transversely (Figure 30.13). Make a second transverse incision just proximal to the urethra. Draw it up with a skin hook. Mobilise the prepuce on either side and swing it down beneath the glans to cover the raw area. The penis now looks as if circumcision has been performed. No catheter is needed as no urethroplasty has been done. This operation has gone out of use and should only be used in selected cases.

An onlay island flap from the prepuce or meatal-based flaps (i.e. the Mathieu technique) can also be used for correction of distal hypospadias without chordee. Use of fine instruments, fine sutures, inversion of epithelium, using dartos flap as barrier layer over the urethroplasty, and a tension-free repair is key to the good outcome.
For those with significant chordee that persists after degloving of the penile shaft, selected penile or proximal hypospadias or a small glans, a two-staged approach is preferred with preputial, buccal, or posterior auricular grafts.

The first stage involves correction of chordee and lying open of the glans and putting the graft in to make a neourethral plate (Figure 30.14), which is tubularised in the second stage (Figures 30.15 and 30.16). The time interval between the two stages is six months [49, 50]. As shown previously, the foreskin could be brought ventrally either as a flap after incising it in midline or as a free-graft (more popular).

In the minor forms of hypospadias, like the granular hypospadias with hooded foreskin and no chordee, the surgery is mainly for the cosmetic reason, and there has to be a clear discussion about need and aim of surgery with family. If surgery is opted, then in most of the cases, a modified circumcision (i.e. involves partial degloving and rearrangement of foreskin to get rid of the dorsal hood) (Figure 30.17) or foreskin reconstruction is sufficient.

In almost all forms of hypospadias surgery, an 8-Fr feeding tube is used as a urethral stent and soft compression dressing around the penis; both are removed after seven days.

### 30.2.5.3 Complications

Early complications include haemorrhage, wound infection, and wound dehiscence. The rationale behind the use of compressive dressing is to reduce bleeding and hematoma formation, which may predispose to infection and wound dehiscence.

Late complications are well known. The urethra-cutaneous fistula can occur in up to 30% of the cases (Figure 30.18) [41]. Except for some of the very small fistulae in the immediate postoperative period most will require surgical closure. Prior to closure of a fistula, it is imperative to exclude meatal or distal urethral strictures to prevent recurrence.

Meatal stenosis is usually secondary to ischemia or inadequate mobilisation of the glans wings. It presents as spraying of urine, thin stream, dysuria, or urinary infections. It responds to meatal dilatation, but some cases need a formal meatotomy or meatoplasty.

Urethral stricture, persistent chordee, BXO of the neourethra, and urethral diverticulum are other late complications that warrant surgical revision.

In summary, despite advances in technique, instrumentation and aftercare, correction of hypospadias remains one of the most challenging conditions in paediatric urology. There is no place for the ‘occasional’ hypospadias surgeon, even in the correction of so-called ‘minor’ hypospadias. Surgeons should have a detailed understanding of the various concepts, be well versed in a variety of surgical techniques, and have a sufficient clinical workload to obtain consistently good results.

### 30.3 Primary Epispadias

Epispadias is defined as presence of urethral meatus along the dorsal surface of the penis. It commonly occurs as a part of the bladder extrophy-epispadias
**Figure 30.14** (a) Two-stage hypospadias repair. First, the chordee is corrected and the meatus allowed to drop back. (b) The glans is slit open, (c) the foreskin is divided to form two thick flaps which are (d) brought round to cover the underside of the penis and (e) left to heal.

**Figure 30.15** At second stage, a full-thickness skin tube is outlined and the skin closed over it to form a new urethra.
complex (incidence 1 in 50,000). When is occurs by itself, it is known as primary epispadias and is relatively rare (incidence ~1 in 120,000 for males and ~1 in 400,000 in females) [51].

30.3.1 Embryology

The caudal most aspect of the cloaca (phallic cloaca) extends distally through the developing genital tubercle. Failure of proliferation of rostral mesoderm of the genital tubercle and the caudal displacement of the cloaca results in epispadias [52].

30.3.2 Types

There is variable diastasis which tends to be less severe than in bladder extrophy. More often the pelvic ring is complete with an apparently normal abdominal wall [51].

In males, the urethra may open on the glans (i.e. glanular epispadias), on the shaft (i.e. penile epispadias), or proximally at the junction with the anterior abdominal wall (i.e. pubic or penopubic epispadias) (Figure 30.19a and b). Involvement of the bladder neck and resulting incontinence is seen in both penile and penopubic type. If there is diastasis, there will be a rotation and widening of the corpora cavernosa, with lateral neurovascular bundles. There might also be associated penile shortening. These may lead to subfertility.

While, in females the urethra is wide open on its dorsal surface, and the bifid clitoris lies on either sides. There is a poorly developed labia (Figure 30.20). Because of a short urethra and deficient bladder neck, incontinence is a rule in female epispadias.

In both sexes, there is a high risk (40–50%) of vesicoureteric reflux (VUR), which might require ureteric reimplantation.

30.3.3 Presentation

Prenatal diagnosis is rare. Severe forms are usually detected at birth due to abnormal appearance of the genitals. In boys, the less severe (glanular) forms the prepuce is intact and the condition may not become apparent until the prepuce becomes retractile or incidentally at the time of circumcision. In girls, the classical presentation is in childhood with a failure of potty training or a history of dribbling or stress incontinence.

30.3.4 Management

Surgical correction is commonly performed in the first year of life (Figure 30.21). Our procedure of choice is Kelly
procedure [53] for all female epispadias and male epispadias with incompetent bladder neck mechanism as assessed on the cystoscopy. The main principals of Kelly procedure are: mobilising the corporal attachments along with the periostium from the symphysis pubis, dividing the pelvic floor muscular attachment from the pubic rami while preserving the pudendal neurovascular supply to penis, tubularisation and ventralisation of the urethra, wrapping the proximal urethra with freed‐up pelvic floor muscles, bladder neck reconstruction, and skin cover to penis.

For the distal epispadias in boys with competent bladder neck, modified Cantwell–Ransley technique is sufficient for penile reconstruction [54]. The urethral plate is fully mobilised off the penile corpora from the proximal urinary outlet and corporeal bodies except at the glans. It is then tubularised and brought to a ventral position, and the corpora cavernosa are positioned dorsal to the urethra. A continent procedure may be required at a later date in case of an incompetent bladder neck that has not picked up and treated at initial stage [54].

In 1996, Michael Mitchell [55] described a single‐stage repair technique, where complete penile disassembly is done, and the urethral plate is separated from the glans making the urethral and glans repair independent of each other.

Bladder reconstruction is performed at a later stage (usually at five years of age) with a Youngs‐Dees‐Leadbetter procedure. However, some might still be incontinent and require an artificial sphincter.

**30.4 Posterior Urethral Valves**

Posterior urethral valve (PUV) is the most common congenital obstructive anomaly of the male urethra. The incidence is between 1 in 5000 to 1 on 8000 male births [56]. Although a few familial cases have been recorded, including in siblings, there is no established genetic predisposition. PUV is a congenital anomaly that is life‐threatening to the foetus. This anomaly is frequently detected by antenatal ultrasound. Its cause is not clearly known.

**30.4.1 Embryology**

The foetus develops an abnormal insertion of the wolfian ducts into the urogenital sinus leading to a parachute like membrane across the prostatic urethra, exaggerating
the folds that normally lead down from the verumontanum, attaching obliquely into the anterior urethra distal to the external urethral sphincter causes a valvelike structure, and obstructing the outflow from the bladder (Figure 30.22).

30.4.2 Classification

Young first described PUV in 1919. He classified them into three types [4]; however, only type I and III are obstructive.

- Type I valves (classical, 90–95%) are the most common and occur in 95% of the cases [57]. They arise from the caudal end of the verumontanum and attach to the anterior urethral wall. Dewan and Ransley's anatomical and endoscopic studies point to a single configuration comprising an obliquely orientated congenital obstructive posterior urethral membrane (COPUM) with a variably sized eccentric aperture located within it. The thin membrane is directed upward and forward, with complete fusion anteriorly, and an open channel posteriorly. Following urethral instrumentation, including catheterisation, the membrane is disrupted in the midline resulting in the appearance of two separate, side-by-side valve leaflets as seen in type I valves.

- Type II valves (this is more of a fold not a valve) extend proximally from the cranial end of the verumontanum. They are nonobstructive folds of mucosa of no clinical significance.

- Type III valves are uncommon (5%) and are best described as a transverse perforated membrane in the bulbar urethra with no attachment to the verumontanum. This is due to incomplete dissolution from the urogenital portion of the cloacal member [4].

30.4.3 Clinical Presentation and Diagnosis

Currently, most of the cases are diagnosed antenatally [4]. Prenatal ultrasound findings are those of high-pressure chronic retention and include unilateral or bilateral hydronephrosis or hydrourereter and thickened bladder with diverticulae and with a dilated posterior urethra giving the so called ‘key-hole’ appearance. There is also reduced amniotic fluid (oligohydramnios) and varying degrees of renal dysplasia.
Postnatally, in addition to the aforementioned findings classically, the posterior urethra is dilated and elongated. Physical findings may include distended, firm bladder, and a weak urinary stream. Abdominal distension as a result of a palpable distended bladder and hydronephrosis (Figure 30.23), urinary ascites, respiratory distress due to pulmonary hypoplasia (due to the oligohydramnios), and stigmata of Potter’s syndrome are seen in severely affected newborns [11].

One must remember, that the newborn’s renal function could be normal in the first few days of life as it reflects the mother’s renal function. However, renal deterioration soon ensues. In addition, the hydronephrosis might not be as evident because of the dehydration of the newborn; hence, scans are repeated after one week of birth.

Older children present with voiding dysfunctions particularly daytime urge incontinence, voiding, lower urinary tract symptoms, and renal failure. Late cases commonly also present with recurrent UTIs.

A series of ‘pop-off’ or ‘by-pass’ mechanisms are seen in nearly 20%, whereby a high-pressure system is reduced, allowing for normal renal development. These include urine leaking intra-abdominally through a ruptured renal pelvis or even bladder (causing urine ascites), unilateral ureteric reflux which will lead to affected side renal dysplasia while contrary side develops normally (valves, reflux, and dysplasia [VURD] syndrome), and formation of large bladder diverticula. However, the protective value of the pop-off phenomenon has probably been overstated, and recent evidence suggests that although this may impart some medium-term benefit, a proportion of boys nevertheless progress to renal failure [57].

Voiding cystourethrogram (VCUG) is diagnostic and demonstrates a dilated elongated posterior urethra with abrupt transition to a narrower distal urethra (Figure 30.24 a and b). Classical findings of VCUG include a distended prostatic urethra, bladder neck hypertrophy, thickened trabeculated bladder with diverticula, and uni- or bilateral VUR.

Figure 30.23 Bilateral dilated ureter behind the bladder.

Figure 30.24 (a) Cystogram showing dilated posterior urethra and trabeculated bladder. Source: Courtesy Prof Sandesh Parelkar, KEM Hospital, Mumbai India. (b) Cystogram showing dilated posterior urethra, small trabeculated bladder, and bilateral vesicoureteric reflux. Source: Courtesy Prof Sandesh Parelkar, KEM Hospital, Mumbai India.
30.4.4 Management

Initial postnatal management involves good bladder drainage. This is usually accomplished with 6-Fr or an 8-Fr soft feeding tube passed per urethra. Adequate care should be taken to ensure that the tube does not coil within the posterior urethra. Fluid and electrolyte management is critical in the initial period. Postobstructive diuresis needs close monitoring and replacement and are best served in close liaison with paediatric nephrologists. Acid-base balance is important, more so in severe renal impairment. Prophylactic antibiotics and circumcision at some stage are recommended, especially in children with VUR or dilated upper tract.

After initial stabilisation, endoscopic valve ablation or resection is the treatment of choice, either at the 4–5, 7–8, or the preferred 12 o’clock positions. Both Bugbee electrode cautery and cold knife incision have been described. The most common complication is the formation of urethral stricture disease; however, there is a lower urethral stricture rate by using cold knife as compared to diathermy [4].

In rare cases of small premature babies with raising creatinine levels or where adequate small cystoscopes are not available, it is reasonable to provide higher diversion in the form of Blocksom vesicostomy [11] as a temporary measure. Once the child gains weight and grows up, the valves are ablated endoscopically and the vesicostomy closed.

Most centres routinely perform a check cystoscopy few months after primary ablation to ensure completeness of resection and re-resect any residual valve leaflets. Children with PUV need multidisciplinary close monitoring along with nephrologists in the initial years of life with regular bloods, ultrasound, and baseline functional imaging.

30.4.5 Prognosis and Long-Term Follow-Up

A long-term outcome in children with PUV is dependent on multiple factors. With improvement in the neonatal care along with optimal nephrourological management, the mortality rates have dropped down to 1–3% from 50% in the 1950s [57, 58].

By early adulthood, half will develop chronic renal disease, a third will develop end-stage renal disease (ESRD) and require renal transplant. Attention to bladder dysfunction and identifying and treating hostile bladders early will delay renal deterioration or protect transplanted kidneys. In bladders that progress to myogenic failure and incomplete emptying, clean intermittent catheterisation with or without overnight drainage may be necessary. Regular follow up with judicious urodynamic assessments of bladder function will identify at-risk patients before they clinically deteriorate.

In adulthood, patients will develop ejaculatory dysfunction, reduced prostatic secretions, and impotence and reduced libido as a result of renal impairment.

30.4.6 Indicators of Renal Outcome in PUV [57]

30.4.6.1 Indictors of a Poor Renal Outcome

30.4.6.1.1 Prenatal

- Maternal oligohydramnios, regardless of the gestational age.
- Early detection on prenatal ultrasound of ‘bright’ kidneys and pelvi-caliceal dilatation.

30.4.6.1.2 Postnatal

- Presentation in the first 12 months of life (if undetected prenatally).
- Proteinuria.
- Bilateral VUR.
- Impaired continence at ≥5 years of age.
- Urodynamics shows poor compliance or detrusor failure when ≥10 years of age.

30.4.6.2 Indicators of Good Renal Outcome

- Protection of the upper tracts by a pop-off mechanism.
- Presentation in later childhood.

30.4.6.3 Role of Foetal Interventions

Foetal intervention for PUV is controversial. Experience with intrauterine valve ablation was reported with enthusiasm and optimism, but no long-term outcomes are available [57].

Elective preterm delivery is a form of intervention, and it may be beneficial in cases of rapidly progressing late-onset dilatation [57]. It is important to balance lung maturity with the risk of progressive renal damage in deciding the optimum timing for preterm delivery.

Termination of pregnancy is controversial but is considered in some centres, particularly when severe hydronephrosis and oligohydramnios are detected in early pregnancy [57]. In these circumstances, irreversible renal dysplasia is almost invariably present. A multidisciplinary process of decision making involving the parents is vital.

Vesico-amniotic shunting (VAS) is being tried as a temporary diversion in the foetus. The procedure itself carries an appreciable risk of foetal morbidity, which although only 5% in skilled hands is higher (up to 60%) in some published series [57]. The Percutaneous shunting in Lower Urinary Tract Obstruction (PLUTO) study was a randomised controlled trial designed to evaluate clinical effectiveness, cost-effectiveness, and acceptability of percutaneous VAS for lower urinary tract obstruction. The trial stopped early with 31 women randomised because of difficulties in recruitment. The limited results showed that survival to 28 days and 1 year appears to be
higher with VAS than with conservative management, but it is not possible to prove benefit beyond reasonable doubt. Notably, prognosis in both arms for survival and renal function is poor. VAS was substantially costlier and unlikely to be regarded as cost effective based on the one-year data. Parents should be counselled about the risks of pregnancy loss with or without VAS insertion [59].

### 30.5 Prostatic Utricle

Prostatic utricle is a small, blind pouch opening at the verumontanum (Figure 30.25). It is normally lined by glandular epithelium and has no function. It is considered by some to be the male homologue of the female uterus and vagina. However, in 1997, needle aspiration of cysts from the utricles in a series of six patients by Yasumoto et al. demonstrated high levels of prostate-specific antigen (PSA). And in 2004, Shapirova et al. demonstrated significant concentrations of immunohistochemical bodies to p63 in foetal tissues destined to form the utricle. This points to urogenital origin of the utricle [60, 61].

From a practical point of view, it is worth remembering that the utricle is enlarged in up to 10–20% of proximal hypospadias. Some series report an incidence as high as 35–57%. Higher incidence are noted with more severe degrees of hypospadias [41, 42, 62, 63]. This may lead to difficulty in catheterising the bladder per urethra. On occasion, urethral sound or a lacrimal probe or cystoscopy is required to guide the catheter into the bladder.

The enlarged prostatic utricles are lined by squamous epithelium and can be symptomatic with UTI, epididymitis, and postvoid dribbling. VCUG, retrograde urethrogramy, and in some cases, urethroscopy is useful for diagnosis. Enlarged prostatic utricles are classified according to a grading system [52].

- **Grade 0**, the opening is located in the prostatic urethra, but the utricle does not extend above the verumontanum.
- **Grade I** the utricle is larger but does not extend to the bladder neck.
- **Grade II**, the utricle extends above the level of the bladder neck, and
- **Grade III**, the opening of the utricle opens into the bulbous urethra rather than the prostatic urethra.

Most of the cases are managed conservatively, and only recurrent symptoms warrant surgical excision with high-risk of injury to vas deference.

### 30.6 Syringocele

Syringocele is a rare anomaly of the male urethra. It involves cystic dilatation of the main duct of the Cowper’s glands which can give rise to urethral obstruction or lower urinary tract symptoms like urinary frequency, urgency, dysuria, postvoid incontinence, haematuria, or UTI. Cowper’s glands are located within the levator ani shelf on either side of the membranous urethra. They secrete a mucous substance during ejaculation that acts as a lubricant. The main duct draining Cowper’s glands drain below the urogenital diaphragm into the ventral aspect of the bulbous urethra. Sometimes, these ducts become dilated and infected. The urethrographic appearances then resemble an anterior urethral valve.

Cowper’s glands are rarely the site of persistent infection with *Neisseria* or other organisms. Clinical examination shows a pea-sized swelling, exquisitely tender, between the layers of the pelvic fascia just anterior to the rectum (Figure 30.26).

Maizels et al. [64] described four types of Cowper’s syringocele:

1. **Simple syringocele**, in which there is reflux into a minimally dilated duct;
2. **Imperforated syringocele**, in which the orifice draining the dilated duct is closed, and there is cystic dilatation of the distal duct at the level of the bulbar urethra;
3. **Perforated syringocele**, in which the orifice draining the duct is patulous, and there is free reflux into the duct resembling a diverticulum; and (Figure 30.27)
4. **Ruptured syringocele**, in which the distal portion of the duct is dilated but is not in communication with the more proximal portion of the main duct.

Diagnosis is made by VCUG, retrograde urethrography, or urethrocystoscopy. Treatment is marsupialization of the syringocele. Attempts to remove them are seldom successful or worthwhile; unless the glands are also removed, the ducts will regenerate.
Anterior urethral valves are composed of folds located on the ventral aspect of the urethra that coapt during voiding, resulting in urethral obstruction. They can be located in the bulbous urethra (40%), penoscrotal junction (30%), and penile urethra (30%). It has been proposed that valves cause proximal urethral dilatation with the formation of a saccular diverticulum or a double-barrelled urethra (Figure 30.28) [52]. When the boy passes urine, the saccular diverticulum fills out and compresses the normal urethra; hence, the term ‘anterior urethral valve’.

Anterior urethral diverticula communicate with the urethra and are found on the ventral aspect of the urethra between the bulbous and mid-penile urethra. Progressive enlargement of a diverticulum can result in a distal valve-like flap. Embryologic theories of formation of diverticula include a developmental defect in the corpus spongiosum, cystic dilatation of urethral glands, and sequestration of an epithelial rest.

Clinical presentation depends on the patient’s age and the degree of urethral obstruction and includes difficulty voiding, incontinence, and recurrent UTIs. Nonetheless, the clinical history is typical. The child has a poor stream. He strains so hard that ‘he dirties when he wets’. The ballooned second urethra slowly empties, and so the boy seems to be continually incontinent. There is a translucent swelling in the midline. Often this collection of urine becomes infected and the child presents with an abscess which is incised and leaves a permanent fistula. There may be severe upper tract obstruction. They may present in adult life with a stone in the sac. VUR can be found in 20–30% cases. Treatment consists of endoscopic incision of the inferior lip (Figure 30.29). In case of large diverticulum with thin urethral wall, excision of the diverticulum and urethroplasty may be needed [52].

Anterior urethral valves in the fossa navicularis, the most distal aspect of the urethra, are referred to as valves of Guerin. Many patients are asymptomatic, and some have been associated with urethral bleeding. VCUG is diagnostic and will demonstrate a small collection of
contrast material at the dorsal aspect of the distal urethra. Marsupialization of the valve into the urethral lumen is the treatment of choice.

### 30.8 Urethral Duplication

Duplication of the urethra is a rare anomaly (Figure 30.30). Postulated theories include abnormal müllerian duct termination and growth arrest of the urogenital sinus or misalignment of the termination of the cloacal membrane with the genital tubercle. Duplication can be associated with hypospadias, epispadias, cleft lip and palate, congenital heart disease, tracheoesophageal fistula, imperforate anus, and musculoskeletal anomalies. VUR is present in a third of the cases [52].

Duplication commonly occurs along the sagittal plane. The ventral urethra is the more functional urethra and contains the verumontanum and sphincters. When
Effmann classified urethral duplication into three types:

I – Partial duplication of the urethra.

II – Complete duplication of the urethra.

IIA1 – both urethrae arise separately from the bladder.

IIA2 – one channel arises from the other.

Y-duplication occurs when one urethra arising from the bladder neck or posterior urethra opens to the perineum. This type of urethral duplication often coexists with stenosis of the anterior portion of the normally positioned urethra and other severe congenital anomalies.

IIIB – duplication with one meatus

Type III – Complete duplication of the urethra and bladder.

Depending on the type of duplication, patients might be asymptomatic. Symptoms include UTI, epididymitis, and incontinence. VCUG or retrograde urethrography help confirm the diagnosis and delineate the anatomy.

Surgical excision of the duplication is mainly reserved for recurrent symptoms.

### 30.9 Urethral Anomalies in Anorectal Malformations

Urethral or bladder neck fistulae to the blind rectal pouch are associated with high or intermediate anorectal malformations in males. Diagnosis is made by VCUG or distal loopogram study following colostomy. Treatment includes the division of the rectal stump close to the urethra (Figure 30.31a and b) and correction of the anorectal anomaly, which is commonly done as a staged operation.

#### 30.9.1 Disorders of Sex Development

An ambiguous genitalia is a phasing-out terminology, a general term used to describe any deviation from the normal appearance of the external genitals. The incidence can be as common as 1 in 4500 births.
DSD originate from the following underlying mechanisms:

- Chromosomal defects (chromosomal DSD)
- Abnormalities of gonadal development (gonadal DSD)
- Defects in the synthesis of sex hormones or relevant receptor (phenotypic or anatomical DSD).

### 30.9.1.1 Nomenclature and Classification [65]

A new nomenclature was proposed at the Chicago consensus (2005) and later in 2006, adopted by the Lawson Wilkins Paediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE). The new terminology was adopted to reflect advances in our understanding of the pathophysiology of these disorders while being sensitive to the needs and concerns of patients affected by them.

**Classification and examples:**

#### 46, XY DSD (previously male pseudohermaphroditism)

- Disorders of testicular development (complete and partial gonadal dysgenesis)
- Disorders of androgen synthesis (complete and partial androgen insensitivity, disorders of anti-müllerian hormone [AMH]/receptor, androgen biosynthesis defect) results in various degrees of feminisation.
- Other (severe hypospadias, cloacal extrophy)

#### 46, XX DSD (previously female pseudohermaphroditism)

- Disorders of ovarian development (ovotesticular DSD, testicular DSD, and gonadal dysgenesis)
- Androgen excess (foetal [e.g. congenital adrenal hyperplasia (CAH)], feto-placental, maternal)
- Other (vaginal atresia, cloacal extrophy)

#### Sex chromosome DSD

- 45,XO (Turner syndrome and variants)
- 47,XXY (Klinefelter syndrome and variants)
- 45,XO/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)
- 46,XX/46,XY (chimeric, ovotesticular DSD)

### 30.9.1.2 Female Subject to Masculinization (46 XX DSD)

1) There may be no synthesis of cortisol from a genetic lack of one of a group of enzymes – of which 17-hydroxylase and 11-hydroxylase are the most common (Figure 30.32).

2) The genetic XX female may be exposed with androgens because her mother has an adrenal tumour or has been given androgens during pregnancy.

### 30.9.1.3 Congenital Adrenal Hyperplasia (46 XX DSD)

In this, the most common and serious type of DSD, there is some urgency about making the diagnosis because of...
the risk of a lethal salt-losing state. CAH (46 XX DSD) account for the majority of DSD, is due to 21-hydroxylase deficiency (cause of >90% of CAH cases), and leads to virilisation of the female genitalia. It is an autosomal recessive disorder as a result of mutations in chromosome 6. There is an impairment in the production of hydrocortisone, which leads to compensatory increase in ACTH and testosterone production. Characterised in more than 60% by having a 'salt-wasting' aldosterone deficiency (i.e. reduced sodium and chloride with increase in potassium) presenting a few weeks after birth with an adrenal crisis (i.e. severe vomiting and dehydration) and should be recognised because it is a neonatal emergency. Investigations will show an elevation of 17-OH-progesterone.

This condition is vital to recognise because it will need urgent aggressive rehydration, potassium-lowering drugs, and steroid replacement with mineralocorticoids and glucocorticoids.

Subgroups of CAH include 11B-hydroxylase deficiency (increased 11-desoxy cortisol: there will be increased sodium and reduced potassium and hypertension) and 3B-hydroxysteroid dehydrogenase deficiency (increased DHEA and 17-OH-pregnoone: salt-losing disorder).

30.9.1.4 Males with Undermasculinisation

The neuter pattern may fail to become masculine for three main reasons (Figure 30.33):

1) Testosterone may not be being formed because of a congenital deficiency of 17-ketosteroid reductase.
2) Testosterone is not converted to dihydrotestosterone because of a genetic lack of 5-alpha reductase.
3) There is an error on the X chromosome, leading to a lack of the cytosol receptor for dihydrotestosterone.

30.9.1.5 46, XY DSD

The most common and severe disorder occurs in testicular feminization, which is a sex-linked inherited condition. The external genital appearance is female, but the vagina is short. Inguinal hernia are common, and the testicles show Leydig cells are present but no spermatogenesis and there is a considerable risk of forming malignant tumours. The various biochemical investigations may be able to discover whether there is a deficiency of the production of testosterone (from want of 17-ketosteroid reductase), failure of activation to dihydrotestosterone, or want of the cytosol receptor protein. If the child is reared as a girl, the testicles should be removed.
to prevent cancer; however, the timing of surgery is decided in the multidisciplinary team meeting.

When the syndrome is incomplete, the clitoris may be very large. With the onset of puberty, these children may rapidly virilise.

There are a large number of genetic males who are only slightly imperfectly masculinized. Some merely have hypospadias. Others may have persistent müllerian structures and more or less maldescent of the testicles [4].

30.9.1.6 Mosaicism (XO/XY)
In these rare chromosomal abnormalities, one gonad may be a testis and the other a ‘streak’ gonad – an ovary without any follicles. Their management calls for great care, and the child should be reared as a boy if there is a well-developed phallus.

30.9.1.7 Klinefelter Syndrome (47 XXY)
Many children with Klinefelter syndrome grow up to be physically quite normal, but their testicles are small, and they are referred because of infertility. More severe cases may be deficient in masculine body hair and require treatment with androgens. The diagnosis is easily made with a buccal smear [5].

30.9.1.8 Turner Syndrome (45 XO)
In Turner syndrome, the child remains in the neuter–female state. The gonads are streaks of connective tissue in the broad ligaments. There are often associated cardiac defects. The patient is short, with a broad chest and webbed neck [6].

30.9.1.9 Diagnosis
Any suspicion of DSD should prompt a cautious approach with thorough history and physical examination by an experienced paediatric urologist, endocrinologist, geneticists, and psychologists. Assigning gender should be delayed until appropriate tests and further assessments are complete. Centres treating DSD have a multidisciplinary team, including but not limited to, a neonatologist, endocrinologist, geneticist, psychologist, and urologist to plan further investigations and management.

A family history should be taken and should include parental lineage, any history of DSD, or genital anomalies, neonatal deaths, primary amenorrhoea or infertility, or any maternal exposure to androgens [4]. The examination should be as equally thorough, focused on determining presence or absence of sexual organs (Figures 30.34 and 30.35). Specialist investigations such as diagnostic laparoscopy (for intra-abdominal testes), cystoscopy, or hysteroscopy may be required to identify organs.

Primary investigations include electrolytes, hormonal analysis (human chorionic gonadotropin [HCG] stimulation test, 17-hydroxyprogesterone, luteinising hormone [LH], follicle-stimulating hormone [FSH], testosterone, cortisol levels, and ACTH), and karyotyping. Ultrasonography to determine the presence of müllerian duct structures.

Investigations are to determine the DSD type; however, the most common occurring DSD is CAH.

Determination of the sex of the child should take into consideration the investigations, but also the age of presentation, fertility potential, penile size, presence of a functional vagina, endocrine function, malignancy potential, antenatal testosterone exposure, the child’s appearance, psychosocial well-being, sociocultural aspect, and parental opinions [4].

Further description of detailed management of each type of DSD is beyond the scope of this chapter.

30.10 Interesting Terminologies

30.10.1 Megalourethra
Megalourethra is ectasia of the urethra in the absence of mechanical obstruction. It is caused by defective formation of the penile corpora secondary to a mesodermal defect. Two types of megalourethra are described [52]:

1) Scaphoid – ventral urethral dilatation and hypoplasia of the corpus spongiosum, and
2) Fusiform – circumferential urethral dilatation and hypoplasia of the corpus spongiosum and corpora cavernosa.

Megalourethra is often associated with other congenital abnormalities including cryptorchidism, renal agenesis, hypospadias, primary megaureter, Prune Belly Syndrome, VACTERL complex, and severe gastrointestinal anomalies (Figure 30.36a and b). These patients have a functional rather than anatomic urethral obstruction, causing stasis and back pressure into the upper urinary tracts. Micturating cystourethrogram (MCUG) helps diagnosis. Reconstructive surgery is required.

Figure 30.34 Bilateral impalpable testes.
30.10.2 Aphallia

Aphallia or penile agenesis occur secondary to developmental failure of the genital tubercle (Figure 30.37). It is extremely rare and has an incidence of 1 in 10 million to 30 million. The urethra opens into the anal verge or the rectum. Historically, early orchectomy with female gender reassignment and urogenital reconstruction has been the treatment of choice [66]. In-utero gender imprinting, the timing and role of gender reassignment, and long-term psychological effects of gender conversion are ongoing concerns with this approach, and current approaches to management remain controversial [58].

30.10.3 Microphallus

The term ‘microphallus’ or ‘micropenis’ indicates a constitutionally normal penis with a stretched penile length (SPL) more than 2.5 standard deviations (SD) below the mean for age [4]. SPL differentiates the cases with buried appearance of the penis (i.e. obesity or penis concealed by abnormal skin attachments).
References

Endocrine input is essential to identify hypogonadotropic hypogonadism (e.g. Kallmann syndrome or Prader-Willi syndrome; inadequate secretion of gonadotrophin-releasing hormone [GnRH]), or hypergonadotropic hypogonadism (e.g. Gondal dysgenesis; failure of the testes to produce testosterone).

30.10.4 Penile Duplication

Duplication of the penis (diphallia) is another rare anomaly resulting from failure of mesodermal banding. It occurs with a frequency of 1 in 5 million births. Presentation varies from simple accessory penis to complete duplication of the urethra, glans, and corporal bodies. Extent of surgery ranges from simple resection of accessory penis to complex reconstruction, depending on the anatomy of the defect.

30.10.5 Penile Torsion

Penile torsion indicates rotational defect of the phallus and is usually counterclockwise to the left. It may be associated with chordee, hooded prepuce, or hypospadias. Torsion of less than 90° is usually asymptomatic and does not require correction [58]. Surgery when indicated entails complete degloving of the penis to the base with division of dysgenetic fibrous bands. Rarely fixing the base of the corpora to the pubic symphysis or dartos flap is required to maintain corrected position [58].

Expert Opinion

Patient should have their management tailored around their condition and support provided at each stage of management. In many instances, a multidisciplinary approach to might be required.

References


31

Penis and Urethra Trauma

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Abstract

Trauma to the genital tract must be professionally recognised and managed to prevent grave consequences. Genital trauma accounts for up to two-thirds of all genitourinary trauma and is more common in males than in females. The majority is secondary to blunt injury.

Urethral trauma can be attributed to iatrogenic and noniatrogenic causes. Blunt trauma to the urethra is the most common noniatrogenic cause. Penetrating trauma by gunshot and stabbing are rare but recognised causes of urethral trauma. The urogenital diaphragm divides the male urethra into anterior and posterior urethra. The posterior urethra includes the prostatic and membranous urethra, while the bulb and pendulous urethra form the anterior urethra. This helps to classify noniatrogenic trauma to the male urethra into anterior and posterior urethral trauma. In females, only the posterior urethra exists and the anterior urethra corresponds to the labia minora.

Frequently, patients with urethral trauma have significant associated orthopaedic injuries and neurological deficits and patients will require initial resuscitation. In these circumstances, management of the urinary tract should be aimed at stabilising the injury and deferring the definitive procedure to a later date to ensure rehabilitation and to minimise surgical complications. This chapter covers the management of penile and scrotal trauma.

Keywords genital trauma; penile trauma; urethral trauma; urethrography

Key Points

- Soft-tissue injuries must be taken seriously because mixed bacterial infection may lead to cellulitis and tissue loss.
- Fracture of penis will require urgent surgical repair to minimise the risk of subsequent development of Peyronie disease and erectile dysfunction; urethral injury must be explored if clinically suspected.
- Retrograde urethrography is the gold standard in the diagnosis of urethral injury.
- In unstable and complicated urethral injuries, placement of suprapubic catheter and delayed reconstruction is advisable.

31.1 Penis and Scrotum

Genital trauma account for up to two-thirds of all genitourinary trauma and is more common in males than in females [1].

31.1.1 Trauma to Foreskin

The foreskin may be injured during minor trauma (e.g. by being jammed in a zip fastener) or may suffer major degloving injuries (e.g. when a vacuum cleaner is used for masturbation) [2]. Industrial or criminal assaults and bites from Homo sapiens or other domestic animals are also seen [3].

All but the most trivial injuries should be taken seriously because mixed infection is apt to lead to cellulitis with more loss of skin. All crushed and nonviable tissue should be excised. No attempt is made at primary closure. Delayed primary or secondary closure is effected after three to four days, during which time intensive antimicrobial therapy is given. With human bites, mixed infection is especially common together with the risk of...
necrotising fasciitis [3]. Co-amoxiclav, doxycycline, cephalosporins, and erythromycin are antibiotics of choice with courses for up to two weeks recommended [4, 5]. It is important to liaise with the local microbiology team, especially considering the increasing prevalence of antibiotic resistance and hospital-acquired infections. With dog bites, there is a risk of rabies infection in certain countries, and consequent treatment and vaccination must be considered.

If there is loss of penile skin, initial wound care simply involves coverage with saline-soaked gauze dressings. Once any infection has been adequately treated, a full-thickness skin graft can be applied in cases of extensive skin loss. Split-thickness skin grafts should be avoided because these can impair expansion during erections, resulting in pain or discomfort.

31.1.2 Penile Trauma

31.1.2.1 Fracture of the Penis

Penile fracture results from trauma to the erect penis during vigorous coitus (most commonly when the partner is on top and the penis slips out of the vagina and forcibly pushed against the perineum or symphysis pubis) or during masturbation. The tunica albuginea splits, often with an audible crack. There is extravasation of blood from the corporal bodies. The corpus spongiosum or urethra may also be torn in 30% cases (Figure 31.1). Patients classically report a popping sound with sudden pain and detumescence during intercourse. A cavernosal defect may sometimes be palpable. The haematoma is usually limited to the penile shaft (the aubergine sign); however, if Buck fascia is ruptured, the haematoma may spread quickly to the lower abdominal wall.

Usually history alone is reliable in diagnosing penile fractures but if in doubt, imaging such as magnetic resonance imaging (MRI) or ultrasound may be useful. The best results follow early exploration, evacuation of the haematoma, and repair of the tunica albuginea [6–8]. A circumferential incision with degloving of the penis is the usual approach to evacuate the haematoma as well as to locate and repair the cavernosal defect. Alternatively, if the injury has been localised with imaging, a linear incision can be made over the injury site. Preoperative urethrography, or more commonly, flexible urethroscopy is useful if urethral injury is suspected.

Conservative management of penile fractures is not recommended because the haematoma may organise, leaving a fibrous plaque in the corpus with the features of Peyronie disease and erectile dysfunction.

31.1.2.2 Amputation of the Penis

Amputation of the penis may occur in an industrial accident, but more often, it follows a domestic or criminal assault or occurs with self-mutilation. It is occasionally seen after unskilled attempts at circumcision. If the penis can be found, an attempt should be made to reimplant it using microsurgical techniques [8]. This approach may involve microvascular anastomosis of at least one of the penile arteries. There is no need to suture any of the veins; the corpora cavernosa will provide adequate

Figure 31.1 Fracture of the penis. (a) The penile skin is pulled back, (b) the tear in the tunica albuginea is repaired, and (c) the skin is replaced (d).
venous return. The urethra is sutured with absorbable sutures over a suitable catheter, and the urine is diverted suprapubically [9]. If the severed penis cannot be found or is unsuitable for reimplantation, the penile wound should be debrided and closed as in partial penectomy. Penile reconstruction or lengthening procedures can be considered at a later date [8].

31.1.2.3 Battery Burn
Severe burns have been caused when an electric battery gets into a baby’s wet napkin [10].

31.1.2.4 Trauma Causing Priapism or Impotence
Cycling may give rise to temporary impotence, which usually recovers spontaneously. Blunt injury has also been reported to cause high-flow priapism [11, 12].

31.1.3 Scrotal Trauma
31.1.3.1 Lacerations and Avulsions of the Scrotum
As with injuries to the penis, all scrotal injuries require thorough debridement because of the risk of infection. When in doubt, it is wise to delay primary suture for three to four days. This is particularly so in gunshot wounds [13]. If there is any suspicion of urethral injury, a suprapubic catheter is inserted. It is astonishing to see how well the scrotum will regenerate, even though the major part has been avulsed. In the management of these injuries, one can afford to be conservative and postpone skin grafting. If the testes have been exposed by the original injury, they should be temporarily placed in thigh pouches or covered with saline-soaked dressings until the time of reconstruction.

31.1.3.2 Blunt Trauma
Blunt trauma usually causes injury to the testicles such as dislocation, haematocoele, and rupture (see Chapter 38).

31.2 Urethral Trauma
31.2.1 Introduction
Urethral trauma can be attributed to iatrogenic and noniatrogenic causes. Blunt trauma to the urethra is the most common noniatrogenic cause. Penetrating trauma by gunshot and stabbing are rare.

The urogenital diaphragm divides the male urethra into anterior and posterior urethra. The posterior urethra includes the prostatic and membranous urethra, whereas the bulbar and pendulous urethra form the anterior urethra. In females, only the posterior urethra exists, and the anterior urethra corresponds to the labia minora.

31.2.2 Noniatrogenic Urethral Injury
31.2.2.1 Male Posterior Urethral Injury
Pelvic fractures as a result of road traffic accidents or falling from heights are commonly associated with posterior urethral injury. The corpora cavernosa are densely attached to the angle between the urethral bulb and the inferior pubic rami and perineal membrane. The prostate gland is firmly attached to the symphysis pubis via the puboprostatic ligaments. In pelvic fractures, severe shearing forces are transmitted to the posterior urethra, leading to complete or incomplete disruption. This is most commonly seen in unstable pelvic fractures, whereby the prostate along with the proximal urethra is wrenched away from the corpora cavernosa which remain joined to the pubic rami (Figures 31.2–31.4). In complete urethral injury, a gap between the severed ends of the urethra may be replaced by fibrous tissue [14]. Although there may be a considerable defect, it is important to note this is not due to loss of urethral tissue; hence, it is possible to undertake direct anastomotic repair to restore urethral continuity.

Many patients with pelvic fractures have other more serious injuries that take priority. In this group of patients, urethral injuries are not life threatening by themselves, but they may result in significant consequences, including urethral strictures, erectile dysfunction, and incontinence [15].

Figure 31.2 The symphysis is forced backwards carrying the prostate with it, stretching and then tearing the membranous urethra.
A massive crush injury may lacerate the urethra and rectum (Figure 31.5) [16]. The external urethral sphincter may be destroyed, but the bladder neck is usually intact, except in young boys where the prostate is often torn across. The laceration may also rupture the anal sphincter.

**31.2.2.2 Male Anterior Urethral Injury**

Anterior urethral injury is more commonly caused by blunt trauma in comparison to penetrating causes. A fall-astride or straddle injury to the bulbar urethra or a blow on the perineum forces the urethra up against the inferior edge of the symphysis pubis (Figure 31.6). There may be complete rupture of the corpus spongiosum and urethral wall. Usually, the corpora cavernosa is not injured, and they hold the ends of the corpus spongiosum together (Figure 31.7), so that even if the injury heals with a stenosis, it is always short and easily treated [17, 18] (Figure 31.8). Penile fractures are also associated with anterior urethral injury in 30% of the cases [19]. Less frequent causes of anterior urethral injury include constriction bands used in management of incontinence in paraplegics, gunshot wounds, stab wounds, and dog bites.

**31.2.2.3 Female Urethral Injury**

Urethral injury is rare in females and is attributed to the shortness and mobile nature of the female urethra. Bony fragments resulting from severe pelvic fractures may cause laceration or contusion of the female urethra.

**31.2.2.4 Urethral Injury in Children**

The urethral injury following pelvic fractures that is seen in boys often differs from that seen in adults. The prostate is so small that the urethra tends to be torn between the bladder and prostate rather than the membranous urethra alone.

**31.2.2.5 Clinical Presentation**

The diagnosis of urethral injury is suspected by the nature of the injury and the appearance of blood from the urethral meatus or vaginal introitus. Patients may report difficulty voiding or haematuria. Penile haematoma or swelling may develop. In anterior urethral injuries, the pattern of the penile haematoma may give a clue.
Figure 31.5 Severe crushing injuries may lacerate urethra and rectum, avulse the adductors, and partially deglove the lower limb.

Figure 31.6 (a) A fall-astride injury forces the urethra up against the edge of the symphysis. (b) Urethrogram showing contrast outside urethral, but splinting of corpus allows for some contrast to enter proximal urethra.

Figure 31.7 The urethra and its corpus spongiosum are splinted by the corpora cavernosa, and the torn ends cannot retract.
to the extent of the injury. Haematoma confined to the penile shaft suggests an intact Buck fascia; otherwise, haematoma or urine extravasation is only limited by Colles fascia, giving rise to the butterfly pattern. Digital rectal examination (DRE) can be helpful but may not be appropriate to perform in patients who are not stable or those with severe pelvic fractures as a result of possible pelvic haematoma, which may mask the palpation of a small prostate gland. A high riding prostate may suggest complete urethral disruption, although this is an unreliable sign [20]. Blood on the gloved finger can imply associated rectal injury.

### 31.2.2.6 Investigation

Retrograde urethrography remains the gold standard for evaluation of urethral injury [21]. In males, the injury is confirmed by the injection of water-soluble contrast medium up the urethra: a 12- or 14-Fr catheter is inserted 1 cm into the urethra so the balloon is in the fossa navicularis. The balloon is inflated with 1–2 ml of water and 20–30 ml of contrast is injected while the patient is preferably in a 30° oblique position with knee and hip slightly flexed and the urethral meatus occluded. Any extravasation signifies some degree of urethral laceration and permits classification and management of urethral injuries. Whatever its extent, this calls for a suprapubic cystostomy if urethral catheterisation is deemed impossible. In females, urethroscopy complements initial physical examination because urethrography is not possible due to the short urethra.

Ultrasound can be useful in placing the suprapubic catheter. MRI and computed tomography (CT) are not part of the initial assessment of urethral injury, but they are useful adjuncts to evaluate other abdominal and pelvic injuries in addition to assessment of the anatomy of the penile crura and urethra [22, 23].

### 31.2.2.7 Management

As previously mentioned, urethral injury can easily be confirmed by retrograde urethrography. If there is any extravasation, one must assume that the urethra has been lacerated and a catheter (usually suprapubic) is placed at once. If the diagnosis is delayed, the patient will have passed urine into the soft tissues of the scrotum (Figure 31.9), and unless this is drained, the combination of hypertonic urine and infection will lead to tissue necrosis, which will in turn lead to necrosis of the overlying skin.

Definitive management of the urethral injury will depend on the circumstances of the injury, whether it is blunt or penetrating, complete or partial, and associated injuries. In blunt posterior urethral injuries (urethral distraction defects), urethral reconstruction is usually deferred for three to six months with urine diverted by means of a suprapubic catheter in the interim. Immediate primary open repair of posterior urethral injury is indicated in patients who are stable with penetrating wounds or with blunt and complete urethral rupture associated with bladder neck or rectal injuries [8] (Figure 31.10). Similarly, patients who are stable with anterior urethral injuries are managed with primary open repair over a urethral catheter if associated with penile fracture or penetrating wounds. It is important to document preoperative erectile function for medico-legal reasons.

Many patients with pelvic fractures have other more serious injuries, which take priority. In complete urethral

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**Figure 31.8** If the urethral injury heals with a stricture it is a short one.

**Figure 31.9** To prevent sloughing both fascial compartments of the scrotum must be drained.
injuries associated with pelvic fractures, if the prostatic urethra heals just behind the bulbar urethra, the lumen of the urethra will form an S-shaped deformity, leaving two shelves, which may need to be incised with a urethrotome (Figures 31.11 and 31.12). Occasionally, it helps to introduce the flexible cystoscope through the cystostomy track and use its light as a guide for the incision of the obstructing shelves or as a means of
Early endoscopic realignment (within two to three days) of urethral distraction injuries is possible but has a high failure rate [25] when compared with the 90% success rate of posterior urethroplasty [25].

Patients with perineal wounds always have many other injuries, and although some of these may take priority, it is urgent that the perineal wound is thoroughly debrided and the urinary and faecal streams are diverted to avoid gas gangrene, which is a common complication and leads to loss of soft tissue that could be useful in the subsequent repair. No attempt is made at primary repair [16, 26].

In gunshot injuries, the damage to the urethra is only one part of multiple injuries involving bone, major blood vessels, and bowel. Again, the first priority is adequate debridement with urinary and faecal diversion by means of a suprapubic catheter and loop ileostomy; no attempt should be made at primary repair [26].

In all cases of urethral injury, the patient should be carefully followed up with re-evaluation after two to three months with urethrogram, MRI, or urethroscopy. If at this stage, a stricture is found, treatment consists of optical urethrotomy or dilatation if the stricture is short and soft; otherwise, urethroplasty can often be performed with excellent results [27, 28].

In children with diagnosed urethral injury, repair is made more difficult by the narrow urethra of the child and the risk of creating a catheter stricture. Immediate primary repair should be avoided because of high complication rates, and there is always a risk that the damage to the bladder neck may be followed by incontinence [29–31].

### 31.2.3 Iatrogenic

Iatrogenic urethral trauma is the most common form of urethral trauma in modern urology. Causes include transurethral catheterisation, instrumentation as in transurethral resection or holmium laser enucleation of the prostate procedures (TURP/HoLEP), radical prostatectomy, and radiotherapy. Almost a third of strictures are a consequence of incorrect or lengthy catheterisation most of which are bulbar strictures [32]. Urethral catheterisation may result in ischaemic necrosis of the urethra as in a bedsore (Figure 31.13).

Urethroscopy in a man catheterised for chronic retention of urine often shows a white ischaemic patch either at the penoscrotal junction or near the external sphincter. These are common sites for ‘postprostatectomy’ strictures, and they are not caused by the prostatectomy but by the pressure necrosis from the catheter [33] (Figure 31.14).
Factors contributing to stricture formation secondary to transurethral surgery include the use of monopolar current, diameter of instrument used, and surgeon’s experience [34, 35]. A clean incision in the urethra made with a urethrotome, and it heals with a linear white scar without stenosis [36] (Figure 31.15).

One important variety of this iatrogenic damage is seen after surgery on the heart or aorta. For a time, a toxic component of the latex rubber or plastic of the catheter was blamed, but it is more likely that the cause is pressure of the catheter, whatever it is made of, on a urethra that has become relatively ischaemic during aortic obstruction or cardiac standstill. These ‘catheter strictures’ may involve the whole length of the urethra and can be difficult to treat (Figure 31.16) [37–39]. Silicone catheters and small-diameter catheters seem to minimise the probability of urethral upset [40].

Management of iatrogenic urethral trauma starts with primary prevention of urethral injury during catheterisation or instrumentation. The majority of patients with a
suspected urethral stricture following traumatic catheterisation present with pain and urethral bleeding, and they may be difficult to catheterise, which can be due to the stricture itself or false passages.

In cases of difficult catheterisation, retrograde urethrography, or flexible urethroscopy may be helpful in establishing the obstructing anatomical lesion, whether it is a stricture or a false passage. In acute cases, endoscopic placement of a catheter with the aid of a guidewire is recommended [8, 41]. Optical urethrotomy is warranted if a short urethral stricture is encountered, with urethral reconstruction considered for patients who develop a recurrent stricture. Suprapubic catheter placement may be necessary to temporarly drain the bladder [8]. Patients with anastomotic strictures following prostatectomy will require bladder neck incision or dilatation. Treatment of complex urethral strictures precipitated by radiotherapy to the prostate may be difficult to treat and urethral reconstruction may be required [42].

Expert Opinion

Penile and urethral trauma constitutes a small portion of the urology emergency workload, but there is an increasing volume of literature to inform decision making. The principles of trauma management should be applied in urological trauma, including determination of the injury mechanism, type of injury (blunt versus penetrating), the pattern of associated injuries (e.g. penile fracture and urethral injury), and careful systems review to exclude other injuries. Likewise, general surgical principles should be followed in wound management, including adequate debridement to remove devitalised tissue and the appropriate choice of wound closure (i.e. primary or delayed). In this age of increasing antimicrobial resistance, antibiotics should be used judiciously in accordance with local guidelines and with the input of the microbiologist.

The management of urethral distraction injuries does arouse considerable intellectual debate (i.e. primary realignment or delayed repair), but in the real world, the patient usually has other injuries that require more immediate attention. Placement of a suprapubic catheter to divert the urine with minimal intervention is safe and does not compromise the outcome of orthopaedic pelvic surgery or delayed bulboprostatic urethroplasty. In addition, not every patient will be fortunate enough to have an expert urethral surgeon on hand, and these operations should not be undertaken by the occasional surgeon.

References

References

32

Penis and Urethra Inflammation

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Abstract

In this chapter, the common inflammatory disorders of the penis and urethra are discussed. Inflammation of the glans and prepuce (balanoposthitis) is classified as acute or chronic. Acute causes include bacterial and fungal infection and the sexually transmitted infections, herpes, syphilis, and trichomonas vaginalis. The chronic causes include lichen sclerosus, Zoon balanitis, and lichen planus. Urethral infection and trauma can give rise to urethral stricture disease. An in-depth review of the management of urethral stricture disease, including the various urethroplasty techniques commonly in use, is described. Other uretho- penile-scrotal disorders including Fournier’s gangrene, paraphimosis, and genital warts are also discussed.

Keywords  urethra; penis; stricture; urethral stricture; balanitis; urethroplasty; Fournier’s gangrene; genital warts

Key Points

- Sexually transmitted infections are increasing in incidence.
- Lichen sclerosus is the most common male and female genital or perineal skin disorder and causes significant sexual dysfunction.
- Urethral strictures are the most common cause of urological symptoms in a young man.
- Recurrence and progression of strictures is common after endoscopic management.
- Urethroplasty is a more complex procedure but has a higher rate of curing a stricture.

32.1 Urethral Inflammation

32.1.1 Urethritis

Inflammation of the urethra can be caused by either infection (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Escherichia coli*, *Trichomonas vaginalis*, *Herpes, Ureaplasma*, and *Mycoplasma* are the most common organisms), autoimmune disorders (i.e. Reiter syndrome, Wegener granulomatosis), or local irritants (i.e. foreign bodies, shower gel and soaps) [1, 2]. There may be associated urinary symptoms such as frequency, urgency, and a sense of incomplete emptying of the bladder. The condition may occasionally be asymptomatic.

A thorough history, including sexual history, should be taken. Examination should look for other sites of possible infection, including kidneys, bladder, prostate, or external genitalia. *Chlamydia* is the more common organism,
followed by *N. gonorrhoeae* and *E. coli*. Chlamydia has a long incubation period of 7–21 days. Symptoms usually have a gradual onset and mild. Gonorrhoea has a shorter incubation period of two to seven days, with a sudden onset of more severe symptoms.

A urethral swab should be sent for culture and sensitivity. Gram staining and nucleic acid amplification tests (NAAT) by polymerase chain reaction (PCR) or ligase chain reactions can quickly identify the organism [1, 2]. The midstream urine and the first 20 ml of urine are also sent for enzyme immunoassay and culturing.

Treatment is with antibiotics based on local guidelines. However, as the most common organisms are Chlamydia followed by Gonococcus, treatment is with dual antibiotics to cover both. For Chlamydia, a single dose of 1.5 g Azithromycin or Doxycycline 100 mg twice a day for 7–14 days is recommended [1, 2]. For Gonococcus, a single dose of Ceftriaxone 1 g, Cefixime 800 mg, or Ciprofloxacin 500 mg [1, 2].

### 32.2 Penile Inflammation

#### 32.2.1 Balanitis

**32.2.1.1 Introduction**

Balanitis is inflammation of the glans penis and is termed *balanoposthitis* when it also involves the prepuce. Patients present with nonspecific itching and burning of the glans and prepuce with associated discoloration. There are several causes of balanitis that can be broadly classified as acute or chronic.

**32.2.1.2 Acute balanitis**

**32.2.1.2.1 Fungal and Bacterial Infection**

When the presentation is acute, the most likely aetiology is fungal or bacterial infection. Predisposing factors include being uncircumcised (particularly when phimosis is present), poor hygiene, build-up of smegma, diabetes, and immunosuppression [3]. General advice for all patients is to improve hygiene by retracting the prepuce and washing with warm water daily, using emollient creams, and avoiding soaps, which can cause further irritation. On clinical examination, the glans will appear erythematous, and in severe cases, there may be preputial oedema with discharge and a foul odour. It is recommended to obtain subpreputial cultures in all cases [4]. Ulcerated areas should be swabbed to specifically test for herpes. The main organism implicated in infectious balanitis is *Candida albicans*, accounting for up to 35% of all cases [5]. The treatment for candida balanitis is topical antifungal cream in the form of 1% clotrimazole or 2% miconazole applied twice daily until symptoms have settled [6, 7]. In severe cases, a single dose of oral fluconazole 150 mg can be given [6]. Bacterial organisms implicated are *Streptococcus* spp., *Staphylococcus aureus*, *Gardnerella vaginalis*, and anaerobes. Treatment of bacterial balanitis is dependent on the organism grown [8].

**32.2.1.2.2 Sexually Transmitted Infections Causing Balanitis**

There are a number of sexually transmitted infections (STIs) that cause balanitis. These include herpes simplex virus (HSV), *T. vaginalis*, and syphilis.

**Herpes Simplex Virus** There are two subtypes of HSV (HSV-1 and HSV-2). HSV-1 is currently the most common cause of primary genital herpes in Western countries [4, 9]. HSV-2 was previously the most common cause of primary genital herpes but is still the form that is more likely to recur [10]. Infection can be primary, nonprimary (i.e. previous infection with a different herpes virus), or recurrent. The patient may be asymptomatic during initial infection.

The infection is transmitted by sexual intercourse, especially orogenital contact. It gives rise to little or no illness in around 50% of patients who are infected. The remainder, after a week’s incubation period, develop local burning, itching, urethral discharge, and pain, sometimes with systemic fever and muscle aches resembling influenza. Small groups of 2-mm red papules appear, form vesicles, and burst, leaving painful ulcers on the prepuce or glans, which scab over and heal but are succeeded by further waves of fresh infection. Headache, neck stiffness, and photophobia signify meningeal infection from which patients recover spontaneously. Infection of the sacral nerve roots may give pain in the thighs and difficulty in voiding. In patients who are immunosuppressed, these symptoms may be much more severe. Female partners of men with genital herpes incur an increased risk of carcinoma of the cervix.

Primary infection is likely to cause systemic symptoms in the form of fever and myalgia. After the primary infection, the virus becomes latent in local sensory ganglia and periodically reactivates. Diagnosis of HSV is performed by swab of a lesion, which is then sent for HSV culture or DNA detection by PCR. Initial management includes saline bathing, analgesia, and topical lignocaine 5% ointment [4, 9]. An oral antiviral such as acyclovir 400 mg three times a day is indicated within five days of the start of symptoms and treatment should last five days [9, 11].

**Syphilis** Syphilis is caused by the spirochete bacterium *Treponema pallidum*. It occurs predominantly in white men who have sex with men (MSM) [12]. The bacterium invades the mucosal surface by direct contact [13]. After an incubation period of approximately 21 days, the chancre of primary disease is formed. The classical Hunterian chancre starts as a dull red papule of variable size on the prepuce, glans or coronal sulcus. There may be more than one papule, mimicking herpes. The papule becomes an ulcer, which may become secondarily infected. Typically, there is
an enlarged lymph node in the inguinal region. If left untreated, 25% will develop secondary syphilis, which results in a widespread muco-cutaneous rash and lymphadenopathy. To a lesser degree, hepatitis, glomerulonephritis, and neurological complications can occur [14]. After a latent period of some 20–40 years, tertiary disease occurs consisting of cardiovascular, neurological, and gummatous disease (i.e. granulomatous lesion affecting skin and bone most often) [15]. Diagnosis is by dark ground microscopy or PCR of swabs from a chancre. Serological tests are performed for suspected latent disease. Penicillins are the antibiotic of choice for the treatment of syphilis.

**Trichomonas Vaginalis** *T. vaginalis* is a flagellated protozoan. It should be considered in a case of balanoposthitis when the female partner has undiagnosed vaginal discharge. The most common presentation is with urethritis and urethral discharge, but this can develop into balanitis [16]. Diagnosis is made by urethral culture or first void urine culture [17]. Treatment is with metronidazole either as a 2 g single dose or 500 mg twice daily for five to seven days [18].

**32.2.1.3 Chronic balanitis**

**32.2.1.3.1 Lichen Sclerosus**

**Introduction** Male genital lichen sclerosus is a chronic inflammatory skin condition affecting the prepuce, glans, and urethra. This condition was originally termed balanitis xerotica obliterans (BXO) by Stuhmer in 1928; however, male genital lichen sclerosus is now the preferred terminology.

**Incidence** The overall incidence of disease is difficult to establish because patients may present to various specialties. It is seen at any age, though relatively rare in children. The incidence of a general uncircumcised male population is about 1%, while reported to be as high as 15% in specialist dermatology clinics [19, 20].

**Aetiology** The aetiology of disease is unclear and likely multifactorial with autoimmune disease, infection, metabolic disease, and contact with urine all implicated [21]. Histologically, there is a loss of the rete pegs that fix the epidermis to the dermis, so the dermis tends to flake off. There is a thickening of the collagen layer of the dermis into which lymphocytes invade, and this collagen tends to contract so that the skin shrinks.

**Presentation** Clinical appearances are initially white flat-topped plaques. As disease progresses, atrophic and sclerotic white patches (i.e. leukoderma) ensue (Figure 32.1). The most common presenting symptom is male dyspareunia as a consequence of preputial dysfunction [22]. Thickening of the prepuce results in difficulty with retraction (i.e. phimosis) with subsequent splitting, tearing, and bleeding of the prepuce or frenulum. Disease of the glans tends to cause pruritus and paraesthesia. Glanular disease can also extend to the meatus and urethra. Stricture of the meatus and urethra leads to symptoms of bladder outflow obstruction and urinary retention in severe circumstances [23].

**Management** Conservative management measures include using soap alternatives for washing and the use of barrier creams to avoid contact with urine [24]. In early disease, treatment should begin with daily application of a medium-strength topical corticosteroid (i.e. clobetasol propionate 0.05%) for six to eight weeks. If there is a good response, application can reduce to alternate days for up to 16 weeks or a less potent steroid could be used [23].

Surgical management is by circumcision. This can be curative, not only for disease of the prepuce, but also for the glans in the majority of cases [25]. When disease of the glans does not resolve, a glans-resurfacing procedure with split-thickness skin graft may be indicated [25]. Disease extending to the urethral meatus and urethra can be treated by urethroplasty with buccal mucosa. In some cases of severe pan-urethral strictureing (image), a perineal urethrostomy may be indicated.

**32.2.1.4 Zoon Balanitis**

Zoon balanitis consists of shiny red plaques with speckled areas (cayenne pepper spots) on the inner prepuce and glans that mirror one another (Figure 32.2). It is a disease of unknown aetiology affecting middle aged and elderly uncircumcised men. It is also known as ‘plasma cell balanitis’ because of the classical histological appearance.
of a band-like infiltrate of lymphocytes and plasma cells [26]. Patients are often completely asymptomatic but may complain of a small amount of discharge from the affected area. Temporary relief may be gained from the use of topical antibiotic or steroid creams [27]. Definitive treatment is by circumcision, which completely cures the disease [28].

32.2.1.5 Lichen Planus
Lichen planus is a chronic inflammatory dermatosis affecting skin, mucous membranes, scalp, and nails [29]. On the penis, these lesions appear as reddish-purple annular plaques on the glans and coronal sulcus (Figure 32.3) [30]. Approximately 25% of patients with lichen planus have genital lesions [31]. Unlike lichen planus on other body parts, penile lesions are usually not itchy. Treatment is with a potent topical corticosteroid [29].

32.3 Other Urethro-Peno-Scrotal Pathologies

32.3.1 Fournier’s Gangrene

32.3.1.1 Introduction
Fournier’s gangrene is a fulminant form of infective necrotising fasciitis affecting the external genitalia, perineum, and a perianal region, which commonly affects men, but can also occur in women and children [32]. Baurienne first described necrotising fasciitis of the genital region in 1764 [33]. However, the disease is commonly credited to Parisian venerologist Jean-Alfred Fournier who, in 1883, described several cases of fulminant gangrene of the penis and scrotum in young men [34].

32.3.1.2 Aetiology
Sources of infection include the gastrointestinal tract (30–50%), genitourinary tract (20–40%), and cutaneous injury (20%) [35]. There is a strong association with systemic comorbidities with diabetes reported in 20–70% and alcoholism associated with 25–50% of cases [36, 37]. The compromised immunity provides an environment for infection to initiate.

32.3.1.3 Pathogenesis
Infection is polymicrobial, and it is thought that synergy between these bacteria allows rapid multiplication and spread of infection. The most commonly isolated organisms are *E. coli*, *Klebsiella pneumonia*, and *S. aureus*. The most commonly isolated anaerobe is *Bacteroides fragilis* [38]. An obliterator endarteritis develops which leads to subcutaneous vascular necrosis and localised ischaemia. Fascial destruction ensues at rates of up to 2–3 cm h$^{-1}$ [39]. This usually starts in the superficial facial planes of the perineum (Colles fascia) and extends to the scrotum via darts fascia, penis via Buck fascia, and abdominal wall via Scarpa fascia. Because of the attachments of Colles fascia to the perineal body posteriorly and pubic rami laterally, the extension of disease is limited in these areas [40]. Testicular involvement is rare because of the separate blood supply to the testes.
32.3.1.4 Presentation
Presentation is usually dramatic with perineal pain and swelling and signs of severe sepsis or septic shock, although an insidious onset is also possible. The systemic signs of infection are often out of proportion with the local disease, which can range from local cellulitis to large areas of necrotic tissue and slough in the scrotum and perineum. Crepitus of the subcutaneous is also a common sign because of the presence of gas forming organisms [38].

32.3.1.5 Management
Management consists of haemodynamic stabilisation, broad-spectrum antibiotics, and early surgical debridement. Debridement is often more extensive than first imagined because subcutaneous involvement is greater than cutaneous appearances might suggest. General surgical input may also be required if the source of infection is perianal and a defunctioning stoma is being considered. Subsequent debridement is usually required at an average of 3.5 per patient [41]. It may also be appropriate to involve plastics surgeons at this point to consider approaches for management of large soft-tissue defects. Options for management of such defects include vacuum-assisted closure (VAC), skin-grafting techniques, or a combination of both. Despite advances in management, mortality remains high at 20–30% [42].

32.3.2 Periurethral Abscess
Periurethral abscesses can occur in patients undergoing urological procedures, such as cystoscopy and urethral catheterisation, whereby bacteria gain access through Buck’s fascia into the periurethral tissue. More commonly seen in uncontrolled diabetes or in patients who are immunocompromised. It can initially present with a painful lump, urethral discharge if the abscess bursts into the urethra, scrotal swelling if it tracks down, and obstructive urinary symptoms because of mass effect on the urethra. However, if left untreated, Fournier’s gangrene can develop and spread to the perineum, buttocks, and abdominal wall. Treatment is early recognition and incision and drainage of the abscess with debridement of any necrotic tissue. Urinary diversion with a suprapubic catheter might be required.

32.3.3 Condyloma Acuminata (Genital Warts)
32.3.3.1 Aetiology
Genital warts are caused by the human papilloma virus (HPV), of which there are more than 100 subtypes. The majority of warts are benign, caused by HPV subtypes 6 and 11. High-risk subtypes 16 and 18 do not tend to cause warty lesions, but do cause dysplastic lesions and cancers. These high-risk subtypes of HPV are implicated in penile and cervical cancer. Transmission is most often by sexual contact.

32.3.3.2 Presentation
Genital warts are classically described as cauliflower-like lesions that can be single or multiple, affecting any part of the ano-genital region. On mucosal surfaces, they tend to be soft and fleshy, on hair-bearing skin firmer and keratinised. Other than the psychological impact of the growth, patients tend to be asymptomatic. Lesions can extend into the urethra resulting in haematuria. A rare subtype of genital wart called giant condyloma acuminatum (GCA) or by its eponymous name – Buschke-Lowenstein tumour – can grow to a significant size and result in local infiltration and destruction.

32.3.3.3 Treatment
There are several topical treatments available, including podophyllotoxin, imiquimod, and cryotherapy. Surgical excision is reserved for treatment failure or for large masses such as GCA. Topical therapy with podophyllotoxin cream 0.15% is the first-line treatment where warts are multiple. Where this fails, imiquimod cream 5% is the second-line treatment of choice. Where there are single or few warts, cryotherapy is considered first-line treatment, with topical therapies second. In patients who are pregnant, podophyllotoxin and imiquimod should not be used [43]. Success rates for monotherapy with podophyllotoxin are 0.15%, imiquimod 5%, and cryotherapy are up to 70, 81, and 92%, respectively [43].

32.3.4 Chancroid
The organism Haemophilus ducreyi causes a large, sloughing ulcer of the penis and prepuce with secondary infection and inflammation of the regional inguinal lymph nodes which often supurate. H. ducreyi is cultured from the exudate. It responds to antibiotics, but the follow up must include tests for unsuspected syphilis.

32.3.5 Granuloma Inguinale
The lesion of granuloma inguinale on the penis produces a shallow painful ulcer with a bright red granulating base from which the typical ‘Donovan bodies’ – Donovania granulomatis in mononuclear cells, can be found in scrapings stained with Giemsa. The urologist is likely to make the diagnosis only in a biopsy. It responds rapidly to tetracyclines.

32.3.6 Paraphimosis
Paraphimosis is a urological emergency, whereby the foreskin fails to protract back to the normal anatomical location. The foreskin becomes oedematous, making protracting it more difficult. In itself, a paraphimosis is
not dangerous, however, if the oedema is sufficient enough to constrict the blood supply, then it becomes painful, and if not alleviated within the first few hours, it can lead to avascular necrosis injuries with small areas of ulcerations developing. A tight band can be felt under the glans. If the swelling progresses, the oedema can constrict the blood supply to the glans as well.

Treatment is focused on attempting to protract the foreskin from its constricting retracted position just proximal to the glans. Penile block with 10 ml of 0.5\% bupivacaine (long-term effect) mixed with 10 ml of 1 or 2\% lignocaine (short-term effect) can help with the pain and manipulation.

### 32.3.6.1 Conservative Measures

- Squeezing the oedema by compressing it for five minutes then attempting to protract the foreskin is usually successful, if the foreskin has been retracted for a few hours only with minimal oedema.
- Applying an ‘iced glove’ to reduce the oedema. Filling a surgical glove with ice and water and tying off the hand entrance then ‘dressing’ the penis by applying the thumb. Giving a double barrier between the penile skin and ice. After five minutes, an attempt is made to retract the foreskin.
- The Dundee Technique. Using a large-bore needle, 20–30 small punctures are made in the oedematous foreskin, then progressive squeezing to reduce the oedema and protract the foreskin to its normal position [44].

Attempt only one of these, and if it fails, a traditional dorsal slit should be made. This is performed by incising the tight band at the 12 o’clock position and then ensuring the foreskin protracts back to its anatomical position with ease. The edges of the foreskin are suture closed. A subsequent circumcision can be organised as a non-emergency procedure.

### 32.4 Stricture Disease of the Urethra

#### 32.4.1 Definition and Incidence

A urethral stricture is a narrowing in the lumen of the urethra caused by scarring of the corpus spongiosum, which surrounds the urethral epithelium. This process is known as ‘spongiofibrosis’ and only affects the anterior urethra which is surrounded by the corpus spongiosum. A stricture of the posterior urethra is more correctly referred to as ‘contracture’ or ‘stenosis’ and is a consequence of healing caused by scarring and fibrosis, leading to the narrowing of the urethral lumen [45].

The functional effect of urethral narrowing leads to obstruction of the lower urinary tract. It is predominately a disease of men with a prevalence of 200 per 10 000 men in their 20s, rising to 900 per 100 000 men in their 70s [46, 47]. There are 17 000 hospital admissions annually in the UK at a cost of more than £10 M [46].

#### 32.4.2 Anatomy

The urethra can be divided into anterior and posterior segments. The posterior includes the prostatic urethra and the membranous urethra (i.e. segment passing through the pelvic floor musculature). The anterior includes the bulbar urethra (i.e. segment enveloped by the bulbospongiosus muscle), penile urethra, glanular urethra (passing through the glans), and the urethral meatus (Figure 32.4).

#### 32.4.3 Aetiology

Traditionally, the most common cause for urethral strictures was bacterial urethritis caused by untreated gonorrhoea. Abscesses would form in paraurethral glands and discharge into the surrounding corpus spongiosum (Figure 32.5). Healing by fibrous tissue led to stricture. The sites affected by stricture are those with the largest number of paraurethral glands at the bulb (Figure 32.6). Bacterial urethritis now accounts for 20\% of strictures [48]. The majority of urethral strictures are iatrogenic in nature, accounting for approximately 45\% [49]. Iatrogenic causes include urethral catheterisation, transurethral procedures, and hypospadias repair. Iatrogenic strictures tend to occur at the junction of the bulbar and penile urethra and are thought to be ischaemic secondary to pressure exerted by the instrument in use. They may also be caused by direct trauma to the urothelium by the instrument. Idiopathic strictures are the next most common, accounting for approximately 30\% [48]. In some

![Figure 32.4 Normal urethrogram. Case courtesy of Dr Ian Bickle, Radiopaedia.org, rID: 22531.](image-url)
cases, this may be as a result of unrecognised trauma in childhood, which manifests as a stricture later in life. The short strictures seen in adolescent and young adults may be congenital in nature [50, 51]. Other causes include pelvic fracture and lichen sclerosus.

Pelvic fractures tend to cause injury to the posterior urethra by causing distraction injury (i.e. the urethra is pulled apart and heals with scar tissue formation). Other causes of stricture to the posterior urethra include radiotherapy, brachytherapy, and focal therapies for prostate cancer.

### 32.4.4 Signs and Symptoms

Symptoms generally start when the urethral calibre falls below 10- to 14-Fr. Once stenosis occurs, infected urine accumulates under pressure upstream of the stenosis and extravasates into the corpus spongiosum. As a result, there is a tendency for the process of scarring and stricture to spread slowly in a retrograde direction (Figure 32.7). The main symptoms of a urethral stricture are those of lower urinary tract obstruction including poor and prolonged stream, incomplete emptying, and urinary frequency. Recurrent urinary tract infections (UTIs) may occur, including cystitis, prostatitis, or epididymo-orchitis because of incomplete emptying [2]. Visible haematuria results because of the straining to force urine out, causing erosions of the strictured urothelium; patients may develop acute or chronic urinary retention. Obstructed ejaculation suggests stricture.
Clinical examination is often unrevealing; however, the glans and prepuce should be inspected for lichen scleroderma (causing meatal stenosis or phimosis). Abdominal examination palpating for a grossly distended bladder. Strictures themselves are often impalpable, but induration may be felt if there is a periurethral abscess. In more severe cases, periurethral abscesses can lead to chronic fistulae, the so-called ‘watering can perineum’.

32.4.5 Complications of Urethral Stricture

1) *Extravasation of urine*. The most dangerous complication of stricture is extravasation of urine into the scrotum and perineum. Unless both compartments are promptly drained (Figure 32.8), infected hypertonic urine causes necrosis of fat and fascia of the perineum, scrotum, penis, and the lower part of the abdominal wall; only the testicles survive thanks to their separate blood supply. The patient who survives this life-threatening complication will often end up with several fistulae.

2) *Periurethral abscess*. An infected periurethral gland may burst outside the corpus spongiosum to form a paraurethral abscess which may discharge spontaneously (Figure 32.9).

3) *Fistula*. Whether such a paraurethral abscess discharges or is incised, urine will continue to leak so long as there is a stenosis downstream. A maze of channels may link one fistula with another (i.e. the watering-can perineum).
4) **Diverticulum.** An abscess may fail to burst through the overlying skin, and so form a diverticulum where a stone may form.

5) **Cancer.** Every patient with a long-standing stricture, who has a swelling upstream of a stricture, should be suspected of having cancer.

6) **Urinary infection.** It is a common sequel of urethral stricture. Stones, epididymitis, and prostatitis are also common complications.

**32.4.6 Investigations**

After a clinical history and examination, uroflometry should be the first-line investigation. This can give a typical box-shaped curve with a sharp rise to maximum flow rate ($Q_{\text{max}}$), reduced flow rate, and a plateau appearance of the $Q_{\text{max}}$ (Figure 32.10). Ultrasound is useful in assessing for the presence of any urinary retention or hydronephrosis as well as a thick-walled trabeculated bladder indicating chronic obstruction. Urine dipstick testing can be used to rule out concomitant infection.

If a urethral stricture is suspected, confirmation of the diagnosis is achieved either by direct visualisation (cystoscopy) or imaging (cystourethrogram). Images are taken in an oblique view to visualise the entire length of the urethra. A urethrogram is performed with the patient lying in a 30° oblique position with the bottom leg flexed. A 12-Fr catheter is placed into the fossa navicularis and the balloon inflated with 2 ml of water. Up to 30 ml undiluted contrast is injected slowly whilst screening. Once the bladder is adequately distended with contrast, a voiding cystourethrogram can be performed. This investigation gives information on the site and length of stricture as well as the presence of a urethral diverticulum or fistula. Urethromograms are vital to establish a management plan because they can distinguish between, small (Figure 32.11), and long strictures (Figure 32.12), as well as panurethral strictures (Figure 32.13).

In some cases, cystoscopy can be used to dilate a soft stricture under vision using the scope at the same time as investigating. However, tight or long strictures will always require a urethrogram to gain information about the urethra upstream of the stricture before planning treatment. Never use force to dilate a stricture because one can cause more damage.

If the presentation is retention of urine with failure of urethral catheterisation, a suprapubic catheter should be placed, followed by combined antegrade and retrograde urethrogram to assess the stricture.

In pelvic fractures, a reconstructed computed tomography (CT) can help assess the fracture and how it relates to the urinary tract; however, a cystogram can easily demonstrate distraction injuries.
32.4.7 Treatment

Most strictures require treatment under general or spinal anaesthesia. The choice between urethrotomy and urethral dilatation is often one of preference of the surgeon, but it is influenced by how tight and how long the stricture is as well as location [47]. Nearly 50% of all strictures recur, but multiple, complex, or long strictures (>2 cm) are even more likely to recur.

To treat a penile urethral stricture:
- With lichen sclerosus: Buccal mucosal urethroplasty.
- Without lichen sclerosus: Flap or buccal mucosal urethroplasty.

To treat a bulbar urethral stricture:
- Urethral dilation or internal urethrotomy.
- <2 cm: Anastomotic urethroplasty.
- >2 cm: Buccal mucosal augmentation urethroplasty

32.4.7.1 Urethral Dilation

‘The skill of the urologist is measured by his gentleness’ [52]. Urethral dilation has been practiced for thousands of years. Dilation is done to stretch the stricture without causing damage to lead to further scarring. This is evident when significant bleeding occurs which signifies tearing of the stricture. There are a number of instruments that can be used. Historically bougies and sounds have been used to dilate strictures. The term bougie is derived from the word Bujiyah – an Algerian port known for the best wax candles and thin wax tapers were found to make excellent dilators. In the recent history, thin pliable metal bougies – filiforms were used. Using this technique, multiple filiforms could be passed until the true lumen was identified. Then a series of flexible screw on dilators could be deployed, commonly known as ‘followers’ (Figures 32.14 and 32.15).

Figure 32.12 Bulbar urethral stricture longer than 2 cm.

Figure 32.13 Panurethral stricture.

Figure 32.14 The technique of using multiple filiforms.
32.4 Stricture Disease of the Urethra

The most common instrument found on cystoscopy sets are Clutton or Lister sounds (Figure 32.16). These are a series of curved metal instruments, sequentially increasing in diameter. These metal instruments were used for ‘sounding’ for bladder stones; hence, the name ‘sound.’ Blind dilation with metal sounds should be performed with caution because there is a risk of producing a false passage, particularly with those of smaller diameter. With an easy stricture and a skilled surgeon, this method provided excellent results; however, strictures that were not easy and were often delegated to junior urologists of varying skill had a considerable morbidity [53]. It is often safer to start with a medium-sized dilator to reduce the risk of this complication. These dilators are also useful in helping to identify the site of a stricture when performing an open reconstruction. The current trend is to perform urethral dilation using hydrophilic-coated, S-shaped curved dilators (Figure 32.17). These are inserted over a guidewire, which has been passed into the bladder cystoscopically. This all but negates the risk of causing a false passage and appears to be less traumatic.

32.4.7.2 Direct Vision Internal Urethrotomy

Direct vision internal urethrotomy (DVIU) is an endoscopic procedure. Using normal saline rather than water (in view of the risk of haemolysis if water is extravasated), the stricture is incised with a blade or laser under direct vision (Figure 32.18). Because this is controlled, the stricture is divided rather than torn or shorn, and healing is by re-epithelializing of the cut surface. Where the urethra proximal to the stricture cannot be seen, a guidewire is passed to direct the incision.

After both dilation and urethrotomy, a catheter is usually placed for at least 24 hours to reduce infective complications associated with extravasation of urine [54]. Once the stricture has been divided or dilated, the patient might require regular intermittent self-dilation. Following the procedure, cure can be expected in approximately 40–70% of patients [55]. There is no difference in recurrence rates between urethral dilation and DVIU [56]. However, it is safer to dilate a stricture after a transurethral resection of the prostate (TURP) that is near the sphincter to avoid damaging it and leading to incontinence. Once a stricture has recurred, further recurrence is almost inevitable requiring repeat DVIU every two years on average [10]. Many would argue that once a stricture has recurred, the next step in management should be urethroplasty [57].

32.4.7.3 Urethroplasty

32.4.7.3.1 Introduction

Urethroplasty is the repair of an injury or defect in the wall of the urethra. The technique used is dependent on several factors. The most important consideration is the site of the stricture. The sites are broadly classified as penile, bulbar, or posterior urethra. The technique used can be classified as follows.

- Anastomotic – removal of the diseased segment with end-to-end anastomosis.
Augmentation – widening of existing lumen with a graft.
Substitution – removal of diseased segment and replacement with a graft.

The most commonly used graft is buccal mucosa, which can be used for both augmentation and substitution. Buccal mucosa has a pandermal plexus allowing it to be harvested and thinned without interrupting the vasculature [58]. Full-thickness grafts (including the inner prepuce) contain a separate intradermal and subdermal plexus joined by communicating vessels. They must be treated with more care and kept free from haemolytic streptococcal infection, thus making them more fastidious than buccal mucosal grafts [59]. A pedicled skin flap can be used in an augmentation urethroplasty. This involves the mobilisation of a patch of skin while keeping its blood supply intact. It is not commonly used for bulbar urethral strictures because the adjacent scrotal skin used is hair bearing, which can lead to recurrent infections and stone formation.

In this section, we will discuss which urethroplasty technique is most suitable based on the site of the stricture. With regards to the posterior urethra, the management of those caused by pelvic fracture, pelvic fracture urethral injury (PFUI), will be primarily discussed.

32.4.7.3.2 Urethroplasty for Bulbar Urethral Stricture
There are several techniques for the management of bulbar urethral stricture. These are primarily anastomotic or augmentation urethroplasties. The technique used depends on the length of stricture and individual surgeon preference or experience.

The Approach The initial approach is similar for all bulbar urethral strictures. The stricture can be assessed endoscopically with a 6- to 7.5-Fr semi-rigid ureteroscopy and a guidewire or 4-Fr ureteral catheter deployed across the stricture. A perineal midline incision is made. The initial layers of dissection include skin, Campers fascia (fatty tissue), and Colles fascia which is a continuation of Scarpa fascia in the abdominal wall. Next the bulbospongiosus muscle with its covering of deep perineal fascia (Gallaudet fascia) will be dissected. The distal extent of the stricture can be assessed by passing a Foley catheter or Clutton’s sound larger than the diameter of the stricture. The urethra can then be mobilised from the corporal bodies as necessary and the sound or catheter used to guide the site of urethral incision.

32.4.7.3.3 Anastomotic Urethroplasty
This is the treatment of choice for short strictures of the bulbar urethra such as those caused by a fall astride injury (Figure 32.11). The urethra is mobilised from the corporal bodies, the strictured segment is excised, and the two ends spatulated and anastomosed (Figure 32.19). One must ensure a tension-free anastomosis and good blood supply is maintained. Long-term success rates for this procedure are high ranging from 91 to 99% [60–62]. The ideal stricture length for this procedure is generally accepted to be less than 2 cm [61]; however, some recommend a stricture length of no more than 1 cm due to the risk of chordee [63]. Attempts at longer stricture lengths of 2.5–5 cm have shown promise [64]. One common criticism of the anastomotic urethroplasty is the interruption of blood flow within the corpus spongiosum caused by complete transection. This can result in a lack of glans engorgement during erection.

32.4.7.3.4 Nontransecting Anastomotic Urethroplasty
To minimise disruption to the corpus spongiosum, the nontransecting anastomotic urethroplasty was developed [65, 66]. The bulbar urethra is mobilised and a dorsal stricturotomy made. The strictured segment is excised, leaving the ventral corpus spongiosum intact.
The ventral surface of the urethra is anastomosed inside the urethra while the dorsal ends are closed transversely (i.e. stricturoplasty). This approach also allows for the option of an augmentation urethroplasty with a buccal mucosal graft if required. It is not recommended where there is complete obliteration of the lumen [65].

32.4.7.3.5 Augmentation Urethroplasty
An augmentation urethroplasty is the treatment of choice for longer bulbar urethral strictures (>2 cm), where there is a limited degree of spongiofibrosis and patent urethral lumen (Figure 32.12). In this procedure, a longitudinal stricturotomy is made, and an ellipse of graft is patched to the incised urethra, thus widening the lumen. The graft of choice is buccal mucosa. Debate remains as to whether dorsal or ventral stricturotomy and patch is preferable. Proponents of the dorsal approach argue that the graft is more secure because it is applied to the tunica albuginea of the corpora cavernosa allowing for better healing and less risk of saculation. The corpus spongiosum is also thinner dorsally, resulting in less bleeding [67]. Conversely, a ventral incision allows for less mobilisation of the urethra and the corpus spongiosum can be closed over the graft to give support and a rich vascular bed. The ventral approach is also technically less challenging. The success rates are similar for both, 88–89% and 88–89% for dorsal and ventral grafting techniques, respectively [68, 69].

To perform a dorsal patch urethroplasty without mobilisation of the urethra, the transventral dorsal inlay urethroplasty technique was developed in 2001 (i.e. Asopa technique), with an average success rate of 87% [68, 70]. Palminteri took this one step further and performed a combination of dorsal and ventral grafting without mobilisation of the urethra, with an average success rate of 91% [68, 71].

Another technique to limit the amount of mobilisation for the urethra is the lateral onlay urethroplasty first described by Barbagli in 2005 [72]. Only one side of the urethra needs to be mobilised; therefore, blood supply to the corpus spongiosum is maintained on the contralateral side. This also avoids a ventral urethrotomy in the thickest part of the spongiosum, theoretically leading to less intraoperative blood loss. Barbagli described this procedure in six patients with a success rate of 83% at 77 months follow up [71].

32.4.7.4 Penile Urethra
Techniques for treatment of penile urethral strictures vary by the type of tissue used: pedicled flap, buccal mucosa, or full-thickness skin and by whether a single-stage or two-staged approach is used. Anastomotic urethroplasty is not suitable in the penile urethra because of the risk of chordee.

32.4.7.4.1 Pedicled or Island Patch Urethroplasty
General considerations include the quality of the native tissue, the length of stricture, and aetiology of disease. For example, a single-stage pedicled penile skin flap, such as the Orandi flap, is likely to be the best option in a long stricture where there have been no previous attempts at reconstruction and no lichen sclerosus. Where there is evidence of lichen sclerosus, this will undoubtedly recur in a graft made of genital skin.

Where there has been previous hypospadias repair, the corpus spongiosum, dartos fascia, and ventral shaft skin are often deficient, and in this situation, a free graft substitution would be more appropriate.

The clear benefit of a pedicled penile skin flap is the long length of stricture that can be treated and that it is a single-stage procedure. As most of the described techniques involve ventral application of the skin flap, they are at risk of saculation with resulting postvoid dribbling [73] (Figures 32.20 and 32.21). A skin graft may be taken from the prepuce (if available) or the penile shaft. Dissecting in the plane between the dartos muscle and the dermis provides the patch of skin with a vascular pedicle which promotes its survival (Figure 32.21). Once the flap of skin has been mobilised, the strictured segment of uretha is laid open and the skin graft anastomosed to the cut edges.

Figure 32.19 Excision and end-to-end anastomosis. The mobilised urethral ends are spatulated and anastomosed as an ellipse.
The skin patch may enlarge to form a pouch; this may take place upstream or downstream of a stenosis (Figure 32.22). Occasionally such a pouch acts as a valve to cause obstruction (Figure 32.23). Other complications include haematoma, skin necrosis, and fistula formation. Long-term overall stricture free rates of a McAninch single-stage penile skin flap for anterior urethral strictures are 95, 89, 84, and 79% at 1, 3, 5, and 10 years, respectively [74].

32.4.7.4.2 Free Graft Urethroplasty
The urethra is laid open by a ventral incision from the meatus until healthy urethra is encountered. If there is a healthy urethral plate, a single-stage inlay of graft and closure can be performed. If this is not the case, a graft should be inlaid as a first stage procedure, allowed to mature for four to six months, followed by a second-stage tubularisation procedure (Figure 32.24). Clearly a single-stage approach is beneficial to the patient where possible because it avoids long periods of discomfort and disability. Again the most commonly used graft here is buccal mucosa. Full-thickness grafts from genital skin are again contraindicated in lichen sclerosus. Manoj et al. have used postauricular full-thickness grafts in 12 patients with lichen sclerosus with a 90% success rate [75].

32.4.8 Female Urethral Stricture
It is rare for women to present with urethral strictures, and the urethra can usually be dilated with no need for more formal surgery.

32.5 Pelvic Fracture Urethral Injury
32.5.1 Incidence
Injury to the urethra is associated with 5–25% of pelvic fractures, and these are predominantly injuries to the posterior urethra [76]. It is also more common in men than women due to lack of urethral attachments to the pubis in women [77].
32.5.2 Aetiology

The aetiology of injury is usually an accident involving great force with vehicular collision and fall from a great height as the most common type of accident [78].

32.5.3 Mechanism

The mechanism of injury is stretching of the urethra caused by cephalad movement of the bladder, prostate, and membranous urethra during the trauma. The membranous urethra is firmly attached to the pubis by the perineal membrane. Distal to this, attachments of the urethra are weak, resulting in a distraction defect between the bulbar and membranous urethra. If the dorsal vein ruptures, the resulting haematoma also contributes to the distraction defect. Once maximum elasticity is reached, rupture of the urethra occurs. This rupture, therefore, tends to occur at the bulbomembranous junction. Direct trauma to the urethra by a bony fragment is less common.

32.5.4 Assessment and Acute Management

The cardinal signs of a pelvic fracture urethral injury (PFUI) are blood at the urethral meatus, distended bladder, or inability to void. Where none of these signs are present, an attempt at urethral catheterisation can be
made. If any of these signs are present, a urethrogram should be performed. In the acute setting, an ultrasound-guided suprapubic catheter may need to be placed and urethrogram deferred.

If the patient is being taken to theatre for management of other injuries, an on-table urethrogram can be performed if the patient is stable. While under anaesthetic, an attempt at primary endoscopic realignment and urethral catheter insertion can be made with little risk of morbidity. Ultimately, a suprapubic catheter can always be sited if urethral catheterisation fails. The only indications for immediate exploration are the finding of concomitant injury to the bladder neck, vagina, or rectum and for removal of a bony fragment. When open exploration is performed in these instances, an attempt at urethral realignment can be made. Overall, primary realignment reduces stricture formation in approximately a third of cases [79]. Early open exploration does, however, result in higher rates of incontinence and erectile dysfunction [80]. The vast majority of patients will be managed with suprapubic catheterisation alone and urethroplasty performed after approximately three months once fractures have healed and haematoma resolved.

This is currently the treatment gold standard for PFUI to the posterior urethra [81]. Based on the degree of rupture and urethographic findings, a grading system for PFUI with recommended approaches to management has been devised (Table 32.1).

### 32.5.5 Surgical Considerations

Delayed urethroplasty consists of excision of a large fibrotic mass and anastomosis between what is left of the bulbar and membranous urethra. Often the defect is quite wide, and extensive mobilisation of the urethra is required. Still the gap may be too wide, resulting excessive tension on the anastomosis. In these cases, adjunctive manoeuvres such as splitting of the crura or infrapubectomy can be used to reduce the distance between the two ends.

When the stricture follows undisplaced fracture of the pelvis, the bulbar urethra is mobilised (Figure 32.25). The upper end is found by cutting down on a bougie
introduced through the suprapubic cystostomy (Figure 32.26). A wide oval opening is made into the urethra through the scar tissue, and the spatulated bulb urethra is then anastomosed to it.

When the fracture of the pelvis has led to much dislocation of the bones, there is a longer gap between the ends of the urethra. The corpora cavernosa must be separated in the midline and retracted laterally to expose the lower part of the symphysis, which may be unusually broad because of the malunited fracture (Figure 32.27).

After scraping the periosteum from the symphysis, a generous window is cut out from its inferior border (Figure 32.28). An oscillating bone saw is used which does not cut the periosteum on the pelvic surface of the bone. A bougie introduced through the suprapubic cystostomy is now felt through the periosteum (Figure 32.29). An ellipse is cut out from the anterior lower part of the symphysis, and an end-to-end anastomosis made after spatulating the urethra. An alternative technique removes the entire symphysis and enwraps the anastomosis in omentum to prevent scar formation.

### 32.5.6 Complications

Erectile dysfunction is a common complication of PFUI, occurring in 34% of all patients, prior to any intervention

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Appearance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Stretch injury</td>
<td>Elongation of the urethra without extravasation</td>
<td>No treatment required</td>
</tr>
<tr>
<td>II</td>
<td>Contusion</td>
<td>Blood at the urethral meatus; no extravasation on urethrography</td>
<td>Grades II and III can be managed conservatively with suprapubic cystostomy or urethral catheterization</td>
</tr>
<tr>
<td>III</td>
<td>Partial disruption</td>
<td>Extravasation of contrast at injury site with contrast visualised in proximal urethra or bladder.</td>
<td>Suprapubic cystostomy and delayed repair or primary endoscopic realignment in selected patients delayed repair</td>
</tr>
<tr>
<td>IV</td>
<td>Complete disruption</td>
<td>Extravasation of contrast at injury site without contrast visualised in proximal urethra or bladder.</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Complete or partial disruption of posterior urethra with associated tear of the bladder neck, rectum, or vagina</td>
<td>Extravasation of contrast at urethral injury site presence of blood in the vaginal introitus in women. Extravasation of contrast at bladder neck during suprapubic cystography rectal or vaginal filling with contrast material</td>
<td>Primary open repair</td>
</tr>
</tbody>
</table>
other than suprapubic catheter placement [82]. The aetiology is primarily neurogenic but may be vasculogenic, associated with pudendal artery injury. There is currently controversy as to whether revascularisation before urethral reconstruction is of benefit. It may reduce the incidence of ischaemic restenosis and reduce long-term erectile dysfunction [83, 84]. After delayed urethroplasty, the overall re-stricture rate is less than 10% and the impotence rate approximately 5% [81].

Figure 32.25 The bulbar urethra is mobilised.

Figure 32.26 The upper end of the prostatic urethra is found by cutting down onto a bougie passed down through the suprapubic cystostomy.

Figure 32.27 (a) The corpora cavernosa are separated in the midline to (b) reveal the lower edge of the malunited symphysis pubis.
Figure 32.28 (a) The periosteum of the symphysis is incised with diathermy and scraped away. (b) An arch is cut out using an oscillating bone saw.

Figure 32.29 (a) Removing the arch of bone reveals the inner layer of periosteum. (b) The inner layer of periosteum is incised onto a bougie passed down the suprapubic track. (c) After spatulating the prostatic and bulb urethra, they are anastomosed.
Expert Opinion

The diagnosis and management of genital dermatoses is made difficult by the inevitable overlap between the specialties of genitourinary medicine, dermatology, and urology. Lesions also overlap in their appearance such that a biopsy, swabs, and scrapings are often required to establish a diagnosis. Development of a multidisciplinary genital dermatology service would be better for cross-specialism opinion and more precise diagnosis.

Management of urethral strictures has moved back and forth between enthusiasm for endoscopic management and urethral reconstruction. With improvements in endoscopic equipment in the 1980s and self-dilating catheters becoming more freely available, endoscopic management was the first-line treatment in most urology departments. This led to a limited exposure in training to learn urethroplasty, and it remained a minority choice until quite recently. With the popularisation of buccal mucosal grafts and the improved outcomes and flexibility of use that they offered, urethral reconstruction has begun to re-establish its place in repairing urethral strictures. There are now many more trained surgeons and surgical departments offering urethroplasty and reducing what can be a lifelong stricture problem and dependency on urethral dilation.

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Penis and Urethra Neoplasm

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Abstract

Penile cancer is a rare neoplasm in the developed world. Its incidence appears to be increasing. In the UK, five-year survival rates approach 70%. The majority of the neoplasms are squamous cell carcinomas and are associated with the human papilloma virus (HPV) in about 40%. Other risk factors include phimosis, smoking, and premalignant conditions such as erythroplasia of Queyrat and extramammary Paget disease. Diagnosis is usually clinical, and magnetic resonance imaging (MRI) and computed tomography (CT) can be employed for staging. Metastases in the lymph nodes are the most important prognostic variable. Surgery is the mainstay of management for the primary lesion, and penile-preserving techniques have been developed to preserve function as well as achieving good oncological outcomes. Penile cancer usually spreads via the lymphatics, in a stepwise fashion to the inguinal and then the pelvic lymph nodes. Micrometastases can be present in clinically impalpable nodes in up to 25% of patients. Traditional inguinal radical lymphadenectomy is associated with significant morbidity. Dynamic sentinel lymph node biopsies are a technique that involves lymphoscintigraphy and sampling of the sentinel inguinal node(s). It can be used for staging purposes and prevents overtreatment. In experienced centres the false negative rate is less than 5%. Palpable nodal disease is managed with lymphadenectomy. Trials are ongoing to delineate the optimal pathway for fixed nodal masses and extranodal spread disease. This may involve adjuvant chemoradiotherapy. Most recurrences are likely to occur within the first two years. Therefore, the follow-up is intensive during this period with clinical and radiological reviews.

Keywords squamous cell carcinoma; human papilloma virus (HPV); organ-preserving surgery; dynamic sentinel lymph node biopsies

33.1 Penile Neoplasm

33.1.1 Benign Penile Lesions

1) Lichen planus is an uncommon chronic inflammatory skin disease with a prevalence of 0.1–0.3%. Though the aetiology is unknown, an autoimmune process is thought to trigger it. It can present with a variety of cutaneous lesions, most commonly a well-defined area of purplish, flat-topped papules with lacy white lines called Wickham's striae. There are a characteristic ‘6 Ps’ of lichen planus: planar (flat-topped), purple, polygonal, pruritic, papules, and plaques [1]. There is no cure of the disease, and management is symptom control and cosmesis with steroids, retinoids, sulfasalazine, and phototherapy.
2) Zoon balanitis is also known as Balanoposthitis chronica circumscripta plasmacellularis or plasma cell balanitis. It is an inflammation of the glans and balanoposthitis when the foreskin is also affected. The appearance is classical with red shiny erosions of the glans with or without the foreskin with erythematous plaques. The main cause is recurrent irritation from urine and poor hygiene underneath the foreskin (rarely seen in men who are circumcised), or repeated trauma or infections (i.e. viral, bacterial, or fungal). Biopsy might be required to rule out cancer; however, the treatment is pulling the foreskin back and thorough cleaning, and if fails, a circumcision should be done [2].

3) Hirsuties coronae glandis is also known as pearly penile papules (Figure 33.1) small papules, 1–3 mm domed shaped, arising in one of several rows circumferentially around the corona of the glans. They are a normal variant of the skin and cause no harm or risk of cancer conversion; however, cosmetically they may cause some distress. They occur in up to 33.3% of males who have not been circumcised and in 7.1% of males who have been circumcised [3]. No treatment is required, but it can be removed with carbon-dioxide (CO₂) laser vaporisation.

4) Balanitis xerotica obliterans (BXO) (lichen sclerosis et atrophicus of genital skin) is an inflammatory disease of unknown aetiology and affects the foreskin and glans, but it can also involve the urethra. Though it can occur at any age, it is more common in men who are uncircumcised, and the incidence increases with age from puberty [4]. It is characterised by hyperkeratosis, atrophic epidermis, sclerosis of dermis, and lymphocyte activity that results in a white thickened scarred foreskin that can lead to a pathological phimosis. Although conservative treatment might work in the early stages of the disease with regular full retraction of the foreskin and cleanliness and the use of topical steroids, circumcision is the treatment of choice.

33.1.2 Malignant Neoplasm of the Penis

33.1.2.1 Incidence and Prevalence
Malignant neoplasms of the penis are rare in Europe (Figure 33.2) and North America, but they are more common in developing nations. The UK age-standardised incidence for 2008–2010 was 1.3–2.0 per 100,000 males. The mortality rate in the UK is 0.3–0.4 per 100,000 males [5]. In Paraguay, Brazil, Angola, and India, the incidence varies between 2.3 and 8.3 per 100,000 males [6] and can account for 10–20% of male cancers.

The incidence of penile cancer has increased over the last four decades, although the overall five-year relative survival rate has increased [7]. Between 1979 and 2009, there has been a 21% increase in incidence in the UK [8]. The reasons for this are most likely to be due to better understanding of the natural history and more aggressive management. Despite this, there is often a delay in diagnosis with men reluctant to seek advice. If left untreated, most men will succumb to their disease within two years, and the sequelae from metastases are significant. Prompt management can result in five-year survival rates approaching 70% in the UK [8].

33.1.2.2 Aetiology and Risk Factors
The most common histological type in malignant neoplasms of the penis is squamous cell carcinoma (SCC), which accounts for more than 95% of all cases. The remaining 5% are made up of malignant melanoma, basal cell carcinoma, sarcomas, and rarely metastasis from the prostate, colorectal, or other tissue cancers.

Risk factors for penile cancer:
- Age: The incidence of penile cancer increases with age [9]. The peak age is during the sixth decade of life, but around 20% of all new cases are in men younger than 50 years of age [10].
- Presence of the foreskin. Penile cancer is rarely seen in a man who is uncircumcised.
- Phimosis is strongly associated with penile cancer. The mechanism is probably secondary to chronic infection and inflammation rather than the carcinogenic effect of retained smegma [11]. The role of BXO is more controversial and is not thought to represent a precancerous condition. However, BXO can cause phimosis so the conditions often coexist.

Figure 33.1 Pearly penile papules.
Human papilloma virus (HPV) infection is an important risk factor. HPV is seen in the majority of penile intraepithelial neoplasia and is found in 30–40% of invasive penile SCC [12]. HPV subtypes 16 and 18 are most common. It is unclear whether HPV confers a worse prognosis. However, penile cancer is more prevalent in areas of high HPV infection, which are also often areas of low socioeconomic status.

Premalignant conditions of the penis are associated with SCC and may be found in up to 40% of patients. The common premalignant conditions are as follows.

**HPV related:**
- Erythroplasia of Queyrat: Penile intraepithelial neoplasia (PeIN) or carcinoma in situ (CIS) of the glans or inner prepuce, associated with up to a 30% increased risk. Initially presenting as a velvety bright red painless lesion which eventually ulcerates and once infected is painful. Treatment is by excision, 5-flourouracil or imiquimod topical use, or photodynamic therapy or cryotherapy.
- Bowen’s disease: PeIN of the keratinising genital (penile shaft) or perineal skin. Presents with a gradually enlarging, well-demarcated erythematous plaque with an irregular border and surface crusting or scaling. Treatment is by excision, 5-flourouracil or imiquimod topical use, or photodynamic therapy or cryotherapy.
- Buschke–Lowenstein tumour (giant condyloma acuminatum): a rare disease characterised by aggressive, wart-like growths, verrucous carcinoma. It is an aggressive locally invasive tumour but rarely metastasises. The warty-like lesions coalesce into a large cauliflower-looking exophytic mass. Treatment is by wide local excision.
- Bowenoid papulosis: discrete pigmented verrucous papules on the penile skin. It is highly contagious and appears as multimaculopapular brown-red lesions. It can be self-limiting, but if it persists, treatment is by excision.

**Non-HPV related:**
- Extramammary Paget disease: a rare intraepithelial adenocarcinoma. Present with velvety-red, soft areas with scattered white islands of hyperkeratosis (i.e. a strawberry and cream appearance). The lesions become erythematous, plaque like, and desquamating especially when located in dry areas which can ulcerate. Symptoms are of itching and burning but when ulcerated become painful. Treatment is by excision.
- Cutaneous horn of the penis: an unusual keratinising skin tumours with the appearance of horns protruding from the skin (Figure 33.3). Treatment is by excision.
- Lichen sclerosis
- Immunosuppression can increase the risk of SCC.
- There is a fivefold increase risk in smokers and tobacco chewers [13].

![Figure 33.2 Annual incidence rate (world standardised) by European region or country.](image-url)
HIV infection [14] due to either immunosuppression or increased risk of synergistic HPV infection or increased risk of reticuloendothelial tumours such as Kaposi sarcoma. Kaposi sarcoma presents as a painful, raised, bleeding papule or ulcer. Treatment is by excision, laser ablation, cryotherapy, or in advanced disease palliation.

### 33.1.2.3 Clinical Features

The presentation of penile cancer can range from an incidental finding (e.g. during a circumcision) to a large fungating destructive mass in the genital area (Figures 33.4 and 33.5). However, isolated lesions of lumps are the most common presentation. Lesions are found on the glans (48%); prepuce (21%); glans and prepuce (9%); glans, prepuce, and shaft (14%); coronal sulcus (6%); and shaft only (2%) [15].

Lesions can be flat red areas, papillary growths, or ulcerative. These can be painful and prone to infections. If ulcerated, they may cause significant bleeding. Palpable inguinal lymph nodes might also be present.

### 33.1.2.4 Diagnosis and Investigations

A physical examination should include a thorough inspection of the penis. This includes retraction of the prepuce to expose the glans. The shaft of the penis should be palpated along its length, tracing it back to the division of the corpora cavernosa if possible. Both inguinal regions should be carefully examined for any evidence of lymphadenopathy.

Biopsy is mandatory if a suspicious lesion is found (whether incisional or excisional). However, if the lesion is a large fungating or destructive mass, then primary surgery can be undertaken without preceding biopsy to speed up definitive treatment.

Tumour markers include overexpression of p53 and SCC antigens, however, are rarely used for clinical purposes.
Whilst ultrasound may be used to determine the extent of invasion in the primary lesion [16], penile magnetic resonance imaging (MRI) is more commonly used and accurate, accompanied by an intracorporeal injection of alprostadil to induce an erection [17]. This is particularly relevant if penile-conserving therapy is being considered and allows better definition of the tunical margin and to assess possible invasion through it (Figures 33.6 and 33.7).

Confirmation of suspicious lymph nodes can be delineated with an ultrasound in the inguinal regions and a chest, abdominal, and pelvic computed tomography (CT) scan for distant metastases.

33.1.2.5 Histopathology

There have been a number of histological subtypes described in penile SCC (Table 33.1). The usual type accounts for about 60% of cases.

The verrucous variant has a number of varieties that have been described, all with a relatively good prognosis and very low rate of metastasis [18]. Furthermore, there are many tumours that show a mixed histology (Table 33.1) [7].

The grade of tumours is based on cellular differentiation from original tissue: G1, well differentiated tumours; G2, moderately differentiated; and G3 and G4, poorly differentiated and undifferentiated.

The single-most important prognostic variable appears to be the presence of metastases in the lymph nodes [19, 20]. Other prognostic factors also play a role, including histological grade, depth of invasion, tumour thickness, and the presence of vascular or perineural invasion [21]. Vascular or perineural invasion are often seen in the specimens of high risk SCC [22].

<table>
<thead>
<tr>
<th>Subtype</th>
<th>% of cases</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual (classic)</td>
<td>50</td>
<td>Depends on grade and stage</td>
</tr>
<tr>
<td>Basaloid</td>
<td>10</td>
<td>Poor</td>
</tr>
<tr>
<td>Verrucous</td>
<td>10</td>
<td>Good</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>5</td>
<td>Poor</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>1</td>
<td>Poor</td>
</tr>
<tr>
<td>Mixed</td>
<td>20</td>
<td>Depends on the subtypes involved</td>
</tr>
</tbody>
</table>

33.1.2.6 Staging

Invasion can be to the corpora cavernosa and corpus spongiosum, including the urethra.

Metastases usually follow a stepwise progression along the lymphatic chain. Spread is normally to the superficial and deep inguinal lymph nodes, then to the obturator and iliac lymph nodes. Some subtypes (i.e. basaloid) are thought to be able to develop skip lesions further up the lymphatic chain or present with unusual distant metastases (e.g. cutaneous or mediastinal).

The current staging uses the tumour, node, and metastasis (TNM) classification (Table 33.2) (Figure 33.8) [23].
33.1.2.7 Management

33.1.2.7.1 General Principles

There have been a number of techniques and technologies used to treat and manage penile cancer, all with variable degrees of success. The difficulty comes with the lack of evidence and robust randomised controlled trials. The aim, as with most cancers, is to remove the disease whilst preserving function as much as possible. It is the paucity of evidence and the improvement in surgical techniques that has led surgery to be the primary treatment option.

When considering management of the primary lesion, the patient has to be carefully counselled and expectations of the resultant functional and cosmetic results must be discussed. The patient’s pre-morbid erectile function should be elicited and considered.

The traditional belief in the size of surgical margins required for oncological control was initially informed by the management of skin cancer. However, the wide margins recommended compromised function and cosmesis of the remaining penis postoperatively. It is now accepted that free margins can be small, less than 5 mm, without compromising oncological control and recurrence rates [24]. Furthermore, the concomitant use of frozen section histopathology at the time of primary surgery has increased confidence of clearance and has helped achieve negative oncological margins as well as preserving function [25]. See Table 33.3.

### Table 33.2 TNM classification of penile cancer.

<table>
<thead>
<tr>
<th>T (Primary Tumour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>Tis</td>
</tr>
<tr>
<td>Ta</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T1a</td>
</tr>
<tr>
<td>T1b</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td>N (Regional lymph nodes)</td>
</tr>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>pN1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>pN2</td>
</tr>
<tr>
<td>N3</td>
</tr>
<tr>
<td>pN3</td>
</tr>
<tr>
<td>M (Distant metastasis)</td>
</tr>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

① PeIN, penile intraepithelial neoplasia; TNM, tumour, node, and metastasis.

### Figure 33.8 Depth of cancer invasion tumour, node, metastasis (TNM) classification.

33.1.2.7.2 Surgical Management of Noninvasive Disease

PeIN is a relatively new histological term that has replaced CIS. Topical chemotherapy can be used for PeIN. The preparations most commonly used are 5-fluorouracil (an antimetabolite: a thymidylate synthase inhibitor blocks the synthesis of the pyrimidine thymidine, a nucleoside
Penile Neoplasm

required for DNA replication) and imiquimod (a promoter of immune response that activates the innate arm of the immune system). These are generally well tolerated but can cause some discomfort to the applied site. Efficacy is around 50% and in light of this close surveillance should be carried out to ensure no recurrence or progression occurs [26].

After failure of a topical chemotherapy, it is reasonable to try an alternative agent, but a repeat biopsy of the area is recommended because there may be occult invasive disease [27]. For persistent and refractory PeIN, other techniques should be employed.

Penile-preserving surgery in the form of excision, glansectomy, and glans resurfacing is the preferred treatment for PeIN and Ta tumours, as well as G1–G2 T1a tumours with reported local recurrence rates between 0 and 6% [28–30]. It is worth considering, however, that invasive disease is seen in 20% of presumed PeIN, so careful consideration is needed when selecting the correct penile-preserving surgery [29].

Glans resurfacing involves removing the glans epithelium only and replacing the raw surface with an autologous split skin graft harvested from the patient.

A number of innovations have been tried such as laser (CO₂ and Nd:YAG) and photodynamic therapy. However, they have not gained widespread use.

### 33.1.2.7.3 Surgical Management of Invasive Disease

Curative surgery can be achieved with tumours confined to the prepuce with a radical circumcision.

For lesions on the glans or penis, consideration is needed to determine the extent of the penile-preserving surgery. Although radiotherapy has been performed in the past, it is now rarely used for primary disease.

For T1 and T2 lesions localised to the glans, a number of techniques can be used with curative intent. Wide local excisions can be used for small lesions. These can be either closed primarily or covered with a split skin graft. For larger lesions, penile-preserving techniques, such as glansectomy, can be employed. This involves the removal of the glans cap with sparing of the corporal bodies. The area left exposed can then be covered with a split skin graft (Figure 33.9). A frozen section can be used to ensure negative margins. It is good practice to include a ‘doughnut’ of urethra as a separate biopsy for frozen section [25]. Good oncological outcomes have been reported with the local recurrence rate to be less than 10% [31].

Partial penectomy can be considered in tumours that involve the corpora or the urethra. Again, frozen can be used at the time of surgery, but it may not be necessary if the patient is not concerned with penile preservation or has significant erectile dysfunction. Depending on the resultant penile length, split skin grafts may be used or primarily closure with penile shaft skin. The penectomy should give the patient an adequate penile stump to allow directable voiding when standing in addition to adequate length to allow for sexual intercourse. The local recurrence rate in partial penectomy varies widely in the published literature but is generally accepted to be lower than other penile-conserving techniques.

For more advanced tumours, a total or radical penectomy is required to ensure negative surgical margins. Total penectomy should also be considered when not enough length remains to direct micturition (i.e. if the partial penectomy results in the penile stump being flush with the skin of the scrotum and ammoniacal dermatitis likely). The aim of the surgery is remove the tumour and the penis completely that classically involved the detachment of the crura from the pubic bones. The scrotum and testes are usually preserved, avoiding bone demineralization and the need for testosterone-replacement therapy. Obviously some form of urinary diversion is required. Dependent of the resultant length of the urethra, a perineal urethropotomy can

### Table 33.3 Treatment options for penile cancers.

<table>
<thead>
<tr>
<th>Grade/Stage of lesion</th>
<th>Treatment modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepuce confined</td>
<td>Radical circumcision</td>
</tr>
<tr>
<td>PeIN</td>
<td>5% 5-flourouricil or 5% imiquimod (4–6 weeks, alternate days)</td>
</tr>
<tr>
<td></td>
<td>Wide local excision</td>
</tr>
<tr>
<td></td>
<td>Glans resurfacing with split skin grafting</td>
</tr>
<tr>
<td></td>
<td>Alternatives: Laser ablation Photodynamic therapy Cryotheraphy</td>
</tr>
<tr>
<td>G1–2 Ta-T1a</td>
<td>Wide local excision</td>
</tr>
<tr>
<td></td>
<td>Glans resurfacing with split skin grafting Glansectomy with split skin grafting or primary closure</td>
</tr>
<tr>
<td></td>
<td>Alternatives: Radiotherapy</td>
</tr>
<tr>
<td>G3–4 T1b or T2</td>
<td>Glansectomy with or without corporal resection with split skin grafting or primary closure</td>
</tr>
<tr>
<td></td>
<td>Partial penectomy</td>
</tr>
<tr>
<td></td>
<td>Alternatives: Radiotherapy with or without brachytherapy</td>
</tr>
<tr>
<td>T3</td>
<td>Total or radical penectomy with perineal urethrostomy or suprapubic catheter</td>
</tr>
<tr>
<td>T4</td>
<td>Neoadjuvant chemotherapy followed by surgery in responders</td>
</tr>
<tr>
<td></td>
<td>Alternatives: Palliative external beam radiotherapy</td>
</tr>
</tbody>
</table>

| PEIN, penile intraepithelial neoplasia. |

---

---
Figure 33.9 (a–g) Pictures showing stages of a glansectomy and split skin graft. (a) SCC involving glans. (b) Penile de-gloving. (c) Plane under glans developed. (d) Glans lifted off corporal heads and urethra transected and spatulated. (e) Glans removed and sent for histology. (f) Split skin graft, usually harvested from thigh, laid down over corporal heads and around spatulated urethra with quilting sutures. (g) Appearance 3 months post op.
be fashioned or the urethra can be closed and a suprapubic catheter inserted (Figure 33.10).

### 33.1.2.7.4 Radiotherapy in the Management of Invasive Disease

Radiotherapy can be either in the form external beam or brachytherapy. It is generally reserved for small tumours (<4 cm) and of stages T1 and T2. The local recurrence rates tend to be greater than that compared to surgery and are between 10 and 30% [32, 33].

A minimum of 60 Gy is used with or without a brachytherapy boost [32]. Brachytherapy can be used without external beam radiotherapy but is not recommended for lesion larger than 4 cm. Local recurrence rates at 10 years is in the order of 20%, but complications such as glans necrosis, ulceration, meatal stenosis, and urethral strictures can be as high as 30% [33]. Furthermore, the resultant penis can be fibrotic and non-functional sexually, and the trophic changes can make it difficult to survey for disease recurrence. Local recurrence rates are inferior to surgery, but salvage surgery can be used to achieve local control.

Metastatic penile cancer arises almost exclusively in the regional lymph nodes. These are the inguinal and pelvic lymph nodes and can be unilateral or bilateral. Positive inguinal nodes usually spread to the ipsilateral pelvic lymphatic and do not cross to the contralateral side. Spread to the retroperitoneal nodes is rare and although clinical observations support these statements, it should be noted that they are assumptions because good evidence has not been reported. The presence and extent of lymphatic metastases to the ilio-inguinal region are the most significant prognostic factor for survival. This is largely independent of the clinico-pathological features of the primary tumour [19].

Stratifying penile cancer into prognostic risk groups helps predict the risk of lymph node metastases [34–36]. The risk groups have been categorised dependent on stage, grade, and the presence of lymphovascular invasion in patients with clinically impalpable nodes (Table 33.4).

![Figure 33.10](image-url) (a–d) Pictures showing the stages of a total penectomy and fashioning of a perineal urethrostomy. (a) SCC requiring penectomy. Incision made around the base of the penis with bi-valving of the scrotum. (b) Penis and crura removed. Testes preserved. Suture on adequate length of urethra to bring to perineum. (c) Scrotum and area reconstructed. (d) Final appearance with catheterized perineal urethrostomy.
The risk of harbouring micrometastasis in clinically impalpable nodes is close to zero for low-risk tumours rising to 25% in high-risk patients [37]. For intermediate-risk patients, the chance of micrometastases is approximately 10%. In patients with palpable inguinal nodes, the risk of metastatic spread is much higher and can be as high as 70% in the high-risk prognostic group [37]. Therefore, careful clinical examination and radiological staging is mandatory in the management of the inguinal nodes in penile cancer.

### 33.2.1 Management of Lymph Nodes

#### 33.2.1.1 Clinically Impalpable Lymph Nodes

A risk-adapted approach is necessary (Table 33.5).

- To operate on those patients who need it.
- To avoid complications and morbidities.
- To have acceptable false-negative results.

Table 33.4 Penile cancer risk group stratification.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Grade and stage</th>
<th>Incidence of metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Tis/PeIN G1 pTa-pT1a no lymphovascular invasion</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Immediate risk</td>
<td>G2 pT1b-pT2 G2pT1a</td>
<td>10–50%</td>
</tr>
<tr>
<td>High risk</td>
<td>G3/4 &gt;pT2 lymphovascular invasion basaloid and sarcomatoid subgroups</td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

The technique for sampling the sentinel inguinal lymph node in patients with penile cancer has been increasingly used for the last 15 years. It evolved from work developed in patients with malignant melanoma and breast cancer [41, 42]. The technique aims to identify the first drainage node (i.e. the sentinel node), although there may be more than one. However, the assumption has to be made that the lymphatic drainage and metastatic spread follows a stepwise and orderly path from the sentinel node to the secondary lymph nodes.

The procedure is multistep and involves the injection of a technetium-99m nanocolloid intradermally around the penile shaft. This can be done up to 24 hours before the biopsy. The patient will then have a dynamic nuclear medicine scan, a lymphoscintogram, which delineates the approximate location of the sentinel node(s). The skin is then marked with the aid of a cobalt source ‘pen’ and an estimation of depth of the nodes is achieved.

Most centres also combine the lymphoscintigraphy with an ultrasound of the inguinal region. The purpose of this is not only to correlate the sentinel node position but also to identify any other suspicious abnormal nodes. In rare circumstances, a regional metastasis may completely replace the sentinel node and alter the lymph drainage to and from it. In these instances, the affected node will not take up any of the nanocolloid tracer and a false-negative result would ensue. The use of ultrasound minimises this potential risk.

For those patients with low-risk disease (i.e. PeIN, pTa, G1pT1), surveillance is a valid option. However, the highest rate of regional recurrence (9%) occurs in patients managed with active surveillance [38]. Furthermore, late recurrence is associated with much poorer outcomes, as are the outcomes in delayed versus early therapeutic node dissections.

Owing to the significant risk of micrometastases in intermediate- and high-risk penile cancer, invasive staging techniques have been developed to address this problem. Ultrasound, CT, and MRI are not sensitive enough to elicit micrometastases. Furthermore, fine-needle aspiration cytology in impalpable nodes is unreliable and has a reported sensitivity of only 35% [39].

The historical procedure was to perform a bilateral radical inguinal lymph node dissection. This gives diagnostic and prognostic information but is probably best viewed as a prophylactic procedure. The procedure is associated with significant morbidity because there is a high rate of complications (occur in more than 50% of patients): wound infection, skin/flap necrosis, bleeding and haematoma formation, wound dehiscence, lymphoedema, and lymphocele [40].

#### 33.2.1.1 Dynamic Sentinel Lymph Node Biopsies (DSLNB)

The technique for sampling the sentinel inguinal lymph node in patients with penile cancer has been increasingly used for the last 15 years. It evolved from work developed in patients with malignant melanoma and breast cancer [41, 42]. The technique aims to identify the first drainage node (i.e. the sentinel node), although there may be more than one. However, the assumption has to be made that the lymphatic drainage and metastatic spread follows a stepwise and orderly path from the sentinel node to the secondary lymph nodes.

The procedure is multistep and involves the injection of a technetium-99m nanocolloid intradermally around the penile shaft. This can be done up to 24 hours before the biopsy. The patient will then have a dynamic nuclear medicine scan, a lymphoscintogram, which delineates the approximate location of the sentinel node(s). The skin is then marked with the aid of a cobalt source ‘pen’ and an estimation of depth of the nodes is achieved.

Most centres also combine the lymphoscintigraphy with an ultrasound of the inguinal region. The purpose of this is not only to correlate the sentinel node position but also to identify any other suspicious abnormal nodes. In rare circumstances, a regional metastasis may completely replace the sentinel node and alter the lymph drainage to and from it. In these instances, the affected node will not take up any of the nanocolloid tracer and a false-negative result would ensue. The use of ultrasound minimises this potential risk.

When the patient has been anaesthetised in theatre, 1 ml of patent blue dye is injected intradermally into the
33.2 Lymph Node Disease

base of the penis to colour the sentinel nodes blue. The sentinel nodes are then located with a hand held gamma-ray detection probe, and small inguinal incisions are made. It is these nodes that are removed for histological analysis. The procedure has minimal morbidity, and it is a potential outpatient procedure (Figure 33.11).

The technique, however, is not without its critics. Opponents point to its false-negative rates and that delaying a more radical lymphadenectomy is a high-risk strategy in some patients. However, in centres of excellence with high output volumes, the false-negative rate is less than 5% [43, 44]. DSLNBs can, in experienced centres, be used for staging purposes regardless of risk groups. This prevents the overtreatment of high-risk groups with bilateral lymphadenectomies.

33.2.1.2 Clinically Palpable Inguinal Lymph Nodes

Although up to 50% of palpable inguinal lymph nodes may be false-positive [45], due to either an infection or reactional from the inflammation of the penile cancer, antibiotic treatment is not recommended and prompt surgical en bloc dissection is required. Fine-needle aspiration cytology may provide useful information in the outpatient setting [46] and is a useful confirmatory test if positive. If negative, surgical management should not be altered on this finding.

A radical or modified inguinal lymphadenectomy is necessary for cN1/2 disease. Radical dissection of the inguinal region is performed from the superior margin of the external ring to the anterior superior iliac spine, laterally from the anterior superior iliac spine extending 20 cm inferorly, and medially to a line drawn from the pubic tubercle 15 cm downwards. The long saphenous vein is divided, the anterior aspects of the femoral vessels are dissected, and later the femoral vessels are covered by the interposition of the sartorius muscle (Figures 33.12 and 33.13) [47]. Thus, the superficial lymph nodes in all five anatomic zones described by Daseler [48] and the deep inguinal nodes are dissected (Figure 33.14).

A modified lymphadenectomy aims to limit the morbidity but preserve the therapeutic benefit [49]. The dissection is less extensive; the long saphenous vein is preserved and no transposition of the sartorius muscle is required. Where the palpable node is on one side only, a DSLNB or a modified inguinal lymphadenectomy can be performed on the contralateral side.

33.2.2 Management of the Fixed Nodal Mass and Nodes with Extranodal Spread

Fixed nodal masses are unlikely to be resected with clear oncological margins. There is no definite consensus on how to manage these patients. Neoadjuvant chemotherapy...
with surgical resection for responders has been recommended [50]. The role of radiotherapy is lacking in evidence; however, chemo-sensitization with subsequent radiotherapy may have a role. Attempt at surgical resection may be require to prevent tumours fungating through the skin or femoral vessels. In these cases, muscle or fascia can be transposed from the rectus abdominus or anterior thigh as protection to allow chemo-radiotherapy to be given. At present, there is little consensus with the management of extranodal spread (i.e. extracapsular spread) and fixed nodal masses. There is not much evidence to support any particular order of management and even the chemotherapeutic regimes have yet to been standardised. Current ongoing trial such as the International Penile Advanced Cancer Trial (InPACT) hopes to address these issues.

### 33.2.2.1 Pelvic Lymphadenopathy

The five-year cancer-specific survival in patients with positive pelvic nodes is much worse than patients with inguinal lymphadenopathy alone (33% versus 71%) [51]. Risk factors for pelvic node involvement include number of positive inguinal nodes, size of positive node, and extranodal spread. If two or more positive lymph nodes are identified on DSLNB or modified lymph node dissection (LND), or CT scans showing enlarged pelvic lymph nodes or extranodal spread are found on one side, an ipsilateral pelvic node clearance is recommended. Pelvic clearance can be performed openly, laparoscopically, or be robotically assisted.

### 33.2.2.2 Distant Metastases

Prognosis is poor with no reported survivors after five years.

Systemic chemotherapy with cisplatin-based chemotherapy or palliative surgical resection of the primary tumour can be offered.

### 33.2.2.3 Follow-Up

Most recurrences, whether local or metastatic, are likely to occur within the first two years [52]. Therefore, the most intensive follow-up is during this time. The development of regional nodal recurrence is significant and reduces disease-specific survival. Local recurrence, if
correctly managed with surgery, does not affect prognosis. Recurrences after five years are much less commonly seen and tend to be local recurrences or new primary lesions [52].

Clinical examination is the mainstay of follow-up, and patients are encouraged to undertake this themselves. Within the first two years, local recurrence is seen in about 25% of patients who have had penile-preserving surgery. In patients who have had partial penectomy, the local recurrence is about 5% [38]. Follow-up regimes should comprise a regular physical examination and scanning for a minimum of five years (Table 33.6) [36].

Given the rarity of penile cancer, the treatment and management of patients have best results where the service is regionalized. This allows the pooling of expertise and experience and provides an academic database for robust research. Furthermore, the concentration of patients can provide valuable peer advice and allow structured and organised support groups.

### 33.3 Urethral Neoplasm

#### 33.3.1 Benign Urethral Neoplasms

These include:

- Polyps can occur secondary to an infection whereby resulting in oedematous polyp formation that can protrude through the meatus.
- Caruncles literally means fleshy lump. Unless significantly symptomatic treatment is not required.
- Haemangioneurofibromas are rare but present with painful haematuria and a bright red swelling on the urethra. Most likely occurs as part of a more extensive hemangioma disease.

The most common occurring of the benign neoplasms is viral warts, such as condylomata acuminate caused by HPV. Diagnosis can be done by biopsy of the lesion, which in itself can be curative.

Treatment is usually unnecessary except for the venereal wart where transurethral resection or laser ablation can be offered. If at the meatus, cryotherapy or chemical ablation with podophyllotoxin, imiquimod, trichloroacetic acid, or interferon can be offered.

#### 33.3.2 Malignant Urethral Neoplasms

Urethral cancer is rare, occurring <1% of all cancers and larger in those >55 years of age [53]. Similar to the penile cancers, urethral cancers are even rarer; the management of patients have best results where the service is regionalized. This allows the pooling of expertise and experience and provides an academic database for robust research.

#### 33.3.3 Aetiology

Risk factors for men include chronic irritation such as urethral stricturing disease, Schistosomiasis, long-term catheters, or intermittent self-catheterization; recurrent urinary tract infections (UTIs), radiotherapy, and HPV-16 have also been implicated [54]. Risk factors for women include urethral diverticula, recurrent UTIs, and HPV-16 infection [55]. However, more commonly occurring is direct extension of bladder or implantation from bladder cancer resection into a traumatised urethra from the resectoscope. Nonetheless, one must consider the risk factors for bladder cancer to also apply to the urothelium of the urethra as well. Prostate cancer can also spread along the urethra and produce multiple rounded fleshy tumours.

#### 33.3.4 Clinical Features

Early presentations: Painless haematuria, urethral discharge, and worsening voiding lower urinary symptoms which mimics outflow obstruction and might initially mislead a clinician towards stricture disease. Recurrent UTIs and malignant strictures lead to periurethral abscesses which can lead to urethrocutaneous fistulas. Late presentations include:

- Locally advanced disease: hard palpable lump, chronic pain symptoms such as pelvic pain, dyspareunia, painful orgasm, or acute or chronic retention.
- Metastatic disease: inguinal lymphadenopathy, shortening of breath from chest metastases, right upper quadrant pain from liver metastases, weight loss, loss of appetite, and general weakness.

### Table 33.6 Follow-up regime for penile cancer.

<table>
<thead>
<tr>
<th>Tumour risk group</th>
<th>Years 1–2</th>
<th>Years 2–5</th>
<th>Cross-sectional imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Clinical examination every 3/12</td>
<td>Clinical examination every 6/12</td>
<td>At 6/12 and 18/12</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Clinical examination every 3/12</td>
<td>Clinical examination every 6/12</td>
<td>Every 6/12 for 2 years then yearly</td>
</tr>
<tr>
<td>High risk</td>
<td>Clinical examination every 3/12</td>
<td>Clinical examination every 6/12</td>
<td>Every 6/12 for 2 years then yearly</td>
</tr>
</tbody>
</table>
Diagnosis and Investigations:
Flexible or rigid cystourethroscopy and biopsy to confirm the diagnosis. Chest and abdominal CT scan and pelvic MRI for staging.

Pathology:
Commonality depends on the location of the lesion as the proximal third of the urethra is covered by transitional cell urothelium, whereas the distal two-thirds is covered by stratified squamous epithelium. If in the anterior urethra or women, 70–80% are SCC, whereas in the posterior urethra, 70–80% are transitional cell carcinoma [56]. Adenocarcinomas are seen in 5–15% of cases and rarer are the sarcomas and melanomas [56].

33.3.5 Staging and Grading
Staging and grading is based on the TNM classification (Table 33.7).
Lymph node metastases also vary depending on locality: The anterior urethra and in women spread to the inguinal lymph nodes (LNs), and the posterior urethral cancer spread to the pelvic LNs.

There are two systems in use. An older historical grading system based on differentiation from the primary tissue type used grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated). The more recent classification divided the transitional cell carcinomas further into papillary urothelial neoplasm of low malignant potential (PUNLUMP), low-grade (well differentiated), and high grade (poorly differentiated) [57].

33.3.6 Prognosis
Risk for survival are the age of the patients, ethnicity, TNM classification, the tumour grade, histological type, size and location of the primary cancer, presence of concomitant bladder cancer, treatment offered, and the recurrence after treatment [58]. However, generally speaking, the five-year survival is usually around 50% [56].

33.3.7 Treatment
33.3.7.1 Localised Disease
This is based on the gender of the patient; however, the options are either surgery which offers better long-term results and less complications, or radiotherapy.
In women, an anterior pelvic exenteration with excision of the bladder, urethra, uterus, ovaries, the upper section of the vagina, and pelvic LN dissection is the gold standard. However, organ-sparing surgery such as transurethral resections can be offered. Urethrectomy and bladder neck closer and Mitrofanoff appendicovesicostomy formation has had good results in some series [59].
In men, treatment is based on tumour extension and locality; however, careful patient counselling is required because of the uncertainty of disease cure and recurrence:
For penile urethra:
- Superficial tumours (Tis, Ta, T1): transurethral resection, local excision and primary urethral anastomosis, or local excision and urostomy formation.
- Deep tumours (>T2):
  - Distal one-half: partial penectomy and if palpable LNs or visible on scanning: bilateral LNDs
  - Proximal one-half: total penectomy and if palpable LNs or visible on scanning: bilateral LNDs
For bulbomembranous urethra:
- Superficial tumours: same as for penile urethra.
- Deep tumours: cystoprostatectomy and penectomy and pelvic LNDs

33.3.7.2 Locally Advanced Disease
This is best treated with a combination of chemotherapy (platinum-based for transitional cell carcinomas and 5-fluorouracil, and Mitomycin C for SCC), radiotherapy, and surgical excision [60].

Table 33.7 TNM classification of urethral cancer.

<table>
<thead>
<tr>
<th>T (Primary Tumour)</th>
<th>Dx</th>
<th>Tx</th>
<th>T0</th>
<th>No evidence of primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades corpus spongiosum, prostatic stroma, or periurethral muscle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades corpus cavernosum, prostatic capsule, vagina, or bladder neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades adjacent organs, including bladder</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N (Regional lymph nodes)</th>
<th>Nx</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single lymph node</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in multiple lymph nodes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M (Distant metastasis)</th>
<th>Mx</th>
<th>Distant metastasis cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

TNM, tumour, node, metastasis.
33.3.7.3 Metastatic Disease
Chemotherapy is the only option available. Palliative radiotherapy can be offered for complications such as pain or bleeding.

33.3.7.4 Follow-Up
These patients need regular follow-up with imaging, and if organ-preservation surgery was done, regular cystoscopic surveillance. However, there is lack of evidence to tailored for each individual patient.

References


34

Penis and Urethra Disorders of Function

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Abstract

Functional disorder of penis and urethra are quite prevalent. These include erectile dysfunction (ED), ejaculatory disorders, priapism, and Peyronie disease.

ED is usually multifactorial and requires careful evaluation and management decisions. This ranges from oral pharmacotherapy to insertion of a penile prosthesis. Ejaculatory disorders, especially premature ejaculation (PE) can cause considerable distress to both patient and partner. Effective management of PE requires behavioural or psychotherapy and pharmacotherapy (e.g. local anaesthesia and oral serotonin reuptake inhibitors). Priapism is an acute urological emergency, and a prompt diagnosis and management is required to avoid irreversible damage to erectile tissues. Peyronie disease is a benign inflammatory condition but can cause penile curvature and ED significantly limiting sexual function.

Keywords  erectile dysfunction (ED); phosphodiesterase type 5 (PDE5) inhibitor; Peyronie disease; premature ejaculation (PE); priapism; retrograde ejaculation

Key Points

● Risk factors, assessment, and management of erectile dysfunction (ED).
● Assessment and management of ejaculatory disorders.
● Priapism: aetiology, assessment, and management.
● Presentation and management of Peyronie disease.

34.1 Erectile Dysfunction

Erectile dysfunction (ED) is defined as persistence or recurrent inability to attain or maintain a penile erection for satisfactory sexual performance. ED is a common male sexual disorder. According to the Massachusetts male ageing study, in men between ages of 40 and 70 years, mild ED was found in 17%, moderate ED in 25%, and severe ED in 10% [1].

34.1.1 Pathophysiology

ED is generally classified as psychogenic and organic, but in most cases, it is combination of both.

34.1.1.1 Psychogenic Erectile Dysfunction

Psychogenic ED frequently coexists with other sexual dysfunctions, notably reduced libido and with major psychiatric disorders particularly depression and anxiety [1].

34.1.2 Organic Erectile Dysfunction

34.1.2.1 Arterial Causes

Arterial insufficiency is a major factor in pathogenesis of organic ED. The arteriopathy usually develops secondary to diabetes mellitus (DM), hypertension, hyperlipidaemia, and smoking, lack of exercise, and obesity or metabolic syndrome. Rarely posttraumatic arterial obliteration or fistula can also lead to ED. ED is found in nearly 50% of patients with coronary arterial disease and precedes cardiac symptoms by an average of three years [2].
34.1.1.2 Venous Causes
In the rigid phase of erection, the venous outflow from the penis is shut off by nervous stimulation and kinking of the veins as they pass through the tunica albuginea. Failure of this venous outflow causes a venous leak, leading to ED. Common causes of a venous leak are:
- Primary large venous leak draining the corpora cavernosa.
- Traumatic injury to tunica albuginea (e.g. penile fracture).
- Acquired shunt e.g. after operative intervention for priapism.
- Degenerative changes associated with old age, DM, and Peyronie disease.

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- Degenerative changes associated with old age, DM, and Peyronie disease.

34.1.1.2.3 Neurological Causes
Disruption of the erectogenic neural pathways (central and peripheral) leads to the development of ED.

Causes of Central Neuropathy
There are a variety of causes of central neuropathy, among them are:
- Multiple sclerosis (MS)
- Cerebrovascular accidents
- Malignancy (e.g. brain and spinal cord)
- Parkinson disease
- Multisystem atrophy
- Spinal cord transection

Causes of Peripheral Neuropathy
There are a variety of causes of peripheral neuropathy, among them are:
- MS
- DM
- Sacral cord injury and pelvic fracture
- Radical pelvic surgery

34.1.1.2.4 Hormonal Causes
Hyperprolactinaemia causing ED is found in about 5% of men. Men reporting lack of libido may have low levels of testosterone. Other endocrine causes include hyper- or hypothyroidism, Cushing disease, and hypogonadism.

34.1.1.2.5 Drugs
Antihypertensives (e.g. beta-blockers, angiotensin-converting enzyme [ACE] inhibitors), diuretics (e.g. thiazides), statins, amiodarone, antidepressants (e.g. tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors), finasteride, cypromodone acetate, luteinising hormone releasing hormone (LHRH) analogues, anticonvulsants (e.g. phenytoin, carbamazepine), and anti-Parkinson drugs (i.e. levodopa).

34.1.2 Assessment
34.1.2.1 Clinical History
- A careful and sympathetic history is essential to determine what a patient describes as ED is not some other sexual dysfunction.
- Patients should be asked specifically about onset of symptoms, early morning erection, loss of libido, and ejaculatory disorders to establish the type of ED (psychogenic or organic).
- Patients should detail past medical history of DM, hypertension, cardiovascular diseases, neurological diseases, pain or angulation of penis, history of trauma or pelvic surgery, drug history; history of smoking, alcohol intake, or substance misuse to establish a possible aetiology. Physicians should confirm any previous treatment for ED and the response.
- Validated ED questionnaires such as the International Index of Erectile Function (IIEF) is useful to record objective evidence of severity of ED (Table 34.1).

34.1.2.2 Physical Examination
Physical examination should consist of a general abdominal, neurological, and cardiovascular examinations.
- Blood pressure and signs of arteriopathy.
- Body mass index (BMI) and waist circumference.
- Secondary sexual characteristics.
- Genital examination (i.e. note size of penis and testes, presence of penile plaque or angulation, phimosis, or hypospadias).
- Evidence of previous trauma or pelvic surgery.
- Penile sensation.
- Bulbocavernosus reflex (i.e. squeezing the glans leads to contraction of the anal sphincter and bulbocavernosal muscles; this tests the integrity of S2–4).
- Testicular examination: size, location, abnormality, or abscess.
- Digital rectal examination (DRE): perineal sensation, anal reflex or tone, and prostate examination (if older than 50 years of age).

34.1.3 Investigations
34.1.3.1 General Investigations
In most patients with ED, the following initial blood tests are recommended:
- Fasting blood glucose and HbA1c.
- Lipid profile.
- Total testosterone level (tested for between 8 and 11 a.m.); if testosterone levels are subnormal, follicle-stimulating hormone (FSH), luteinising hormone (LH), and prolactin levels should be performed. Other investigations can be done based on relevant history and examination findings (i.e. prostate-specific antigen [PSA] and thyroid function tests).

34.1.3.2 Specialised Investigations
- Penile Doppler Ultrasound: a peak systolic blood flow of >30 cm s⁻¹, an end-diastolic velocity of <5 cm s⁻¹, and a resistance index of >0.8 before and after intracavernosal injection of prostaglandin E1 (PGE1) is considered normal.
34.1 Erectile Dysfunction

● **Nocturnal penile tumescence and rigidity testing:** An objective record of nocturnal erection is made with two strain gauges fitted around the base and distal penis (Figures 34.1 and 34.2). A good or functional erection is with a minimum of 60% rigidity recorded on the tip of the penis that lasts for >10 minutes. A paper strip which records its expansion during sleep to demonstrate the presence of nocturnal erections, which can be useful for psychogenic ED (Figure 34.3).

● **Penile arteriography:** In younger patients with trauma‐related ED or in patients considered for vascular reconstruction surgery.

● **Cavernosography:** Intracavernosal contrast and artificial erection is used to determine evidence of venous leak. The pressure in the venous sinuses of the corpora can be recorded during an erection (Figure 34.4). Fluoroscopy shows whether the penile veins are being effectively closed during the phase of rigid erection (Figure 34.5).

### 34.1.4 Management

General measures should be considered before pharmacotherapy for ED.

- Identify any reversible cause of ED (e.g. drug induced or hormonal abnormalities).
- Correction of underlying disorder (e.g. good glycaemic control, correction of hyperlipidaemia, hyperprolactinemia management, cessation of smoking, weight loss, and exercise).
- Lifestyle changes and risk factor modification (e.g. exercise, weight reduction, and avoidance of precipitating factors) can improve ED but more importantly improve overall health and reduce cardiovascular risks.
- All patients with significant cardiovascular disease need to see a cardiologist before ED treatment. Sexual activity is equivalent to walking a mile on a flat surface in 20 minutes or climbing two flights of stairs in 10 seconds.
- Psychosexual therapy for patients with psychiatric disorders and younger patients with ED.

#### 34.1.4.1 First-Line Medical Therapy

##### 34.1.4.1.1 Phosphodiesterase 5 inhibitors

Three phosphodiesterase 5 (PDE5) inhibitors are approved by for treatment of ED (Table 34.2). All of these agents have shown successful efficacy in management of ED [3, 4]. However, these agents cannot initiate erection, and hence, require sexual arousal to facilitate erection.

##### 34.1.4.1.2 Mechanism of Action

In the smooth muscle lining (of the trabecular network of the cavernosal tissue) of the penis, PDE5 enzyme hydrolyses cyclic guanosine monophosphate (cGMP) to 5 cGMP (Figure 34.6). PDE5 inhibitors prevent this hydrolysis, and hence, results in prolonged smooth muscle relaxation, increased arterial flow, and penile erection.

##### 34.1.4.1.3 Pharmacokinetic and Side Effects of PDE5 Inhibitors

Key pharmacokinetic features are summarised in Table 34.2.

##### 34.1.4.1.4 Specific Considerations

- Cardiovascular disease: there is no evidence that PDE5Is have a negative effect on these patients (i.e. do

---

**Table 34.1 IIEF-5 scoring:** The IIEF-5 score is the sum of the ordinal responses to the five items.

<table>
<thead>
<tr>
<th>Over the past 6 months</th>
<th>Very low</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) How do you rate your confidence that you could get and keep an erection?</td>
<td>Almost never/never</td>
<td>A few times (&lt;50% of the time)</td>
<td>Sometimes (about half the time)</td>
<td>Most times (&gt;50% of the time)</td>
<td>Almost always/always</td>
</tr>
<tr>
<td>2) When you had erections with sexual stimulation, how often were your erections hard enough for penetration?</td>
<td>Almost never/never</td>
<td>A few times (&lt;50% of the time)</td>
<td>Sometimes (about half the time)</td>
<td>Most times (&gt;50% of the time)</td>
<td>Almost always/always</td>
</tr>
<tr>
<td>3) During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?</td>
<td>Extremely difficult</td>
<td>Very difficult</td>
<td>Difficult</td>
<td>Slightly difficult</td>
<td>Not difficult</td>
</tr>
<tr>
<td>4) During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?</td>
<td>Almost never/never</td>
<td>A few times (&lt;50% of the time)</td>
<td>Sometimes (about half the time)</td>
<td>Most times (&gt;50% of the time)</td>
<td>Almost always/always</td>
</tr>
<tr>
<td>5) When you attempted sexual intercourse, how often was it satisfactory for you?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Score

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
</table>

Total score: 22–25 = No ED, 17–21 = Mild ED, 12–16 = Mild to moderate ED, 8–11 = Moderate ED, 5–7 = Severe ED.
not increase infarction rates or negative effect on exercise testing).
- Nitrates are absolutely contraindicated as the result in accumulation of cGMP which can lead to severe blood pressure drops and symptomatic hypotension.
- All PDE5 inhibitors show some interaction with alpha-blockers and may result in orthostatic hypotension.

### 34.1.4.1.5 Assessment of Non-Responders
- Establish that the patient is following appropriate instruction (i.e. ensuring adequate sexual stimulation and allowing for the medication to take effect before attempting sexual intercourse). Some PDE5 inhibitors have a reduced efficacy with high-fat foods.
- Appropriate dose has been used.
- Check patient is using licenced medication and not buying from black market.

#### 34.1.4.2 Second-Line Therapy

##### 34.1.4.2.1 Intracavernosal Injections

Alprostadil, a synthetic PGE1, is used as a second-line agent for treatment of ED. It results in corporal and glandular smooth muscle relaxation by increasing cyclic adenosine monophosphate (cAMP) (Figure 34.7).

Alprostadil is the only drug approved for intracavernous treatment of ED. Usually, the starting dose is 5μg, but the dose can be increased up to 20μg. The first injection is conducted by a professional as training. The needle is inserted into the corpus cavernosum on the lateral aspect of the mid-penile shaft at a 90° angle. The erection appears after 5–15 minutes and lasts according to the dose injected. Efficacy is reported in >70% of patients with ED.
Adverse Effects
- Penile pain (50%).
- Prolonged erections (5%).
- Fibrosis (2%).
- Priapism (1%).

Contraindications
- History of hypersensitivity to Alprostadil.
- Men at risk of priapism.
- Bleeding disorders (Sickle Cell disease).

34.1.4.2.2 Intra-urethral Alprostadil
A specific formulation of Alprostadil in a medicated pellet (medicated urethral system for erection [MUSE]) is approved for use in ED [5]. The dose ranges from 125 to 1000μg.

With intra-urethral Alprostadil, erections sufficient for intercourse are achieved in 30–70% of patients.

Adverse Effects
- Local pain (35%).
- Dizziness with possible hypotension (1.9–14%).
### 34.1.4.3 Vacuum Erection Device

#### 34.1.4.3.1 Principle
A vacuum erection device (VED) consists of three components: a vacuum chamber, pump, and a constriction band. It provides passive engorgement of the corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the corpora.

Satisfaction rates range between 27 and 94%. However, because of adverse effects, the long-term use of VEDs decreases to 50–64% after two years.

#### 34.1.4.3.2 Adverse Effects
- Penile pain.
- Inability to ejaculate.
- Petechiae or bruising.
- Penile numbness.
- Skin necrosis (can be avoided if patients remove the constriction ring within 30 minutes).

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![Figure 34.5](image1.png)

**Figure 34.5** Using radio-opaque fluid, leakage of contrast medium during erection can be detected. 120 ml of contrast were injected into one corpus cavernosum at 3 ml s⁻¹. The corpora have both filled, but not the corpus spongiosum and glans (normal). Subtracted image towards the end of the injection shows no satisfactory tumescence, due to venous leak from the penile root with numerous veins draining into the right iliac venous system (arrow).

![Figure 34.6](image2.png)

**Figure 34.6** Mechanism of action of PDE5 inhibitors. NOS enzyme cleaves L-arginine to L-citrulline and NO. NO stimulates guanylate cyclase which results in conversion of GTP into cGMP. The cGMP causes reduction in intracellular Ca²⁺ producing smooth muscle relaxation and hence erection. PDE5 rapidly convert the cGMP into an inactive form, 5GMP. PDE5 inhibitors prevent this conversion and hence facilitate erection. cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; NOS, nitric oxide synthase; PDE5, phosphodiesterase type 5.
34.1 Erectile Dysfunction

34.1.4.4 Third-line Therapy: Penile Prostheses

A penile prosthesis may be considered in patients who do not respond to pharmacotherapy or who prefer a permanent solution to their problem. The two currently available classes of penile implants are:

- Inflatable (two and three piece).
- Semi-rigid (Figure 34.8).
- Malleable devices (Figures 34.9 and 34.10).

Prosthesis implantation has one of the highest satisfaction rates (92–100% in patients and 91–95% in partners) [6].

Patients must be warned that they will have a floppy glans and will need exchanging of the device after 10 years.

Insertion of a penile prosthesis can be associated with the following complications:

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Table 34.2 Key characteristics of PDE 5 Inhibitors.

<table>
<thead>
<tr>
<th>Key Features</th>
<th>Sildenafil (Viagra)</th>
<th>Vardenafil (Levitra)</th>
<th>Tadalafil (Cialis)</th>
<th>Avanafil (Spedra)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>30–60 min</td>
<td>30–60 min</td>
<td>60–120 min</td>
<td>15–30 min</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.6–3.7 h</td>
<td>3.9 h</td>
<td>17.5 h</td>
<td>4–5 h</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>Up to 12 h</td>
<td>Up to 10 h</td>
<td>Up to 36 h</td>
<td>Up to 6 h</td>
</tr>
<tr>
<td>Available doses</td>
<td>25, 50, 100 mg</td>
<td>5, 10, 20 mg</td>
<td>5, 10, 20 mg</td>
<td>50, 100, 200 mg</td>
</tr>
<tr>
<td>High fat meal efficacy effect</td>
<td>Decrease efficacy</td>
<td>Decrease efficacy</td>
<td>Not affected</td>
<td>Not affected</td>
</tr>
</tbody>
</table>

Side effects:
- Headache
- Flushing
- Dyspepsia
- Nasal congestion
- Dizziness
- Abnormal congestion
- Back pain
- Myalgia

Source: Adapted from European Association of Urology (EAU) guidelines.

**Figure 34.7** Mechanism of action of PGE1 stimulates adenylate cyclase which results in conversion of ATP into cAMP. The cAMP causes reduction in intracellular Ca++, producing smooth muscle relaxation and hence erection. ATP adenosine triphosphate; cAMP cyclic adenosine monophosphate; PGE1 prostaglandin E1.
Premature ejaculation (PE) is the most common sexual disorder in men younger than 40 years of age. However, 30–70% of males can be affected by PE at one time or another. PE is a condition in which the entire sexual process of arousal, erection, ejaculation, and climax occur more rapidly, often in just a few minutes or even seconds, leaving the partner unsatisfied.

The International Society of Sexual Medicine defines it as 'a male sexual dysfunction characterised by ejaculation which always or nearly always occurs before or within about one minute of vaginal penetration; and the inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences such as distress, frustration and/or the avoidance of sexual intimacy' [7]. The ejaculatory latency is measured by the
intravaginal ejaculatory latency time (IVELT), defined as the time between vaginal intromission and ejaculation.

The mechanism of ejaculation (Figure 34.11) requires five coordinated functions:

1) The seminal vesicles contract rhythmically to pump up.
2) Peristaltic contractions of the vas deferens eject a small volume of semen containing sperm through the common ejaculatory ducts.
3) This is followed by contraction of the seminal vesicles which squirt the sperm-rich fraction of semen into the prostatic urethra.
4) At the same time the bladder neck closes and the external sphincter relaxes, preventing the sperm from flowing back and expelling it down the urethra, assisted by the contractions of stage 5.
5) Rhythmic contractions of the bulbospongiosus muscle take place.

The smooth muscle fibres in the neck of the bladder and seminal vesicles are alpha adrenergic. Diabetic neuropathy, sympathectomy, alpha-blocking drugs for hypertension, or surgical injury to the sympathetic chain or presacral nerve will prevent contraction of the vesicles and closure of the bladder neck.

Prostatectomy or bladder neck incision should not affect contraction of the seminal vesicles, but the semen will tend to flow back into the bladder rather than squirt out from the urethra (i.e. retrograde ejaculation). Prostatectomy may inadvertently injure and obstruct the common ejaculatory ducts.

### 34.2.1 Aetiology

#### 34.2.1.1 Biological Factors
- Penile hypersensitivity
- Hyperexcitable ejaculatory reflex or abnormal reflex activity of ejaculatory system (e.g. 5-hydroxytryptamine (5-HT) receptor sensitivity.
- Inflammation or infection of prostate.
- Abnormal hormone level (e.g. testosterone).
- Side effect of some drugs (e.g. antihypertensive).
- Nervous system damage (e.g. surgery or trauma).

#### 34.2.1.2 Psychological Factors
- Fear (often stems from previous experience of PE).
- Stress, anxiety, or relationship problems.
- Early sexual experience.
- Reduced frequency of sexual intercourse.
34.2.2 Classification of Premature Ejaculation

- **Lifelong PE**: onset from the first sexual experience and remains so during life. Characterised by ejaculation before vaginal penetration or <1–2 minutes IVELT and usually caused by genetic or neurological factors. In most cases pharmacotherapy is required (see below).
- **Acquired PE**: gradual or sudden onset following normal ejaculation experiences. Characterised by short IVELT and caused by medical or psychological disorders. Management includes psychotherapy and pharmacotherapy.
- **Natural variable PE**: inconsistent and irregular early ejaculations, a normal variation with men having PE occasionally. IVELT 3–8 minutes. Reassurance and psychotherapy is mainstay of management.
- **Premature-like ejaculatory dysfunction**: subjective perception of consistent or inconsistent rapid ejaculation during intercourse and IVELT 3–30 minutes (normal to prolonged). Reassurance and psychotherapy is needed; this group should not be considered to have manifestations of true medical pathology.

34.2.3 Assessment

History should include medical and sexual history and to ascertain which classification the patient is in. Specific questioning on the duration time of ejaculation, degree of sexual stimulus, impact on sexual activity and quality of life (QoL), drug use or abuse, situational PE (under specific circumstances or with a specific partner), and any coexisting ED.

Latency estimation by patient self-estimated IVELT is sufficient to establish classification. Stopwatch-measured IVEPT can also be used. Patient reported outcome questionnaires can also be used; however, lack sufficient evidence (e.g. PE Diagnostic Tool and the Arabic Index of PE are two of the more popular questionnaires).

Physical examination including general, neurological, and genitourinary examinations to establish underlying conditions. While laboratory investigations are tailored around further investigating underlying conditions.

34.2.4 Management

Any serious primary medical condition should be treated, as should any accompanying ED. To achieve the best outcome, the female partner should be included in the treatment and counselling sessions.

34.2.4.1 Behavioural and Nonpharmacologic Therapy

The following behavioural and nonpharmacological measures should be use as first-line therapy, except in lifelong PE.

- Psychosexual counselling and education: Efforts to relieve underlying performance pressure on the male.
- Sex therapy instruction in the stop-start manoeuvres: The partner stimulates the penis until the urge to ejaculate, at which point stimulation is stopped until the sensation subsides, and then resumed [8] or a modified version, the squeeze-pause technique (i.e. similar to stop-start, but the partner squeezes the glans until the urge subsides). It is usually applied in three cycles before preceding to orgasm.
- Second attempt at coitus: If another erection can be achieved shortly after an episode of PE, ejaculatory control may be much better second time.
- Masturbation: This can teach the patient to recognise the signs of increased sexual arousal and how to keep his level of sexual excitement below the intensity that elicits the ejaculatory reflex [9].
- Exercises: The aim of pelvic floor muscle exercise is to strengthen the bulbocavernosus and ischiocavernous muscles.
- Treat ED and genitourinary infection.

34.2.4.2 Pharmacologic Therapy

34.2.4.2.1 Topical Anaesthetic Agents

Use of topical desensitising agents (e.g. lignocaine and prilocaine) for PE can reduce the sensitivity of the glans penis, thus delaying ejaculation. Usually are used with condoms to prevent vaginal absorption leading to vaginal numbness.

**Lignocaine-Prilocaine Cream**

Topical lignocaine-prilocaine cream has shown significant increase in the IVELT in various randomised, double-blind, placebo-controlled trials [10]. Patients are advised to use the cream (5%) for 20–30 minutes prior to intercourse.

**Severance-Secret (SS) Cream**

SS-cream is a topical anaesthetic agent made from herbal extracts. It is known to increase the vibratory threshold and hence can improve PE.

34.2.4.2.2 Oral Medication

Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants have had good efficacy for PE. These include paroxetine, citalopram, fluoxetine, fluvoxamine, sertraline, and clomipramine.

Dapoxetine is the only on-demand medication licenced for PE; it is a potent short-acting SSRI with quick absorption (Tmax = 1.3 hours) and rapid clearance (half-life: 95% clearance rate after 24 hours). On-demand Dapoxetine has been evaluated in various trials and has shown promising results in the management of PE [11].

PDE5 inhibitors can increase confidence, the perception of ejaculatory control, and overall sexual satisfaction in patients with PE and ED; however, there is limited evidence on their efficacy for PE alone [12].
34.3 Retrograde Ejaculation

Retrograde ejaculation is defined as ‘failure of adequate closure of the bladder neck during ejaculation resulting in propulsion of ejaculate into the bladder’.

34.3.1 Aetiology

Common causes of retrograde ejaculation are:

**Anatomical disruption of bladder neck**
- Post-transurethral resection of prostate [TURP] or open prostatectomy
- Post-bladder neck incision
- Trauma to bladder neck
- Transurethral resection of ejaculatory ducts due to obstruction

**Neurological damage**
- Retroperitoneal lymph node dissection
- Spinal cord injury
- DM neuropathy

**Congenital causes**
- Bladder extrophy
- Spina bifida
- Ectopic ejaculatory ducts

**Other causes**
- Medications (e.g. alpha-blockers)

34.3.2 Presentation

- Typically a patient presents with dry orgasm or low (<1 ml) ejaculate volume and cloudy urine (first voided urine post-intercourse or orgasm).
- Infertility

34.3.3 Diagnosis

Presence of >10–15 sperms per high power field in post-intercourse or orgasm confirms the diagnosis of retrograde ejaculation.

34.3.4 Management

Retrograde ejaculation is not known to have any adverse health effects. However, for patients with infertility due to retrograde ejaculation, the following options can be considered:

- **Sympathomimetics**: For example, ephedrine and pseudoephedrine 30 minutes before intercourse. Due to sympathomimetic effects, these medications close the bladder neck and facilitate antegrade ejaculation.
- **Tricyclic anti-depressants**: Such as Imipramine have mixed sympathomimetic and anti-cholinergic effect.

Overall success of medical therapies is 50–60%. If medical therapies are not successful, for in-vitro fertilisation, sperm can be retrieved from post-ejaculatory urine. First the urine is rendered alkaline by giving the patient sodium bicarbonate 6 g every 4 hours for 24 hours beforehand. The bladder is emptied, and after ejaculation, the patient can ‘urinate’ before withdrawing, or the voided urine is centrifuged and placed in a plastic cup over the cervix or injected into it.

Artificial insemination using the husband’s semen is seldom worthwhile when his sperm is of poor quality, and before embarking on any programme, it needs to be understood by everyone involved that it can take multiple attempts before pregnancy is achieved if at all, even with normal semen. The greatest tact and care is necessary when setting up such a service, for the recurring monthly disappointment demands great sympathy.

34.4 Anejaculation

‘Anejaculation is the complete absence of an antegrade or retrograde ejaculation’.

Orgasm and ejaculation constitute the final phase of the sexual response cycle. There are three basic mechanisms involved in normal antegrade ejaculation: emission, ejection, and orgasm [13]. Ejaculatory dysfunction can result from disruption at any point in this cascade of events.

34.4.1 Aetiology

True anejaculation is always connected with central or peripheral nervous system dysfunctions or with drugs (Table 34.3).

34.4.2 Anorgasmia

Anorgasmia is defined as the inability to reach orgasm.

The causes of anorgasmia are usually psychological but may be related to drugs or reduced penile sensation (e.g. peripheral neuropathy).

<table>
<thead>
<tr>
<th>Neurological causes</th>
<th>Pharmacological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord injury cauda equina lesions</td>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Retroperitoneal lymphadenectomy</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Colorectal or pelvic surgery</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Others</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>Alcohol excess</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td></td>
</tr>
</tbody>
</table>

Table 34.3 Causes of anejaculation.
Mainstay of management is psychotherapy; however, neurological investigated may be required in selected patients.

### 34.4.3 Management

Drug treatment for anejaculation due neuropathy is not very effective.

- In all these cases, especially in men with spinal cord injuries, vibrostimulation (i.e. the application of a vibrator to the penis) is the first-line therapy.
- In patients not responding to vibrostimulation, electroejaculation is the therapy of choice. Electroejaculation involves an electric stimulation of the periprostatic nerves via a rectal probe.
- When electroejaculation fails or cannot be performed, sperm retrieval from the seminal ducts may be achieved by:
  - Sperm aspiration from proximal vas deferens
  - Seminal tract washout
- In case of failure of sperm retrieval, epididymal obstruction or testicular failure must be suspected. If there is clinical suspicion of possible ejaculatory duct obstruction, transrectal ultrasonography or vasography may be required.

### 34.5 Priapism

Priapism is the presence of a persistent, prolonged (>4 hours), painful or painless erection of the penis unrelated to sexual stimulation or desire for more than four hours.

#### 34.5.1 Pathophysiology

Priapism is the result of persistent engorgement of the corpora cavernosa of the penis, developing as a result of disturbance in the mechanism that controls normal penile detumescence. In most cases, the corpus spongiosum and glans penis remain flaccid.

Failure of detumescence is associated with hypoxia, acidosis, and glucopaenia, causing impaired smooth muscle contraction resulting in thrombosis and necrosis after 24 hours.

#### 34.5.2 Aetiology and Classification

Priapism is idiopathic (primary) in more than half of all patients; the remainder it is secondary to other diseases or conditions (see below). Three subtypes of priapism are well described.

##### 34.5.2.1 Low-Flow (Ischemic) Priapism

It is an acute urological emergency (e.g. penile compartment syndrome) resulting from veno-occlusion. A patient usually presents with a painful rigid erection with little or low cavernosal arterial blood flow. Low-flow priapism accounts for 95% of all priapisms. By 12 hours, the corporal interstitium is oedematous if left untreated and leads to destruction of the sinusoidal endothelium and exposure of the basement membrane with thrombocyte adherence at 24 hours. By 48 hours, thrombi are found in the sinusoidal spaces, and smooth muscle necrosis with fibrosis has ensued.

Common causes are:

- Thromboembolic disorders: Sickle cell anaemia, leukaemia, multiple myeloma, thalassaemia, fat emboli, and haemodialysis.
- Neurogenic: Spinal cord injury, autonomic neuropathy, anaesthesia, syphilis, cauda equine syndrome, lumbar disc herniation, spinal stenosis, cerebrovascular accident, and brain tumour.
- Drugs: Intracavernosal injection of PGE1 (rare <1%) or with PDE5 inhibitors combination injections (up to 35%), alpha-blockers, anti-depressants, anti-psychotics, anticoagulants, antihypertensives, hormones, and recreational drugs.
- Regional or metastatic infiltration from cancer.
- Infections (toxin-mediated) scorpion sting, spider bites, rabies, or malaria.

##### 34.5.2.2 High-Flow (Nonischemic) Priapism

Usually related to trauma (i.e. pelvic or perineal), resulting in laceration of the cavernosal artery leading to a high-flow fistula between the artery and the sinusoidal spaces and aberrant and unregulated arterial blood flow. There is usually a two- to three-week period between the initial trauma and the priapism presentation. Intracorporeal blood is well oxygenated, and hence, it is less likely to cause injury to erectile tissues. Patient present with painless semi-rigid erection.

##### 34.5.2.3 Stuttering (Recurrent or Intermittent) Priapism

Characterised by repetitive and painful episodes of prolonged erections. The erections are self-limiting with the frequency and duration of episodes varying. Nonetheless, single episodes can develop into a major period of ischaemic priapism. Causes are similar to low-flow priapism, however, it is more commonly seen in patients with sick cell disease.

#### 34.5.3 Assessment

- History and clinical examinations is vital in initial assessment and distinguishing between various types of priapism. Duration of erection, presence of pain, previous episodes, medication, trauma, and presence of any haematological illnesses should be elicited in the history. General examination as well as evaluation of the priapism to establish low (fully rigid or painful) or high (semi-rigid or painless) flow.
A full blood count (rule out leukaemia). If Sickle Cell status is unknown, a haemoglobin S determination is useful. Platelet count and coagulation profile as well. Further investigations depend on the history.

Blood glass analysis of the corpus cavernosa aspirated blood is useful to differentiate between high- and low-flow disease. Values similar to venous blood suggest a low-flow priapism can also be hypoxic and acidic and will be dark in colour. Values similar to arterial blood suggest high-flow priapism; the colour will be bright red.

Radiological investigations are not usually required. However, if in doubt, colour flow penile Doppler imaging is the study of choice. Furthermore, in patients with high-flow priapism, selective penile angiography (i.e. pudendal artery) can identify the site of the fistula before embolisation.

### 34.5.4 Management

- **Conservative measures**: Immediate treatment includes ice packs to the perineum and penis, asking the patient to walk upstairs, and masturbation.
- **Treatment of underlying cause**: Treat the underlying cause whenever possible. Priapism secondary to Sickle Cell disease is treated with intravenous hydration, alkalinization with bicarbonates, narcotic analgesia, and oxygenation to prevent further sickling. Exchange and transfusions may be required to increase the tissue delivery of oxygen.

#### 34.5.4.1 Management of Low-Flow Priapism

This is a urological emergency as such no delay in initiating management, which has a stepwise approach for priapism >4 hours to try and attain detumescence and preserve potency, whereas for priapism >72 hours is to relieve the erection and if present associated pain as at this point potency is lost.

**Therapeutic aspiration** is considered to be the first manoeuvre (after diagnostic aspiration). Via large-bore needles (19g) inserted into the corpora laterally (you can place two on either side), aspirate 20–30ml of blood with or without normal saline irrigation, and the procedure is repeated until the aspirate is bright red. Aspiration achieves detumescence in approximately 30% of cases.

#### 34.5.4.1.1 Pharmacotherapy

If therapeutic aspiration fails, the next step is direct corporeal administration of a sympathomimetic agent, Phentylephrine, a selective α1 adrenergic agonist, has the best cardiovascular side-effect profile and is thus recommended [14]. It is diluted with normal saline at a concentration of 100–200 μg ml⁻¹ and given in 0.5–1ml doses every 5–10 minutes for a maximum dose of 1g for no more than 1 hour. Side effects include headaches, dizziness, tachycardia, hypertension, and arrhythmias.

It can be expected to induce detumescence in 65–80% of cases if aspiration with or without saline irrigation is coupled with intracavernosal sympathomimetic or alpha-agonist injections.

Other medications used: etilefrine, ephedrine, epinephrine, norepinephrine, oral terbutaline, and metaraminol have been used; however, one must be cautious of the cardiovascular risks.

#### 34.5.4.1.2 Surgical Interventions

For refractory cases not resolved by first-line intervention within one hour of initiating treatment, prompt surgical intervention is required. The basic principle is to establish a shunt to drain trapped blood from the corpora by an opening in the tunica albuginea.

**Distal Shunts**  Distal shunts establish a communication between the erect corpora cavernosa and either the glans penis.

**Percutaneous Distal Shunts**

- Winter shunt: using venflon or true cut needle to create a fistula between the glans and each corpora cavernosa body.
- Ebbehøj shunt: using a scalpel-blade, multiple tunical incision windows between the glans and each tip of the corpus are created percutaneously.
- Lue shunt: a scalpel is paced vertically through the glans until fully within the corpora then rotated 90° (away from urethra as not to damage it) and pulled out (T-shunt).

**Open Distal Shunts**

- Al-Ghorab shunt: excision of disc of corpus cavernosa tip.
- Burnett shunt: a modification of Al-Ghorab shunt, same excision is done then a dilator is inserted into the corpus (Figures 34.12 and 34.13).

**Proximal Shunts**  If distal shunts are unsuccessful, proximal shunts can be used.

**Open Proximal Shunt**

- Quackles shunt (i.e. corporospongial shunt): creating a communication between the corpus spongiosum and cavernosa (Figure 34.14).
- Sacher shunt: same as Quackles, but bilateral Venous shunts
- Grayhack shunt: the saphenous vein is anastomosed (end to side) to the corpus cavernosa (Figure 34.15).

Shunt procedures have combined success rates of 66–77%; proximal procedures are associated with the highest resolution rates but increased complications, particularly ED.
34.5.4.1.3 Penile Prosthesis
Erectile dysfunction is a major complication of prolonged priapism, 90% of men with a priapism lasting >24 hours develop ED. It is for this reason that immediate penile prosthesis insertion, initially with a temporary malleable prosthesis, is often considered for failed shunting or late presentation (>48 hours) of priapism.

34.5.4.2 Management of High-Flow Priapism
This is not an emergency because there is no ischaemia. If initial aspiration of the corpus cavernosum reveals bright red blood, consider an arterial cause for priapism and institute the steps noted.

34.5.4.2.1 Conservative Management
Observation alone may be sufficient as erectile function is usually unimpaired. Ice-pack pressure or compression therapy to the perineum may be successful, especially in children.

Selective Arterial Embolisation Patients who do not respond to conservative measures. High success rate (90%), with varying recurrence rates (7–27%), and a high preservation of sexual function rate (80%) [15].

Surgical Management In rare cases, surgical ligation of the fistula may be required. However, potential complications of this procedure include long-term ED. For surgical ligation, a transcorpororeal approach under colour Doppler guidance is adopted.
34.6 Peyronie Disease

Majority are acquired but rarely can be congenital.

34.6.1 Congenital Peyronie Disease

Prevalence has been reported to vary from <1 to 10% [16, 17]. Assessment by medical and sexual history can establish the diagnosis, with an examination to exclude other causes and to document curvature. The only treatment modality for the congenital form is surgical correction with plication in adulthood, which has a high correction rate (67–97%) [18].

34.6.2 Acquired Peyronie Disease

An acquired benign condition, resulting in various degree of penile curvature, secondary to formation of a fibrous plaque within the tunica albuginea of the penis. Prevalence rates are between 0.4 and 9% with most patients between 40 and 60 years of age [19].

34.6.3 Aetiology

The aetiology of Peyronie disease is unknown. Repetitive microvascular injury or trauma to the tunica albuginea (during intercourse) is the most widely accepted hypothesis [20]. This leads to bleeding into the tunica albuginea, resulting in inflammation and fibrosis.

Common associated comorbidities and risk factors are:

- DM.
- Hypertension.
- Lipid abnormalities.
- Ischaemic cardiomyopathy.
- ED.
- Low testosterone.
- Tymanosclerosis.
- Smoking.
- Excessive consumption of alcohol.
- Dupuytren contracture (i.e. more common in patients with Peyronie disease affecting 9–39% of patients, while 4% of patients with Dupuytren contracture report Peyronie disease).

34.6.4 Pathogenesis and Natural History

A prolonged inflammatory response results in the remodelling of connective tissue and formation of a
fibrotic plaque. The fibrous tissue in Peyronie disease can affect any part of the tunica albuginea around the corpora cavernosa or the septum between them. When the fibrosis affects one side more than the other, or dorsal more than the ventral, the penis bends during erection (Figure 34.16).

Two phases of the disease have been described [21].

- The first phase is the acute inflammatory phase (active phase), which may be associated with painful erections, formation of a soft plaque, and penile curvature.
- The second phase is the fibrotic phase (stable phase) with the formation of hard palpable plaques (which may be calcified), penile curvature, and disease stabilisation (no pain).

Pain is present in 35–45% of patients during the early stages of the disease, and in 90% of men, it resolves within 12 months. With time, penile curvature is expected to worsen in 30–50% of patients or stabilise in 47–67% of patients, while spontaneous improvement has been reported in 3–13% of patients [21].

34.6.5 Clinical Features

At first, there is pain on erection with a lump (the plaque) which may become tender. When the penis is erect, it bends to the side of the lump (Figure 34.17). Sometimes intercourse may be impossible. ED is seen in 40% of patients. Complex deformities can lead to significant shortening or indentation.

- Assessment and history must include duration of the disease, penile pain, any penile deformity, difficulty in vaginal intromission due to deformity, and associated ED.
- Physical examination should include assessment of palpable nodules or plaque, its location, any tenderness, penile length, extent of curvature (e.g. self-photograph, vacuum pump/pharmacological-induced erection), and any other possibly related diseases such as Dupuytren contracture.
- Investigations are seldom necessary. However, if required a Doppler ultrasound or a cavernosogram can delineate the plaque, but more importantly, it provides an assessment of vascular parameters. Magnetic resonance imaging (MRI) is helpful in complex deformities.
34.6.6 Management

34.6.6.1 Nonoperative Treatment
Conservative treatment of Peyronie disease is mainly for patients in the early stage of the disease where the plaque is not stable, the deformity still changing, and there is still pain. The role of conservative treatment in stable or chronic disease is not well established.

34.6.6.1.1 Oral Agents
No single drug has been approved by the European Medical Association for the treatment of Peyronie disease; only potassium para-aminobenzoate (POTABA) has been classified as possibly effective by the FDA.

Potassium Para-aminobenzoate POTABA is thought to exert an anti-fibrotic effect through an increase in oxygen uptake by the tissues, a rise in the secretion of glycosaminoglycans, and an enhancement of the activity of monoamine oxidases. Treatment with POTABA may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilisation [22]. Adverse effects of POTABA include nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion, and difficulty in concentration.

34.6.6.1.2 Other Oral Agents
These include vitamin E, tamoxifen, colchicine, acetyl esters of carnitine, pentoxifylline, and PDE 5 inhibitors. Vitamin E acts as a natural antioxidant and is commonly prescribed by the majority of urologists at because of its wide availability, low cost, and safety. However, it has not shown any significant improvement in pain, curvature, or reduction of plaque size.

Intralesional Treatment XIAFLEX® (collagenase clostridium histolyticum) is the first and only FDA- and EMA-approved biologic therapy indicated for the treatment of Peyronie disease in men with a palpable plaque and a curvature of 30° or greater at the start of therapy. Investigation for Maximal Peyronie Reduction Efficacy and Safety Studies (IMPRESS) I and II examined the clinical efficacy and safety of collagenase Clostridium histolyticum intralesional injections in subjects with Peyronie disease. The meta-analysis of IMPRESS I and II data revealed statically significant improvement in penile curvature and Peyronie disease symptom bother score was significantly improved in treated men [23]. Verapamil (a calcium-channel antagonist) can result in modification of the inflammatory response and the inhibition of fibroblast proliferation in the plaques. Dosage: 10 mg diluted to 10 ml injected into the plaque every two weeks for 12 consecutive treatments. Several clinical studies have reported that intralesional verapamil may induce a reduction in penile curvature and plaque size. However, in a randomised, placebo-controlled study, this benefit was not proven [24]. Similarly, intralesional steroid injections failed to show statistical significant benefits [25].

34.6.6.1.3 Topical Treatment
Topical verapamil (gel 15% applied twice daily) can improve penile curvature, plaque size, and penile pain, with significant improvement seen after nine months over three months, implying importance of a prolonged treatment [26]. Iontophoresis (also known as electromotive drug administration ([EMDA]) with verapamil 5 mg and dexamethasone 8 mg can improve penile curvature and plaque size.

34.6.6.1.4 Shock Wave Lithotripsy
Shock wave lithotripsy (SWL) is thought to work either by directly damaging and remodelling of the penile plaque or as a result of increase vascularity or inflammatory reaction with increased macrophage activity, resulting in plaque lysis and resorption. SWL has not been shown to improve penile curvature and plaque size but provides improvement in penile pain.

34.6.6.1.5 Traction and Vacuum Devices
Traction and vacuum devices are thought to increase the activity of degradative enzymes, leading to a loss of tensile strength and ultimately solubilisation. Both these methods have shown some improvement in penile curvature.

34.6.6.2 Surgical Treatment
The aim of surgery is to correct curvature to allow satisfactory intercourse. Surgery is indicated only in patients with stable disease for at least three months. Stability of the disease is based on resolution of the pain and stability of the curvature. Three types of surgical options are considered for Peyronie disease:

1) Penile-shortening procedures.
2) Penile-lengthening procedures.
3) Penile prosthesis.

34.6.6.2.1 Choosing Surgical Options
Choosing the most appropriate surgical intervention is based on penile length assessment, curvature severity, and erectile function status, including response to pharmacotherapy in cases of ED. Before surgery, a careful discussion with the patient is required focusing on following points:

- Penile shortening: Patients often perceive the loss of length as greater than it actually is [27]. It is therefore advisable to measure and document the penile length perioperatively, both before and after the straightening procedure.
● ED.
● Penile numbness.
● Recurrence of curvature.
● Potential for palpation of knots or stitches underneath the skin.
● Need for circumcision at the time of surgery; penile degloving with associated circumcision (to prevent postoperative phimosis) is usually performed for all types of procedures. However, in cases where the foreskin is normal circumcision is unnecessary.

Penile-Shortening Procedures Penile-shortening procedures include the Nesbit wedge resection and the plication techniques performed on the convex side of the penis (contralateral site to the Peyronie plaque). These procedures are the first treatment options for Peyronie disease in patients with adequate penile length and function, curvature <60°, and absence of more complex deformities (e.g. hour-glass or hinge).

Nesbit Procedure The Nesbit procedure was first described for congenital penile curvature. Subsequently this procedure was successfully applied for management of Peyronie disease. This operation (Figure 34.18) is based on a 5- to 10-mm transverse elliptical excision of the tunica albuginea (from convex side, that is, opposite the deformity) or approximately 1 mm for each 10° of curvature. The overall short- and long-term results of the Nesbit operation are excellent.

- Complete penile straightening is achieved in >80% of patients.
- Recurrence of the curvature and penile hypoesthesia (~10%) and the risk of postoperative ED is minimal [27].
- Penile shortening is common in Nesbit procedure [27]. About 1–1.5 cm loss of penile length has been reported in nearly 85% of patients.

Plication Procedures The plication procedures (Figure 34.19) share the same principle as the Nesbit operation but are simpler to perform. They are based on single or multiple longitudinal incisions on the convex side of the penis (opposite side of deformity) sutured in a horizontal way, or simple plication is performed without incisions, but suture opposite side of the deformity to straighten the penis. Another modification has been described, the ‘16 dot’ technique with minimal tension under local anaesthesia [28].

Penile-Lengthening Procedures Penile-lengthening procedure are the preferred treatment option for patients with Peyronie disease with inadequate penile length, curvature >60°, and presence of complex deformities. Penile-lengthening procedures (e.g. Lue procedure) are performed on the concave side of the penis (incisions of the plaque) and insertion of a graft to minimise penile shortening. A variety of grafting materials (e.g. autologous dermis, vein grafts, tunica albuginea, tunica vaginalis, allograft; cadaveric pericardium, cadaveric fascia lata, and synthetic grafts; Gore-Tex, Dacron) have been reported.

Plaque removal can cause venous leak and hence the grafting procedures are associated with ED in 25% of patients. Additionally long-term failures result in reoperation in up to 17% patients [29].

Penile Prosthesis Penile prosthesis implantation is typically reserved for the treatment of patients with Peyronie disease and ED not responding to pharmacotherapy.

34.7 Late Onset Hypogonadism

Late onset hypogonadism (LOH) is also called ‘andropause’; however, unlike menopause, the reduction of testosterone is a slow gradual drop. Incidence varies based on age, can be around 4% in those <30 years of age, 20% in men older than age 60, 30% older than age 70, and 50% in men older than 80 years of age [30].

34.7.1 Definition

LOH is also known as age-associated testosterone deficiency syndrome and is defined as ‘a clinical and biochemical syndrome associated with advancing age and characterised by symptoms and a deficiency in serum testosterone levels (below the young healthy adult male reference range). This condition may result in significant detriment in the QoL and adversely affect the function of multiple organ systems’ [31].

34.7.2 Pathophysiology

Production of testosterone decreases by 1–2% every year after the age of 40 years [32, 33]. Natural reduction in
Late Onset Hypogonadism

Testosterone production by ageing testicles leads to an increase in LHRH and LH secretion from the hypothalamus and pituitary glands; however, there is lack of sensitivity to LH and the testosterone levels stay low. With time, the production of LHRH and LH also decreases. Furthermore, sex-hormone binding globulin (SHBG) bind to testosterone, reducing availability of testosterone even further. SHBG levels increase with age, cirrhosis, hyperthyroidism, use of anticonvulsants and oestrogens, and in HIV infections.

Testicular volume decreases by 15% between 25 and 80 years of age, with a 50% reduction of Sertoli and Leydig cells [34]. Furthermore, there is an age-related reduction in seminal fluid production, sperm production with less motility, and increased abnormal morphology; however, sperm concentration remains constant lead to infertility or subfertility [34].

34.7.3 Aetiology

Primary hypogonadism (testicular) causes low testosterone levels and impaired spermatogenesis, with elevated or normal LHRH, LH, and FSH levels.

- Congenital: Chromosomal (e.g. Klinefleter syndrome [47 XXY]), Turner syndrome, disorders of sexual development giving rise to enzyme defects (e.g. 17-α-hydroxylase deficiency), androgen receptor defects (e.g. androgen insensitivity syndrome or 5-α-reductase deficiency), and condition leading to testicular atrophy such as undescended testes and more common cause, testicular tumours.
- Acquired: Bilateral testicular atrophy (e.g. torsion, infection, trauma, autoimmune disease, toxins, alcohol), bilateral orchiectomy, chemotherapy, or radiotherapy.
Secondary hypogonadism (nontesticular or central) causes disruptions in the LHRH and LH secretions.

- Congenital: Kallmann’s syndrome (most common), Prader-Willi syndrome, and congenital adrenal hypoplasia.
- Acquired: Hyperprolactinemia (e.g. prolactin secreting pituitary adenomas or drug induced [dopamine antagonises]) and hypopituitarism (e.g. pituitary tumours) surgical excision, or radiotherapy.

34.7.4 Risk Factors Increasing the Likelihood of LoH

Obesity and metabolic syndrome, DM, chronic illnesses especially steroid or opiate requirements (e.g. chronic obstructive lung disease and inflammatory arthritic), end-stage renal disease on dialysis, HIV-related diseases, cardiovascular disease, and pituitary lesions [31, 33].

34.7.5 Clinical Features

Clinical features are a lack of testosterone, the most prevalent symptoms being loss of libido, ED, and hot flushes; others include loss of vigour and strength, decreased muscle mass, small testes, delayed puberty, decreased body hair, lethargy and fatigue, metabolic syndrome and increased body fat visceral obesity, decreased bone mineral density, osteoporosis, decreased vitality, depressed mood, reduced concentration and lack of sleep, infertility or subfertility, and reduced bone mineral density [31, 33].

34.7.6 Diagnosis

History looking for the signs and symptoms and a general examination with a focused urological examination include a prostate examination.

Investigation [31, 33, 35, 36]:

- Early morning (7–11 a.m.) total testosterone: Total testosterone level above 12 nmol l⁻¹ (350 ng dl⁻¹) does not require substitution. Patients with serum total testosterone levels below 8 nmol l⁻¹ (230 ng dl⁻¹) will usually benefit from testosterone treatment. If the serum total testosterone level is between 8 and 12 nmol l⁻¹, repeating the measurement of total testosterone with SHBG to calculate free testosterone or free testosterone by equilibrium dialysis.

  Total testosterone levels of 8 nmol l⁻¹ leads to a loss of libido and 8.5 nmol l⁻¹ ED.
  
  - LH and FSH levels, in addition to serum prolactin if testosterone level <5.2 nmol l⁻¹ (150 ng dl⁻¹).
  - PSA, full blood count, liver function tests, and renal function tests.
  
  - Equilibrium dialysis is the gold standard for free or bioavailable testosterone measurement. Free testosterone when the serum total testosterone concentration is not diagnostic of hypogonadism, particularly in men who are obese; a free testosterone level below 225 pmol l⁻¹ (65 pg ml⁻¹) can provide supportive evidence for testosterone treatment.

34.7.7 Treatment [31, 33, 35, 36]

Management is aimed to improve QoL through testosterone replacement. Symptoms in general will improve with testosterone replacement within three to six months, with longer replacement periods needed for improvement in bone mineral density. Therefore, treatment should not go beyond six months if symptoms do not improve and will require re-evaluating the diagnosis. Figure 34.20 outlines the diagnosis and treatment of LoH [36],

Contraindications for testosterone replacement

- Breast cancer: due to peripheral aromatization of testosterone.
- Prostate cancer: controversial, but should be avoided or used with caution in men with high risk of developing prostate cancer or PSA levels >4 ng ml⁻¹.
- Primary liver cancer.
- Polycythaemia (haematocrit >50%).
- Untreated obstructive sleep apnoea.
- Untreated congestive heart failure or renal failure or liver failure.
- Obstructive benign prostatic enlargement (unlikely, as lack of testosterone will likely cause involution of the prostate).

Side effects of testosterone replacement

- Polycythaemia.
- Headaches.
- Depression.
- Liver toxicity and obstructive jaundice.
- Gynaecomastia.
- Baldness.

Regular follow-up during treatment is essential to maintain a symptom-free status. Testosterone replacement can improve libido after three weeks of initiation of replacement and plateau at six weeks; erectile function improvement can take up to six months, and overall improvement of symptoms might be evident by the first four weeks [33].

- Full blood count every three to four months for first year, then annually to maintain haematocrit below 52–55%. Effects may be evident at 12 weeks and peak at one year.
Late Onset Hypogonadism

Rectal examination and PSA every three to six months for first year, then annually.

Bone mineral density if abnormal before replacement therapy. Improvements can be detectable from six months and may continue for three years.

Various testosterone preparations are available (Table 34.4) and should be tailored around the patients’ needs and compliance.

Table 34.4 Testosterone replacement preparations.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (testosterone undecanoate)</td>
<td>Need to be taken with fatty foods, but as metabolised in the liver has lower efficacy with variable testosterone levels.</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Undecanoate is long-acting injected every three months. Good level control, however, cannot withdraw if significant side effects develop. Cypionate and enanthate are short-acting injected every two to three weeks. Difficult to control levels, therefore, causes varying responses from improvement to no change in symptoms.</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Daily use with good replacement of testosterone levels; causes skin irritation.</td>
</tr>
<tr>
<td>Sublingual and buccal</td>
<td>Daily use with good replacement of testosterone levels; causes local mucosal irritation.</td>
</tr>
<tr>
<td>Subdermal depot injections</td>
<td>Long-acting injected every five to seven months. Increased risk of infections and extrusion of implants.</td>
</tr>
</tbody>
</table>

Figure 34.20 Algorithm for diagnosis and treatment of late onset hypogonadism. DRE, digital rectal examination; FSH, follicle-stimulating hormone; Hb/Hct, hemoglobin/hematocrit; LH, luteinising hormone; MRI, magnetic resonance imaging; PRL, prolactin; PSA, prostate-specific antigen; SHBG, sex-hormone binding globulin.

Expert Opinion

Sexual dysfunction in men represents a group of common medical conditions that require multidisciplinary perspective. A careful and thorough assessment of these patients is mandatory. Mainstay of management is understanding and establishing underlying causes of these disorders and targeting therapies accordingly. Management options include medical, psychological, and operative intervention. Choice of these options is depend on underlying cause, severity of disorder, and patient’s expectations.
References


Part VI
Comparative Anatomy

In many mammals, the testes enlarge and shrink with the seasonal rise and fall in testosterone. In man, there is a rapid increase in testicular size at puberty and a slower decline in old age. The location of the testes varies widely in different mammals. In elephants, the testes are located in the abdomen and are just caudal to the kidneys; in whales they are near the bladder; the internal ring in hedgehogs; the superficial inguinal pouch in pigs. In sheep and man, they hang at the bottom of a pendulous scrotum (Figure 35.1).

Most mammalian testes reside intra-abdominally for the majority of the year, descending into the scrotum only during mating season. Although the testicles lie in the scrotum in the majority of primates, the testicles are able to move freely in and out of the scrotum in some species [1, 2].

The epididymis is only found in mammals. It was once thought to be involved in the fertilisation of the ovum at the time of ovulation; however, immunochemical studies have been unable to establish a difference between sperm found in the ejaculation and sperm in the vasa efferentia [3, 4].
35.2 Topographical Anatomy

The normal adult testis hangs in the scrotum, the left usually hanging lower than the right. The left testis is often larger than the right. The epididymis is located behind the testis.

35.2.1 Testes

The testis consists of a multitude of convoluted tubules which empty into the rete testis at the hilum, where about 12 vasa efferentia cross into the beginning the epididymis (Figure 35.2) [1].

Each testicular tubule has a basement membrane, lined by spermatogonia and Sertoli cells. The outside of the tubules consists of connective tissue spaces with blood, lymphatic vessels, and Leydig cells.

In the foetal testis, the tubules contain germ cells and immature Sertoli cells between the tubules the Leydig cells become particularly abundant just before birth, but disappear afterwards to be replaced by fibroblasts. At puberty luteinizing hormone secreted by the pituitary gland stimulates the Leydig cells to reappear, the Sertoli cells to become mature, and the dormant germinal cells to spring into activity. The spermatogonia divide by mitosis; some progeny will become spermatocytes, and others continue as stem cells. Each spermatocyte divides by meiosis to produce haploid secondary spermatocytes, which eventually become spermatozoa. The changes pass along the testicular tubules in waves so that a biopsy of the adult testis will show several different phases in the sequence of division and maturation from spermatogonia to mature sperms (Figure 35.3). A testicular biopsy must therefore include several tubules to give a useful picture of spermatogenesis [5].

35.2.2 Coverings of the Testicle

The testes are surrounded by three layers of tissues, the most superficial layer being the tunica vaginalis, then the tunica albuginea, and the deeper tunica vasculosa. The median raphe separates the right from the left.

The tunica vaginalis is the distal continuation of the processus vaginalis which is the evagination of the abdominal peritoneum into the scrotum. In the foetus it is formed prior to the descent of the abdominal testes into the scrotum. Once the descent is complete, the proximal part of the tunica vaginalis is obliterated to form the sac in which the testes reside. It contains two layers, the visceral and parietal layer which are formed as a result of the reflection of the tunica from the testis onto the internal surface of the scrotum. Most of the testes is encompassed by the visceral layer except for the posterior part. When it reaches the posteriomedial aspect of the testes, it is reflected anteriorly to form the parietal layer, and the posterolateral aspect passes the epididymis and reflects to form the parietal layer on the lateral side. The parietal layer also continues below the testes and connects to the anteromedial aspect of the spermatic cord.

The tunica albuginea, which is located within the tunica vaginalis, is a fibrous connective tissue. It facilitates the entry of the blood vessels and nerves at the epididymal head and tail and the posterior part of the testes, where it is not covered by the visceral layer of the tunica vaginalis. The tunica albuginea continues into the interior of the testis to form the mediastinum testis, an incomplete fibrous septum containing the testicular vessels. It also contains within it the tunica vasculosa, which contains blood vessels and soft connective tissue.
35.3 Blood Supply and Lymphatic Drainage

35.3.1 Arterial Supply

The testes receive their arterial supply from the testicular (also called spermatic of gonadal) arteries. They originate from the anterior of the aorta just below the renal arteries. Both arteries cross anterior to the genitofemoral nerve and the ureter before taking its path along the deep inguinal ring and enters into the spermatic cord which runs through the inguinal canal to reach the scrotum. The testicular artery divides into two branches, the medial and lateral branches, first inserting into the tunica albuginea and then the tunica vasculosa.

An additional minor arterial supply is provided by the long artery of the vas which anastomoses with a branch from the testicular artery to the epididymis (Figure 35.4).

35.3.2 Venous Drainage

The testicle has a profuse venous drainage arranged in three layers between the external spermatic fascia, the cremasteric muscle, and the internal spermatic fascia. They arise from the posterior aspect of the testes and merge to form the pampiniform plexus. The plexus ascends through the spermatic cord anterior to the vas deferens. The different tributaries then coalesce in the abdomen to form two distinct veins which ascend either side of the testicular artery. The two veins then conjoin to form the testicular vein which inserts directly into the inferior vena cava on the right and the renal vein on the left (Figure 35.5). A minor collateral drainage exists through the cremasteric vein into the deep epigastric vein.

35.3.3 Lymphatic Drainage

The lymphatics of the testes arise in the spaces between the tubules and flow through the testicular hilum into the cord. They retrace the testicular artery to the para-aortic lymph nodes around the origin of the testicular and renal arteries.
35.3.4 Nerve Supply

The testicular nerves originate from the tenth and eleventh thoracic spinal segments via the autonomic plexuses. The testis has visceral afferent and efferent fibres and lacks somatic nerves [1]. The superior spermatic nerve arises from the spermatic ganglion, which receives fibres from the coeliac and intermesenteric plexuses, as well as the lumbar and thoracic splanchnic nerves and the vagus.

From the spermatic ganglion the nerves run with the internal spermatic artery as a discrete nerve which accompanies the artery to the testis. The tunica albuginea has an abundant sensory nerve supply which is quite distinct from the innervation of the scrotum. The role of the autonomic motor nerves to the testicle is unknown [1].

35.4 Epididymis

The epididymis is a structure located in the posterior aspect of the testis and lateral to the vas deferens. It consists of a single convoluted ductus epididymis which arises from the joining of the efferent ducts of the testis. The tube of the epididymis is said to be 3–4 m in length when unravelled [3, 6, 7]. It is arranged in three parts the expanded head (globus major), body (corpus), and tail (cauda or globus minor). In most mammalian species as well as man, it has the shape of a dumb-bell with a distinct waist (Figure 35.6). Between the epididymis and testis is a sulcus which forms a pocket facing laterally,
which is a useful guide for the surgeon when replacing the testicle after scrotal operations. The epididymis is lined by columnar ciliated epithelium. The cilia of the epididymis resemble the cilia of the bronchioles, with which they share the structure of a dynein arm as well as a susceptibility to poisoning with mercury salts [7–10]. The lumen of the epididymis becomes progressively wider as it goes from head to tail, where muscle begins to surround the tubule which continues on as the vas deferens [11].

### 35.4.1 Blood Supply

The blood supply to the epididymis comes from a branch of the testicular artery which enters the caput epididymis, runs down the epididymis, and anastomoses with the terminal branch of the artery of the vas, which runs alongside the vas inside its connective tissue sheath.

### 35.5 Vas Deferens

The vas deferens is a 45 cm long firm cord with a small lumen and a thick wall of smooth muscle, which is convoluted at each end (Figure 35.7). It is the distal continuation of the epididymis, and its main function is to transport sperm to the ejaculatory ducts. Its tall columnar epithelium is lined with ‘stereocilia’ which are not motile and resemble structures in the ependymal of the canal of the spinal cord, and the tympanic cavity [12].

The vas starts lateral to the epididymis and ascends along the posterior aspect of the testis and continues into the posterior part of the spermatic cord. It leaves the spermatic cord at the deep inguinal ring, curves around lateral to the inferior epigastric artery and follows the inside of the pelvis, crossing the external iliac vessels and the ureter, where it follows the cleft between the inner and outer zones of the prostate (Figure 35.6). Just before it enters the prostate, the vas gives off a diverticulum, the seminal vesicle.

![Figure 35.7](image1.png)  
**Figure 35.7** Surgical anatomy of the vas deferens.

![Figure 35.8](image2.png)  
**Figure 35.8** The seminal vesicle develops as a diverticulum of the ejaculatory duct.
35.5.1 Blood Supply

The artery of the vas is a branch of the superior vesical artery which arises from the internal iliac artery. Its venous drainage leads to the pelvic venous plexus along with the venous drainage of the seminal vesicles.

35.6 Seminal Vesicle

The embryology of the seminal vesicle has been meticulously studies [13]. Starting as a modest pouch of the vas deferens, it enlarges in puberty and in the adult each may hold up to 2–10 ml of fluid in a convoluted hollow sac with a strong muscular coat and a columnar epithelium with folds like a honeycomb (Figure 35.8) [14]. The common ejaculatory ducts emerge in the prostatic urethra either side of the verumontanum. Interesting to note that its secretion were tasted and found to be sweet by John Hunter, due to the rich fructose content.

35.7 Verumontanum

The verumontanum contains spongy tissue resembling that of the corpora of the penis. Its summit contains the utriculus masculinis, the vestige of the lower ends of the müllerian ducts, on either side of which are the ejaculatory ducts (Figure 35.9).

35.8 Spermatic Cord

During early life the intra-abdominal testes travel towards the scrotum carrying its blood supply, nerve supply, and the vas deferens along with it. The spermatic cord is formed when these reach the deep inguinal ring. It contains four layers, each representing a component of the abdominal wall (Figure 35.5). The core of the spermatic cord contains the vas deferens, the testicular artery, and the venous drainage. This is surrounded by peritoneum in infants, but in adults, the peritoneal layer has shrivelled to a thin strip into the processus vaginalis.

The next layer of peritoneum is a thin layer derived from transversalis fascia, the internal spermatic fascia. This is surrounded by muscle fibres continuous with the internal oblique muscle of the abdominal wall, the cremasteric muscle, which covers the entire testicle. Overlying the cremaster, the external spermatic fascia is a continuation of the external oblique aponeurosis.

35.9 Testicular Physiology

The Latin ‘testiculus’ means ‘witness’ of virility and enlightens us to the primary function of these gonadal endocrine organs. The main function of the testes is spermatogenesis and androgen synthesis.

35.9.1 Hypothalamic-Pituitary-Gonadal Axis (Figure 35.10)

The hypothalamus produces gonadotrophin-releasing hormone (GnRH) which stimulate the anterior pituitary to release gonadotrophins: Luteinizing hormone (LH) and follicle-stimulating hormone (FSH). GnRH is discharged in a pulsatile manner every 90–120 minutes, continuous GnRH release causes inhibition of LH and FSH release. LH controls Leydig cell function and FSH controls Sertoli cells. The secretion of GnRH is in a pulsatile manner, which dictates the

![Figure 35.9 Structure of the verumontanum. Note the presence of erectile tissue.](image-url)
corresponding pulsatile secretion of LH and FSH. LH at approximately 8–14 pulses per 24 hours, and FSH at a lower amplitude [15]. The secretion of LH and FSH is dependent on this pulsatile stimulation of the gonadotroph cells by GnRH, continuous administration or intermittent administration of GnRH equivalents suppresses the release of LH and FSH. This is due to GnRH receptors requiring replenishment once stimulated, when stimulated in a pulsatile manner replenishment is optimum; however, when stimulates in a nonpulsatile manner, the replenishment of GnRH receptors is inhibited so that insufficient receptors are available for function. This mechanism is used in the clinical treatment of prostate cancer, whereby GnRH analogues are administered intermittently in a nonpulsatile manner and therefore lower LH and FSH levels, reducing stimulation to testicular cells so the production of prostate-stimulating androgens is reduced [15].

**35.9.2 Leydig Cells**

Leydig cells are located in the supportive connective tissue; their primary function is to secrete androgenic hormones, which are essential to the development of masculine sex characteristics and sperm production. LH stimulate G-coupled receptors on Leydig cells membranes, and via cyclic adenosine monophosphate (cAMP) and kinase pathways activate gene transcription that increases enzymes necessary for the steroid synthesis of testosterone from cholesterol [16].

**35.9.3 Sertoli Cells**

Sertoli cells are located in the testicular seminiferous tubules, these tubules make up 80% of the testis. FSH binds to receptors on Sertoli cells, leading to increase in protein synthesis. Several proteins are synthesised;

1) Androgen-binding protein-secreted into luminal space of seminiferous tubules near developing sperm cell.
2) P-450 aromatase which converts testosterone into estradiol.
3) Growth factors that support sperm cells and spermatogenesis, increasing the fertility potential of sperm.
4) Inhibin secreted has a negative feedback on the hypothalamic-pituitary-gonadal axis preventing further secretion of LH.

In addition, during foetal life, Sertoli cells release the müllerian duct inhibitory factor (MIS) in the seventh week.
35.9.4 Production and Action of Testosterone

Cholesterol is the essential precursor for androgen synthesis by Leydig cells, which use a series of 5 enzymes to produce testosterone, 3 of which are P-450 enzymes. Multiple pathways exist for the formation of testosterone beginning in the mitochondria where the long side chain of cholesterol is removed by cytochrome P-450 enzyme, this produces pregnenolone, then at the smooth endoplasmic reticulum (SER), 17a-hydroxylase adds a hydroxyl group to from 17a-hydroxy-pregnenolone. A further P-450 enzyme removes another side chain resulting in the steroid called dehydroepiandrosterone. A non-P-450 enzyme in the Leydig cells forms androstenediol, the hydroxyl group is finally oxidised to a ketone to form testosterone [17].

Several other tissues also produce testosterone: adipose tissue, brain, muscle, skin, and adrenal cortex. Peripheral organs and tissues can convert testosterone to the weaker hormone androstenedione, a hormone with different actions, estradiol, or through the microsomal enzyme 5α-reductase to a more potent hormone-dihydrotestosterone [18].

Testosterone travels in the circulation, 60% of which is bound to testosterone-binding globulin also known as SHBG, 38% to albumin and corticosteroid-binding globulin, approximately 2% circulates free in plasma; hence, 40% available for biological activity. In adults, testosterone maintains the male phenotype, sexual function, and exerts anabolic effects. While in the foetus, dihydrotestosterone is responsible for the differentiation of the external genitalia and its deficiency of absence leads to intersexual states.

35.9.5 Spermatogenesis

During embryological development, germ cells migrate into the testicles; they are immature germ cells and are called ‘spermatogonia.’ These spermatogonia lie next to the basement membrane of the seminiferous tubules, and beginning at puberty, they divide mitotically so having the normal 2 pairs of 22 chromosomes, plus x and y (46) (Figure 35.3). Spermatogonia will then undergo meiosis in two stages. In stage 1 (prophase), primary spermatocytes are formed each containing a duplicated set of 46 chromosomes, 22 pairs of duplicated chromosome plus duplicated x and y (92). The secondary spermatocytes are formed, containing a haploid number of duplicated chromosomes and a duplicated x or y. The second meiotic division then occurs stage 2, resulting in smaller cells containing a haploid number of unduplicated chromosomes; these are called ‘spermatids’ and form the inner layer of the epithelium of the seminiferous tubules [18].

Spermatids convert into spermatozoa by spermatogenesis. Spermatogenesis takes approximately 74 days. The production rate is approximately 6.5 million sperm per testicular gram per day in a 20-year-old male, decreasing to 3.8 million per gram per day for 50–90-year-old men [18].

Sertoli cells are the support or ‘nurse’ cells of the spermatids. Sertoli cells form tight junctions forming the blood-testis barrier. The barrier separates the testicular interstitial blood from the lumen of the seminiferous tubules, thus creating an immuno-privileged site. The Sertoli cell permits entry of nutrient and chemical mediators to spermatids. The processes of the Sertoli cell surround the spermatids. As spermatogenesis progresses and spermatids transform they progressively move closer to the lumen of the seminiferous tubules to eventually lose all contact with the Sertoli cell and are released as spermatoza. The spermatoza at this point, however, are still immature and are not motile, and so travel passively assisted by flowing secretions and luminal epithelial ciliary action into a network of tubules that the seminiferous tubules open up into the rete testes and then to the epididymis via the efferent ductules. The spermatoza undergo maturation at the epididymis and are now motile able to fertilise. It takes 12–26 days from the release of spermatoza to the full maturity present in the ejaculate [18].

Expert Opinion

An understanding of the anatomy and physiology of the testicular structures allows for an understanding of both benign and malignant disease pathophysiology and is the first step in understanding their treatment. Furthermore, understanding the hypothalamic-pituitary-gonadal-axis and androgen production also allows for understanding of other disease such as prostate cancer and its various treatment modalities.

References

36

Testes Congenital and Childhood Anomalies
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Abstract
Congenital and acquired abnormalities and illnesses can have a lasting effect on children; therefore, an understanding of the conditions and their managements is the first step to ensuring patient safety and improved quality of life in adulthood. In this chapter, we will discuss the embryology, the congenital anomalies of the testis, the common conditions that present with painless scrotal swelling, and the acute scrotum.

Keywords anomalies of the testis; inguinoscrotal masses; scrotum

Key Points
- Congenital anomalies of the testis
  a) Anomalies of descent
  b) Anorchia/monorchism
  c) Polyorchism
- Inguino-scrotal masses
  a) Inguinal hernia or hydrocele
  b) Varicocele
- The acute scrotum
  a) Testicular torsion
  b) Torsion of the appendix testis/appendix epididymis
  c) Epididymo-orchitis
  d) Idiopathic scrotal oedema
  e) Trauma

36.1 Congenital Anomalies of the Testis

36.1.1 Embryology Review
Testicular embryology and descent depend on a complex interaction amongst endocrine, paracrine, growth, and mechanical factors.

Bipotential gonadal tissue located on the embryo’s genital ridge begins differentiation into a testis during weeks six and seven under the effects of the testis-determining SRY gene. Sertoli cells begin to produce müllerian inhibitory substance (MIS) soon thereafter, causing regression of müllerian duct structures. By week nine, Leydig cells produce testosterone and stimulate the development of wolffian structures, including the epididymis and vas deferens. In the third trimester, the testis descends through the inguinal canal into the scrotum.

There are two stages of testicular decent, each under the influence of specific genes and hormones.

The first stage takes place between the 8th and 15th weeks. The MIS and insulin-like factor 3 (Insl3) cause the development of the gubernaculum from the genitoinguinal ligament [1]. The contraction of the gubernaculum causes testicular descent. Foetal androgens also play a role by causing the regression of the cranial gonadal ligament.

The second stage of descent, the inguinoscrotal phase, takes place between the 25th and 35th gestational weeks. During this phase, the gubernaculum grows outside the inguinal region migrating to the scrotum. This stage is under androgen control and the calcitonin gene-related peptide (CGRP) gene in the
genitofemoral nerve and its neurotransmitters. At this time a fold of peritoneum (the processus vaginalis) adheres to the gubernaculum, which gives rise to a communication between the abdominal cavity and the scrotum, along which the testes descend [2]. Abnormalities in the first stage of descent are rare and result in an intra-abdominal testis, whereas the failures of the second stage are more common, resulting in inguinal and high scrotal testis.

36.1.2 Undescended Testis (Cryptorchidism)

36.1.2.1 Incidence
Undescended testis occurs in 0.7–5% of the term infant boys and in 30–45% of premature boys [2]. A spontaneous postnatal descent is observed in about 7% of the boys [3]. The majority of testes descend within the first 9–12 months. At age one year, the incidence of undescended testis is 1%, descent after one year is unlikely. Occurs bilaterally in 20–30% of cases [3, 4].

36.1.2.2 Classification
36.1.2.2.1 Nonpalpable Testis (20%)
A testis may be impalpable (Figure 36.1) because it is absent (10–20%) (monorchidism in unilateral cases), atrophic or rudimentary (20–30%), or because it is not accessible to palpation (50%) (intra-abdominal (40–50%), intra-inguinal (30–40%), or pre-scrotal (10–20%) testis) (Figure 36.2) [4]. Intra-abdominal impalpable testis are more commonly found close to the internal inguinal ring (Figure 36.3), other locations include near the kidneys, anterior abdominal wall, or retrovesical space. A testis may be in the groin but may still be impalpable either due to body habitus or due to the lack of cooperation of the child during examination. About 20% of them become palpable when examined under an anaesthetic.

36.1.2.2.2 Palpable Undescended Testis (80%)
Undescended Testis The testis is located along the path of normal descent and halted on its way down its normal descent into the scrotum (Figures 36.4 and 36.5). With palpation, it may or may not be manipulated into the scrotum. At times, it is difficult to differentiate a truly undescended testis from a retractile testis with strong cremasteric reflex.

36.1.2.2.3 Ectopic Testis
The testis is neither in the scrotum nor along the normal path of descent, the testis has gone off course guided there by an errant gubernaculum. Locations of ectopic testis:
1) In the fat of the abdominal wall above the external ring (the superficial inguinal ectopic pouch).
2) At the root of the penis.
36.1 Congenital Anomalies of the Testis

3) In the perineum near the midline.
4) ‘Crural’ in the fat of the thigh over the adductor muscles where it may form part of the so-called popliteal pterygium syndrome.
5) Crossed ectopia, where the testis from one side is found in the hemiscrotum on the other side.

However, the most frequent location is in the para-scrotal region. Ectopic testis will not descend and will need surgical treatment.

Testes located in the superficial inguinal pouch (Brown’s pouch) are no longer considered an ectopic location. This happens due to initial displacement of the gubernaculum [5].

36.1.2.2.4 Retractile Testis

The testis is found anywhere along its normal descent. Retractile testis is usually in the inguinal canal and can be brought down to the scrotum where it remains for an undefined period of time and may go up again with the overactive cremasteric reflex [4]. Squatting or crossed leg positions somehow impairs the reflex facilitating the testis to remain in the scrotum. This occurs between the ages of 1 and 14 years [6].

36.1.2.3 Ascending Testis

The descended testis retracts back to the inguinal canal, incidence 1–2%, occurring between seven to nine years.
of age. The cause is usually unknown, however, can be due to inadequate growth of the spermatic cord or a patent processus vaginalis [7]. Nearly 70% of the ascending testes are reported to spontaneously descend at puberty [8]. Orchidopexy is still required as the ascended testes undergo degenerative changes similar to those of undescended testes.

### 36.1.3 Aetiology

Normal testicular descent requires: [5, 9–12]

- Adequate function of the hypothalamic–hypophyseal–gonadal axis (i.e. hormones: androgens, human chorionic gonadotropin [HCG], luteinising hormone [LH], or MIS) and normal androgen receptors.
- The exposure to endocrine disruptors (pesticides, etc.) that can inhibit the synthesis of cholesterol and testosterone.

Abnormal testes or gubernaculum, or anatomical structural abnormalities (prune belly syndrome and the Beckwith–Wiedemann syndrome, that is, exophthalmos, macroglossia, gigantism, macrostoma, hemihypertrophy, hypoglycaemia, and multilobulated kidneys) can also lead to undescended testes.

Cryptorchidism is not associated with a specific gene; however, it is seen in many chromosomal anomalies and is present in several syndromes. There is also familial predisposition, with a 3.6 times risk of development if a close relative was affected [13].

Nongenetic risk factors can be maternal (e.g. advanced age, obesity, placental insufficiency, diabetes, and twin gestation), environmental (endocrine disruptors), or foetal (e.g. preterm baby, low birth weight or small for gestational age) [14, 15].

### 36.1.4 Pathophysiology

A scrotal testis has a lower temperature than the core body temperature (33°C instead of 35–37°C). An extrascrotal testis suffers biochemical and physiologic alterations and has an abnormal maturation [16]. Because of the higher temperature, undescended testes undergo degenerative changes to the cells, leading to abnormal spermatogenesis [4]. Biopsy of the undescended testis frequently shows a decreased number of germ cells and an absence of progression beyond the formation of spermatocytes in the testicular tubules. Interestingly, as if in compensation Leydig cells are abundant.

### 36.1.4.1 Fertility

As male fertility is dependent on the maturation of gonocytes to adult spermatocytes within the first three months of life, undescended testes will be unable to mature the cells, leading to a reduced fertility [17].

The estimated risk of infertility is about 30% for bilateral undescended testes and lower, but not normal (7% amongst control group) for unilateral cases. Because epididymal anomalies are commonly associated with cryptorchidism, it is likely that a small number of boys may be infertile subsequently because of epididymo-testicular dissociation, even if germ cell maturation is normal [18].

The paternity rate in unilateral undescended testis is 70–90%, reducing to 45–65% if bilateral. Fertility seems to improve if orchidopexy is done before two years of age. Untreated bilateral undescended testis shows 100% of patient have oligosperma and 75% have azoospermia. Although treated bilateral undescended testis that show 75% are still oligospermic, 40% azoospermic [4].

Microscopic degeneration changes are seen in testes of boys who have had orchidopexy done after two years of age and significantly less changes seen in those who had it at <2 years. Though more technically challenging, the ideal age is one year to reduce the degenerative changes.

### 36.1.4.2 Malignancy

The estimated risk of testicular cancer in a previously undescended testis is greater (two- to eightfold) than in the general population [7, 19, 20]. In addition to a 4% lifelong chance of cancer development with intra-abdominal testes. Most paediatric surgeons anticipate that orchidopexy in early infancy (<1 year of age) may avoid this [7]. Tumours may develop in the third or fourth decades of life, mainly seminomas.

### 36.1.4.3 Other

Undescended testes are at a higher risk of torsion, trauma, or can lead to indirect inguinal hernias due to the patent processus vaginalis. Cosmetic and social stigma of having one or not testis can cause a huge impact on the psychology, especially in adolescent years.

### 36.1.5 Diagnosis

History should include whether the testis was palpable at birth, any exposure to hormones during pregnancy, and genetic or hormonal disorder run in the family. Examination to establish if the testes is palpable, if in the inguinal region, can it be brought down. Examination of infants can be difficult and at times done with the baby on the mother’s lap and generous use of lubricants or soaps and careful advancement of the examining fingers along the inguinal canal to the pubis region, to milk the testes down to the scrotum. Examining ectopic locations for possible lumps, as well looking for features of disorder of sex development (DSD), such as genital ambiguity or scrotal hyperpigmentation.
In bilateral impalpable testes, it is important that karyotype is established and the presence of testosterone-producing testicular tissue be confirmed (with HCG stimulation test). In anorchia with a 46XY karyotype, LH and follicle-stimulating hormone (FSH) are elevated, testosterone and inhibin B are low and MIS is undetectable. In addition, genetic studies, ultrasonography, or magnetic resonance imaging (MRI) for looking for müllerian structures in cases of DSD suspicion [21, 22]. However, most proceed to an examination under anaesthesia with or without laparoscopy with and out look to treat during surgery [23].

36.1.6 Treatment

The objectives of treatment is to improve fertility [24, 25], prevent malignant transformation [26], and allow an easy examination for early diagnosis of malignancy.

Retractile testes require no treatment, but the child should be examined annually because they have a risk greater than 30% of becoming ascending testes [6].

36.1.6.1 Hormonal Treatment

Use of HCG or gonadotropin-releasing hormone (GnRH) to stimulate testicular descent with a claimed success rate of about 20% [4, 27]. However, there is not sufficient evidence for a beneficial effect of hormonal therapy before or after surgery [27–32].

Therefore, hormonal treatment is not usually used, however, considered on an individual basis [32].

The Nordic consensus group [33] unanimously concluded that surgery was preferred to hormonal treatment on the basis that:

- the success rate of hormonal treatment is much lower than this of surgery [32].
- treatment with HCG may also have adverse effects, such as accelerated germ cell losses impairing future spermatogenesis [33], aggressive behaviour, penis enlargement, and pubic hair growth during administration [32].

36.1.6.2 Surgical Treatment

The recommended age for orchidopexy is between 6 and 12 months, hoping to improve fertility [7, 8, 25, 26, 34–36].

The operation varies depending on whether the testis is palpable or not.

Palpable testes are approached through a classical inguinal incision or a high scrotal incision (Bianchi approach). Unilateral nonpalpable testes are first examined under anaesthesia with or without diagnostic laparoscopy with or without proceeding to treatment [37]. Preoperative imaging in any form is inaccurate and not recommended due to false-positives and -negatives [22].

In bilateral nonpalpable testes, preoperative hormonal studies and karyotype are mandatory [23, 38].

In palpable testes, the operation normally includes different steps.

36.1.6.2.1 Orchidopexy

The incision is in the crease of the groin, centered over the mid-inguinal point (Figure 36.6). Slit up the external oblique muscle taking care of the genitofemoral nerve. Separate the cremaster muscle fibres to expose the internal spermatic fascia which is deliberately incised to reveal the processus vaginalis, which usually envelopes the cord (Figure 36.7). It is carefully dissected from the cord; separating the peritoneum is the key to successful orchidopexy (Figure 36.8).

Further length may be gained by freeing the vessels as they lie in the retroperitoneal space by blind dissection using a wet swab. The tunica vaginalis is opened to inspect the testis and the testiculo-epididymal junction and to remove testicular appendages.

Make a pocket for the mobilised testis between the skin and the dartos muscle in the scrotum (Figures 36.9 and 36.10). This pocket should be large enough to receive the testis. A buttonhole is made in the dartos to allow the testicle to be brought through and fixed in a subdartos scrotal pouch [39].

Figure 36.6 Crease incision for orchidopexy.
Figure 36.7 The cremaster is split along its fibres revealing the processus vaginalis.

Figure 36.8 (a) The sac is dissected off the cord. (b) The sac is retracted, and (c) the crescentic fibrous bands that connect the peritoneum and the cord are divided to give length to the testicular vessels.
For impalpable testis, the groin is carefully palpated once the child is under anaesthesia. If, at this point, the testis is palpable, inguinal orchidopexy is the procedure of choice. If not, laparoscopy is performed [18, 23, 37, 40–43]. The three likely findings in laparoscopy are:

- Blind ending vas and vessels short of the internal inguinal ring (vanishing testis).
  In this scenario, nothing further is required. Contralateral fixation orchidopexy can be carried out because torsion could have been the cause of the contralateral testes ‘vanishing’.
- Cord structures entering the inguinal ring. Inguinal exploration is carried out, and if a viable testis is found, the testis is relocated to the scrotum. If a remnant nubbin is found, it is excised, to remove the nidus of germ cells and prevent the occurrence of malignancy later.
- A viable intraabdominal testis. The limiting factor to relocate intra-abdominal testis to the scrotum is the length of the gonadal vessels. The testis is supplied by three main arteries: the main testicular, the vassal, and the cremasteric arteries. The decision to perform either a single-stage orchidopexy [37] or a two-staged (Fowler-Stephens) laparoscopic orchidopexy must be made before any extensive dissection. If the testis is within 2 cm of the deep ring and in cases of peeping testis single stage laparoscopic orchidopexy without division of vessels may be undertaken [37]. In the two-staged approach, the testis is treated by laparoscopic ligation of the main testicular vessels, giving extra length, with the testis relying on the vassal and collateral vessels for blood supply (Figure 36.11). The second-stage orchidopexy is performed six months later.

Using microsurgical techniques, it is possible to anastomose the testicular artery to the inferior epigastric with preservation of viability in the testicle: an exercise that is not pointless when both testes are undescended [40].

The postoperative recovery is rapid, with return to full activity within a few days.

The most common complications are wound infection or haematoma, both of which can be minimised by careful haemostasis at operation. Other complications include injury of the vasa deferens, the spermatic vessels, and rarely, the testis.

The boys are reviewed again at 6–12 months to ensure testis is viable and in the scrotum. The risk for testicular atrophy is 1%.

There is a small risk of retraction of the testis, which may require redo-orchidopexy [44, 45].

36.1.7 Agenesis or Absence of the Testis

If the entire urogenital ridge fails to develop, there is no kidney, ureter, testis or vas deferens on one side.

Aplasia may be limited to the gonadal ridge, in which case the kidney and ureter develop, but there is no vas deferens, epididymis, or testis (Figure 36.12). If the müllerian duct inhibiting factor fails to be secreted by the Sertoli cells, then the male child has fallopian tubes and uterus, with a gonad of indeterminate kind, often presenting in a hernia [2].

Anorchia is an XY disorder of sex development in which individuals have both testes absent at birth. Congenital anorchia is infrequent and rarely (<1%) occur bilaterally [4]. Unilateral anorchia or monorchidism is more common. Vascular accidents in gestation appear to be the major cause of anorchia; however, agenesis can also be the cause.

Bilateral anorchia is associated with changes in LH, FSH, and testosterone levels.

Once the diagnosis of bilateral anorchia is made, both sterility and the requirement for androgen-replacement therapy need to be considered.

For treatment, androgen-replacement therapy induces pubertal virilisation and maintains it in adult life.

Torsion and orchiectomy or failed orchidopexy for maldescent are the most common causes of acquired anorchia. Clinical evaluation and androgen-replacement therapy for acquired anorchia are as for congenital anorchia.

It is common to find a vas and an imperfectly formed epididymis but no testis, kidney, and ureter being present. In such cases, the testicle may have undergone torsion in utero.

When the testis is present, the vas deferens may be partly or completely absent from one or both sides. There is a wide variety of such defects, causing obstructive azoospermia. They are often seen in...
Figure 36.10  (a) A pocket is made for the testicle by dissecting between the dartos and skin of the scrotum. (b) The testicle is brought through a buttonhole in the dartos. (c) The skin is closed with sutures that just catch the tunica albuginea testis.

Figure 36.11  Laparoscopic division of the testicular artery as the first stage of the Fowler–Stephens manoeuvre.
association with undescended testes and represent errors in the union of the gonad with the wolffian duct (Figure 36.13) [19, 20].

36.1.8 Polyorchism

Duplication of the testis on one or both sides is so rare, that it calls for exploration to rule out cancer [46–49]. Equally rare is the duplication of the vas deferens with a single testis. This can cause failure of the vasectomy if the surgeon fails to notice the additional vas [50].

36.2 Inguinoscrotal Masses

36.2.1 Embryology Review

The processus vaginalis is present in the developing foetus at 12 weeks of gestation. The processus is a peritoneal diverticulum that extends through the internal inguinal ring. As the testis descends, a portion of the processus attaches to the testis as it exits the abdomen and is dragged into the scrotum with the testis. The portion of peritoneum (processus) enveloping the testis becomes the tunica vaginalis. The remainder of the processus within the inguinal canal eventually obliterates. In a significant number of individuals, the processus vaginalis remains asymptomatically patent. A patent processus is only a potential hernia and becomes an actual hernia only when bowel or other intra-abdominal contents exit the peritoneal cavity into it. Thus, the vast majority of childhood hernias are indirect.

Hydrocele develops if the patency enables passage of only intra-abdominal fluid. Hydroceles can be categorised into communicating and noncommunicating types.

36.2.2 Indirect Inguinal Hernia and Hydrocele

Indirect inguinal hernias occur when abdominal contents protrude through the deep inguinal ring, lateral to...
the inferior epigastric vessels, due to failure of closure of the processus vaginalis (Figure 36.14). The incidence of indirect inguinal hernias approximates 1–5% of all children, with a male predominance (~7:1). About 60% is right-sided, 30% is left-sided, and 10% is bilateral [51].

The risk factors include prematurity (16–25%), previous abdominal wall repair (i.e. exomphalos, extrophy, and gastroschisis), increased intra-abdominal fluid (i.e. ascites and ventriculoperitoneal shunt), chronic cough, and cystic fibrosis.
Hydrocele is a collection of fluid between the two layers of the tunica vaginalis (i.e. the parietal and visceral layers). The process vaginalis normally obliterates, however if remains patent, leads to a primary hydrocele with communication with the abdominal cavity (i.e. a communicating hydrocele). This can lead to collection of fluid or even bowel content. It remains patent in about 80–90% of newborns; however, only 20% will have it patent by adulthood [4].

With a noncommunicating hydrocele, the process vaginalis partly closed, leading to hydrocele of the cord (a saccular swelling of just the cord) or a scrotal hydrocele.

### 36.2.2.1 Clinical Presentation

The child with a hydrocele is in a good condition. An elastic, painless swelling is palpable in the scrotum, extending eventually up to the groin. Intermittent filling is usually described by the parents. The differential diagnosis with hernia is facilitated by trans-illumination.

The child with hernia may present with an inguinal bulge or enlarged scrotum (or labia). Inguinal asymmetry and thickening of the spermatic cord (silk glove sign) might be found.

The principal symptom of incarceration of bowel containing hernias is pain (Figure 36.15). A tender, firm mass is palpated in the groin. Initially the abdominal findings are normal; however, with the development of mechanical obstruction, ileus and lethargy appear.

Testicular tumours will present as a painless hard mass, though a few might present with pain (Figures 36.16 and 36.17).
36.2.2.2 Management
Noncommunicating hydroceles, whose size over time remains constant, tend to resolve spontaneously in the first year of life. If a hydrocele persists beyond two to three years of age or is symptomatic, surgical repair is indicated.

Both hydroceles and hernias are approached through a small inguinal incision. The subcutaneous fat and fascia of Scarpa are opened. The external oblique aponeurosis and external ring are exposed. The patent processus vaginalis (PPV) is separated from the vas deferens and the spermatic vessels. The PPV is then ligated and divided.
In the case of a hydrocele, the distal part of the sac is widely slit, allowing adequate drainage of the fluid.
In girls, the operation is even more straightforward because there is no risk for the vas or the vessels.
In the last years, the laparoscopic hernia repair has been preferred because it offers the ability to visualise the contralateral side and to minimise the risk of injury to the vas deferens [52].

36.2.3 Varicocele
Varicocele is an abnormal dilatation of the pampiniform plexus, caused by reno-testicular reflux, which leads to venous stasis.
It can be classified as primary, due to venous insufficiency, or secondary, caused by obstruction of the spermatic vein by a retroperitoneal mass or the thrombosis of the left renal vein or vena cava.
About 90% of varicoceles are left sided. This is suggested to arise from the different mode of entry of the right and left testicular vein into the vena cava or left renal vein. The right junction is acute, whereas the left junction is at 90°. The ‘nutcracker phenomenon’ is another theory, according to which, the left renal vein is compressed between the superior mesenteric artery and the aorta.
Varicocele is associated with male subfertility, causing decreased sperm motility [53].
The mechanisms by which it affects spermatogenesis are hypothesised to be the increased scrotal temperature caused by the venous stasis, as well as the reflux of adrenal catecholamines from the left spermatic vein.

36.2.3.1 Clinical Presentation
Usually asymptomatic, varicoceles are found on routine physical examinations in pubertal boys. Occasionally they are noticed by the patient or cause discomfort and diffuse scrotal pain.
Varicoceles are categorised as:
Stage 0: subclinical detected only on ultrasound
Stage I: palpable only on Valsalva.
Stage II: palpable without Valsalva and not visible at rest.
Stage III: palpable and visible at rest.

36.2.3.2 Diagnosis
The diagnosis of varicocele is usually established by physical examination with the classical description of a ‘bag of worms’ (Figure 36.18). The boys must be examined in both standing and supine position with the Valsalva manoeuvre.
The size of the testicles must be documented.
A scrotal ultrasound confirms the diagnosis and an abdominal ultrasound is necessary to exclude renal pathology or vascular abnormality.

36.2.3.3 Treatment
Surgical treatment aims to prevent testicular damage and possibly infertility or subfertility.
The surgical principle is to occlude the venous drainage. Different surgical methods are available; the most popular of which has been described by Palomo (high retroperitoneal ligation by an open surgical or a transperitoneal laparoscopic approach) and Ivanissevich (ligation within the inguinal canal) [54]. The antegrade scrotal sclerotherapy has also been described [55].

The ligation of the testicular artery decreases the recurrence rate but is associated with a 5% risk of testicular atrophy and a 5% risk of hydrocele due to ligation of the associated lymphatics [54, 56, 57].

36.3 The Acute Scrotum

The acute scrotum refers to the common clinical scenario of a boy seen with pain in the scrotum, normally accompanied by swelling and redness of the overlying skin (Figure 36.19). An emergency differential diagnosis is required to manage properly and prevent irreversible changes.

The differential diagnosis of the acute scrotum is divided between those affecting the content and those affecting the wall of the scrotum (Table 36.1).

### Table 36.1 Differential diagnosis of an acute scrotum.

#### Conditions affecting the content of the scrotum
- Testicular torsion
- Torsion of the appendix testis or appendix epididymis
- Epididymitis or orchitis
- Trauma
- Hernia or hydrocele
- Tumour

#### Conditions affecting the wall of the scrotum
- Trauma
- Idiopathic scrotal oedema
- Henoch-Schönlein Purpura
- Fournier gangrene

36.3.1 Testicular Torsion

Torsion of the spermatic cord is a surgical emergency with two anatomical types: extravaginal, where the twist is outside the tunica vaginalis and is found in neonates (Figure 36.20), and intravaginal, where the twist is within the tunica vaginalis due to the bell-clapper deformity. It is important to recognise that the bell-clapper malformation...
is usually bilateral and therefore both sides may be at risk. Intravaginal testicular torsion can occur at any age but is more common in peri-pubertal boys.

36.3.1.1 Presentation
Outside the neonatal period, the testicular torsion is an acutely painful event. The testis might be at higher position with an abnormal position (horizontal) as compared to contralateral side and normally the cremasteric reflex is absent. Elevation of the testis reduces pain in epididymitis, but has no effect or even increases in torsion. With passage of time the swelling and the inflammation increases and if not corrected quickly the testis might be lost.

36.3.1.2 Diagnosis
Typically, the diagnosis is clinically established by the history and clinical presentation. No investigation is 100% specific and sensitive to diagnose testicular torsion. Moreover, the urgency of the situation is such, that the surgical exploration and eventual detorsion should not be delayed or postponed. Colour Doppler examination can be helpful to confirm the diagnosis when doubt exists; however, presence of blood flow does not exclude the torsion and may be associated with low blood flow at an early stage or intermittent torsion.

36.3.1.3 Treatment
History and clinical findings that do not exclude testicular torsion should lead to urgent surgical exploration. Manual detorsion can be attempted by an outwards rotation of the testis, unless there is increased pain or resistance [4]. However, surgical exploration is the gold standard. Once the testis is untwisted, then its colour must be observed, to see whether any recovery is likely (Figure 36.21). You may find even dark testis can slowly recover. If the testis recovers, it should be fixed in the scrotum with nonabsorbable sutures. In case of doubtful recovery, a small incision can be made in the tunica albuginea to see if it bleeds. Necrotic testes should be removed. It is important to explore the contralateral side and fix the testis as well.

The recovery is rapid; however, the patients must be followed up to ensure that atrophy of the affected testis does not occur and that testicular growth is maintained.

36.3.1.4 Outcome
It has been shown that testicular torsion of longer than six hours is unlikely to be accompanied by testicular recovery. Testicular atrophy occurs after four hours of the cessation of the blood supply, which leads to breaking of the blood-testes barriers, leading to an immune response to the testicular cells [4]. After six hours of ischaemia, changes are seen in the contralateral testis. The exact mechanism is unknown. It is thought to be the result of an autoimmune-mediated injury of the contralateral testis [58].

The long-term outcome of torsion on fertility is variable with 20–50% of patients having abnormal spermatogenesis [4]. Early detorsion (<13 hours) can preserve fertility, while delayed (>3 days) detorsion with or without orchiectomy, can significantly jeopardise fertility [4, 58].
Testicular atrophy after torsion can be related to the direct ischaemic injury or even after detorsion by postischaemic reperfusion injury. Anti-inflammatory medication and ice packs can reduce this. There seems to be no effect on endocrine function after torsion with hormonal levels remaining within normal range [4].

36.3.2 Perinatal Testicular Torsion

The torsion of the testis in a newborn is usually seen as a firm scrotal mass. It is an extravaginal torsion and happens before firm fixation of the tunica vaginalis to the scrotal wall occurs. The ultrasound may show a nonhomogenous texture of the testicle and fluid collection in the tunica. The colour Doppler ultrasound confirms the absence of blood flow to the affected testis, which makes the decision favour excision rather than salvation the testis.

Testicular tumour should be kept in mind when facing nontender scrotal masses [59].

36.3.3 Torsion of the Appendix Testis or Appendix Epididymis

The appendix of the testis is a remnant of the müllerian duct and is located on the upper pole of the testis. The appendix of the epididymis originates from the wolffian duct and is situated on the head of the epididymis. The appendices have a thin vascular pedicle that is prone to torsion.

The torsion of the testicular appendix is the most common cause of the acute scrotum. The common age group for presentation of this condition is 7–10 years.

36.3.3.1 Presentation

The onset of pain is gradual but can occasionally be accompanied by nausea and vomiting. Modest tenderness of the scrotum during physical activity is the most common symptom.

During physical examination, a round tender mass might be distinguished at the upper pole of the testis. In up to 25% of patients, the ‘blue-dot’ sign can be seen (i.e. the appreciation of the discoloured testicular appendix through the scrotal skin) (Figure 36.22) [4].

36.3.3.2 Diagnosis

The scrotal ultrasound shows a cystic lesion at the upper pole of the testis, an enlarged head of epididymis, and reactive hydrocele. The perfusion of the testicular parenchyma is preserved. The urine dipstick is normal.

36.3.3.3 Treatment

The treatment is symptomatic control (nonsteroid anti-inflammatory drugs and rest). The pain and redness disappear within a few days. If a testicular torsion cannot be excluded at initial examination, a scrotal exploration and excision of the torted hydatid has to be performed urgently.

36.3.4 Epididymitis, Orchitis, and Epididymo-Orchitis

These infections are a rare condition in children (0.1%) [4]. Possible aetiology is haematogenous viral infection, chemical inflammation due to intravesal reflux of urine in dysfunctional voiding, or in ectopic ureter opening into the vas. Rare bacterial epididymitis is a consequence of canalicular spreading of a urinary tract infection in urethral stricture, urethral anomaly, or ectopic megaureter. In adolescence, the incidence of infection is increasing due to sexually transmitted diseases (mostly chlamydia). Mumps orchitis can be associated with orchitis. Rarely seen in prepubertal boys, but can occur in 15–30% of adolescents, usually four to eight days after the parotitis.

Infections can cause a reduced testicular size in 50% of prepubertal patients, and abnormalities in semen analysis in about 25% (mainly due to pressure necrosis).

36.3.4.1 Presentation

Gradually increasing tenderness, swelling, erythema of the scrotum, and general signs of inflammation bring the patient to the doctor. The cremasteric reflex is active. Fever and systemic symptoms occur infrequently, (<20% of patients) [4].
36.3.4.2 Diagnosis
The ultrasound shows swollen epididymis with increased blood perfusion. Reactive hydrocele is a usual accompanying finding.

Urine analysis is necessary to exclude or diagnose a bacterial condition. In adolescents who are sexually active, the microbiological investigations are done to appropriately workup for chlamydia and ureoplasma.

36.3.4.3 Treatment
If a testicular torsion cannot be excluded at initial examination, a scrotal exploration and has to be performed urgently.

Broad-spectrum antibiotics should be administered until the urine culture and sensitivities are reported, and then they should be corrected accordingly.

In case of recurrent presentation, an ultrasound of the kidneys and bladder should be performed.

36.3.5 Idiopathic Scrotal Oedema
The aetiology of the idiopathic scrotal oedema (ISE) is unknown. The onset is sudden and begins with swelling in either the perineum or the inguinal region, which spreads into the scrotum. The scrotal wall is thick, with firm oedema. It usually affects boys between five and nine years of age. The key distinguishable symptom between ISE and an acute scrotum is pain. ISE is painless, whereas an acute scrotum is painful.

The examination reveals a nontender testis and discomfort in the scrotum. Management is conservative with nonsteroid anti-inflammatory drugs.

36.3.6 Testicular Trauma
Open injuries and lacerations are frequent in active boys. Boys affected by testicular trauma usually have an acutely painful and swollen testis together with swelling and bruising of the scrotum. Scrotal ultrasound may reveal a haematocele, intratesticular haematoma, or rupture of the tunica albuginea.

Testicular contusion with a small haematoma is treated conservatively. Laceration of the tunica albuginea, larger haematoma, or haematocele must be surgically revised.

References

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Testes Trauma and Inflammation

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Abstract

Scrotal pathology is commonly encountered by the urologist. Problems range from acute presentations due to trauma, torsion, or acute infection to chronic inflammatory conditions with chronic pain which can be difficult to manage. This chapter addresses the management of testicular trauma and inflammatory conditions relating to the testis.

Various types of testicular trauma including testicular rupture, haematoceles, testicular dislocation, and cord disruption are reviewed. The role of radiological imaging is explored along with treatment strategies.

The second half of this chapter is dedicated to reviewing acute and chronic inflammatory conditions affecting the testis. Investigations and treatment of acute bacterial and viral orchitis are examined, as well as complications thereof. The different types of chronic inflammatory conditions are reviewed, as are the range of conservative, medical, and surgical treatments which will provide the clinician with a strategy for these difficult conditions.

Keywords testis; trauma; infection; inflammation; orchitis; epididymitis

Key Points

- Scrotal trauma accounts for nearly 85% of testicular injuries.
- Ultrasound provides a useful tool for assessing testicular trauma and should be considered an extension of clinical examination.
- Disruption of the tunica albuginea (i.e. testicular rupture) should be surgically explored early to improve the chances of testicular salvage.
- Haematoceles consist of bleeding confined to the tunica vaginalis. Large and tense haematoceles often necessitate early exploration.
- Epididymo-orchitis usually begins in the epididymal tail, spreading along the epididymis and into the testis. The source of infection is primarily urethral but can also be haematogenic.
- The most common causes are sexually transmitted organisms such as chlamydia or gonorrhoea in men younger than 35 years old; whereas in older patients, it is usually due to common urinary pathogens such as Escherichia coli.
- Mumps and other viruses can cause an acute orchitis, which can be bilateral. Treatment is essential; viral infections are usually self-limiting.
- Chronic epididymitis is poorly understood and may be infectious, inflammatory, or obstructive, with many cases having no identifiable cause noted. Medical treatment of the chronic pain has variable success, with surgery reserved for more debilitating cases.
37.1 Testicular Trauma

Scrotal trauma may either be blunt or penetrating. Blunt injuries arise from direct blows or straddle injuries and account for nearly 85% of testicular injuries [1]. Penetrating trauma is less common and includes stab wounds or gunshot injuries.

When considering blunt scrotal trauma, it is important to appreciate the mechanism and force of injury and to consider the risk of collateral damage. The testis can withstand approximately 50 kg of blunt trauma before the tunica albuginea ruptures [2]. If the injury is sustained with a fall astride pattern, the urethra can also be injured.

Typically, blunt scrotal traumas are unilateral injuries. Conversely, penetrating injuries are more likely to be bilateral, especially when related to gunshot wounds (i.e. bilateral damage in approximately 1% after blunt injury, compared to 30% with penetrating injuries). Gunshot wounds from low-velocity handguns (up to 300 m/s) cause less trauma than high-velocity rifles (up to 1000 m/s). It is important to appreciate that the blast effect may cause more tissue damage than is evident initially, and such wounds will often be contaminated with debris.

Depending on the severity, there are varying manifestations from trauma, including subcutaneous haematoma, hydrocele, haematocoele, testicular dislocation, fracture, or rupture. Trauma-induced testicular torsion is also a well-recognised entity, with a reported incidence of 4–8% in most studies [3]. Scrotal trauma may also result in injury to the epididymis including contusion, haematoma, rupture or fracture, whilst injuries to the spermatic cord can involve damage or transection of the vas deferens and vascular structures.

Presentation is invariably with acute pain, usually with significant scrotal swelling and visible bruising. Delayed presentations may be further complicated with local or systemic signs of infection. Marked scrotal swelling can make accurate clinical assessment of the scrotum difficult, and ultrasound should be used as the first-line investigation.

37.1.1 Investigations

Ultrasound should be considered an extension of the clinical assessment of the scrotum [4]. It can be effectively used to assess the integrity and vascularity of the testes and can distinguish testis rupture from other injuries such as haematocoele, hydrocele, torsion, and epididymal injury.

The seminiferous tubules have a homogenous appearance on ultrasound and alteration of the normal uniform echo pattern to reveal heterogeneity in the echotexture of the testis following trauma suggests testicular rupture or intratesticular haematoma [5]. Disruption in integrity of the tunica albuginea is highly suspicious of a testicular rupture [6].

Ultrasound has been reported as having a specificity of 75–98% and sensitivity of 64% for detecting testicular rupture following trauma [1, 7].

Magnetic resonance imaging (MRI) may be useful in equivocal cases of rupture, but due to expense and length of time required to perform the examination, it is not widely used [8].

37.1.2 Management

37.1.2.1 Testicular Rupture

Testicular rupture is said to have occurred when the tunica albuginea is disrupted. Therefore, surgical exploration should be undertaken in all cases of testicular rupture [9]. Early exploration can improve testicular salvage when exploration is conducted within 72 hours of trauma [1, 10]. Patients must be warned of the possible need for orchidectomy if the testis cannot be salvaged.

Conservative management of significant blunt scrotal trauma is associated with greater risk of infection, testicular atrophy, and orchietomy.

The principles of surgery are to evacuate any haematoma, debride any extruded and nonviable semi-niferous tubules, and close the tunica albuginea (Figure 37.1). Any testicular tissue, which is potentially viable, should be salvaged if at all possible for endocrine function as well as for psychological reasons. Postoperatively, a drain is left in situ for the first 24 hours and broad-spectrum antibiotics given. The patient should be managed with a scrotal support in the immediate postoperative period.

In cases where the tunica albuginea cannot be easily closed without tension, but the seminiferous tubules look viable, a vascularised tunica vaginalis flap can be used to close over the tunica albuginea defect in a double-breasted manner [11]. It is important not to close the tunical albuginea in a situation where the underlying tubules will be under pressure, which will result in testicular damage with subsequent tubular dysfunction.

37.1.2.2 Haematocoele

A haematocoele is bleeding confined to the tunica vaginalis, whereas in haematomas, the blood extends beyond the tunica vaginalis and extrudes into the layers of the scrotum. A haematocoele may accompany testicular rupture.

Large and tense haematocoeles often necessitate early exploration due to the significant pain and discomfort, and more importantly the testes may be under high pressure leading to ischaemia, necrosis, and testicular atrophy. Exploration allows evacuation of the clot, relieving symptoms of pain and risk of infection. Conservative
management of smaller, stable scrotal haematomas, hydroceles, and contusions is achieved with ice, rest, and elevation [9].

37.1.2.3 Testicular Dislocation
Testicular dislocation is rare, and the testis may be found in the inguinal canal or abdominal cavity. This may be repositioned manually primarily and will require subsequent orchidopexy.

37.1.2.4 Cord Disruption
In cases of cord disruption seen with penetrating injuries, the testis may be salvaged with cord realignment if detected early. The primary realignment should aim to re-establish the vascular supply microsurgically. A subsequent staged microsurgical vaso-vasostomy can be performed at a later date if the testis remains viable and functional.

37.2 Inflammatory Diseases of the Testicle

37.2.1 Acute Inflammation
Inflammation of the testicle may involve the testis, epididymis, or both. Most inflammation of the epididymis will eventually involve the testis. The epididymis is relatively soft and when inflamed it expands to form a tender mass behind the testis. The rigid tunica albuginea cannot expand, and the increased pressure inside the tunica may cause ischaemia of the testis. Inflammation in either testis or epididymis will lead to a secondary hydrocele as is seen with free fluid in the peritoneal cavity from peritonitis.

37.2.1.1 Viral Orchitis
Mumps and other viruses can cause an acute orchitis, which is sometimes bilateral. Worldwide, 290 cases per year per 100,000 population were diagnosed between 1977 and 1985 [12]. There has been a dramatic reduction in the incidence of mumps since the introduction of the measles-mumps-rubella (MMR) vaccine. Recently there has been an increase in the incidence of mumps [13], mainly in adolescents; this has occurred for two reasons: 20 years ago there was a shortage of the MMR vaccine and a measles-rubella vaccine was used instead, and there were links between the MMR vaccine and autism spectrum disorders, which caused a reduction in the uptake of the MMR vaccine. Subsequent reviews have shown that no such link exists [14].

Mumps usually present with a prodromal illness associated with unilateral or bilateral parotid swelling. Mumps orchitis is the most common complication in adolescent pubertal males, and testicular swelling occurs 10 days after the onset of parotitis. It occurs in 15–40% cases, and it can be unilateral or bilateral.

Diagnosis is usually made on history of exposure, although real-time polymerase chain reaction (RT-PCR) is a good sensitive diagnostic technique [15]. Virus-specific IgM antibody can be measured using direct or indirect enzyme-linked immunosorbent assay (ELISA) techniques, though the sensitivity is variable [13]. Generally, most cases are diagnosed with normal white blood cell count, raised C-reactive protein, negative urine analysis, and midstream urine sample. Ultrasound shows diffuse hypervascularity and enlargement of the testes and epididymis.

Treatment is essentially supportive because the mumps virus is usually self-limiting. Supportive measures include bed rest, scrotal support, and analgesia and anti-inflammatory drugs. The role of steroids has been controversial. While effective at reducing pain and swelling, its role in preserving fertility is uncertain. Likewise, mixed reports exist on the benefit of interferon-α2B in such cases [16]. Complete infertility is a rare complication, but subfertility occurs in an estimated 13% of patients. In cases where azoospermia does develop, sperm may still be retrieved microsurgically for...
use in assisted conception. Testicular atrophy can occur in up to 30–50% of affected testes [17].

Many other viruses can also cause acute viral orchitis: Coxsackie [18], infectious mononucleosis [19], hepatitis B [20], herpes virus 2 [21], bat salivary gland virus, and dengue [22].

37.2.1.2 Bacterial Epididymo-orchitis / Orchitis

Epididymo-orchitis is inflammation of both the epididymis and testes. Infection usually begins in the epididymal tail, before spreading to the rest of the epididymis and into the testis. It is usually unilateral, but in cases of severe infection may become bilateral. The source of infection is primarily urethral but can also be haematogenic.

The majority of cases in sexually active males younger than 35 years of age are due to sexually transmitted infections (STIs) such as chlamydia (more commonly) or gonorrhoea. In older patients, it is usually due to common urinary pathogens such as Escherichia Coli and can arise as a complication of urethral instrumentation or catheterisation or as a result of prostatic obstruction complications [23, 24]. Acute epididymitis was so common after urological operations that 50 years ago vasectomy was always performed before prostatectomy. This has generally been replaced by using effective antibiotic prophylaxis. However, a ‘chemical epididymitis’ is still reported after selected endoscopic cases such as transurethral resection of the ejaculatory duct (TURED), due to reflux of noninfected urine through the urethra into the open resected ejaculatory ducts of the prostate [25, 26]. Bacterial orchitis can also occur from haematogenous spread, where it forms a lump, which may resemble a tumour.

In certain cases of bacterial epididymo-orchitis due to a urinary pathogen, urological investigations may be required to exclude any anatomical or functional abnormality. In such cases, a flow rate, postvoid residual ultrasound, and cystoscopy may prove useful.

37.2.2 Clinical Features

Characteristically patients present with rapid onset scrotal pain, which is usually unilateral. There may be symptoms of urethral discharge, urinary tract infection (UTI), or prior history of bacteriuria. At first there is a painful swelling, involving the epididymis, but development of a secondary hydrocele, erythema, and oedema of the scrotum and extreme tenderness can make it impossible to distinguish testis from epididymis. In severe cases, the changes may be bilateral and associated with local abscess formation, especially in those who are more susceptible to infection (patients with diabetes or are immunocompromised or elderly). Patients may also describe fever, shivers, or rigours, depending on severity.

37.2.3 Investigations

The primary aim is to isolate the infective cause to confirm the diagnosis and to guide antibiotic therapy. A midstream urine sample should be sent for microscopy and culture. In those who are sexually active, a urethral swab should be taken. Gram staining of a urethral smear (≥ 5 polymorphonuclear leucocytes [PMNLs] per high power field × 1000) or Gram-stained preparation from a centrifuged sample of first passed urine (FPU) (≥ 10 PMNLs per high power field × 1000) should be performed. The presence of gram-negative intracellular diplococci suggests Neisseria gonorrhoea. A urethral swab should be sent for N. gonorrhoeae culture and FPU or urethral swab for nucleic acid amplification test (NAAT) for N. gonorrhoeae and Chlamydia trachomatis [27, 28]. It is important that the urethral swab is not taken within two hours of passing urine because this can decrease the sensitivity of the test. Patients with an infection suspicious of a STI should be screened in a sexual health clinic to exclude any other concurrent sexual health infection and have contact tracing.

Additional investigations should include a Doppler ultrasound to confirm the presence of inflammatory changes in the epididymis and testis. Blood tests to confirm a raised white cell count and inflammatory markers (i.e. C-reactive protein) are useful. In cases of systemic infection, a blood culture should also be performed.

37.2.4 Differential Diagnosis

37.2.4.1 Testicular Torsion

The key condition to differentiate in cases of acute testicular pain and swelling is testicular torsion. Torsion is a surgical emergency and rapid restoration of flow to the testis should happen within six hours to allow the best chance of testicular salvage [29]. Torsion is more common in young men (<20 years) but can occur at any age. A lack of definitive clinical findings often leads to misdiagnosis, with the most common incorrect diagnosis being epididymo-orchitis. Ultrasound and Doppler scanning are not completely reliable at excluding torsion and may miss torsions in cases of low-level twists (<360°), in children, and in cases of intermittent torsion. If torsion cannot be safely ruled out clinically, then scrotal exploration must be undertaken, and ultrasound should not delay intervention [30–33].

37.2.4.2 Idiopathic Scrotal Oedema

Acute idiopathic scrotal oedema may affect the scrotum [34, 35], particularly in young boys, and torsion must again be excluded. A similar appearance is seen in children with fat necrosis, giving rise to an inflammation of the scrotum, and if correctly diagnosed, can be treated conservatively [36].
Other differentials include trauma, testicular tumours, and torsion of the testicular appendage.

### 37.2.5 Treatment

Systemic antibiotic therapy is the mainstay of treatment and should be managed in conjunction with local microbiological advice. In men younger than 35 years of age, where a STI is the likely underlying cause, a fluoroquinolone such as ofloxacin combined with doxycycline will cover chlamydial and gonococcal infections.

In older men where the most likely pathogen is a gram-negative bacilli, with *E. coli* being the most common, then treatment again with a fluoroquinolone such as ofloxacin is the best first line due to its excellent testicular tissue penetration.

Treatment should continue for 14 days; bed rest and analgesia are suggested as required. Anti-inflammatories and a scrotal support can provide additional relief. Patients should be seen after two weeks to ensure an adequate response to treatment, and persistent changes with a failure to respond to the correct antibiotic regime raises the possibility of a tumour mimicking the initial presentation.

### 37.2.6 Complications

An abscess may form a fluctuating swelling which discharges pus. This will require urgent incision and drainage. Acute infection can also give rise to chronic pain, infertility, and testicular infarction. Infarction will require subsequent orchidectomy.

### 37.3 Chronic Inflammation

There is little written in the literature on chronic epididymitis, and the incidence and natural history of the disease are not truly known and poorly understood. Nickel proposed a definition for chronic epididymitis: 'symptoms of discomfort and/or pain at least three months in duration in the scrotum, testicle, or epididymis, localised to one or each epididymis on clinical examination' [37]. The aetiology of the condition is thought to be infectious, inflammatory, or obstructive, with many cases having no identifiable cause noted.

#### 37.3.1 Tuberculous Epididymitis

Tuberculous epididymitis may have a surprisingly acute onset and should also be considered in cases of acute epididymitis where no other bacterial pathogen is found. Tuberculous epididymitis can be the sole presentation of genitourinary tuberculosis.

The more common situation of urine-borne infection travels along the vas deferens to the cauda epididymis and can be difficult to diagnose in the absence of renal involvement [38]. Blood-borne tubercle bacilli may lodge in the caput epididymis to form a tuberculoma [39]. In either situation, there may be an acute inflammatory response, which is followed by a chronic phase in which the caseating tuberculoma of the epididymis forms a chain of bead-like swellings continuing up the vas and involving the seminal vesicle.

Tuberculous epididymitis may be seen in patients from countries where tuberculosis (TB) is prevalent, those who have had TB previously or are immunocompromised. Three early morning urine samples should be sent for acid-fast bacilli stained with Ziehl-Neelsen stain and cultured on Lowenstein-Jensen medium. Polymerase chain reaction of urine can also detect the bacterium.

#### 37.3.1.1 Complications

A small abscess may point to the skin of the scrotum and breakdown to form a sinus from which tubercle bacilli may be recovered. When there is no evidence of TB elsewhere in the urinary tract, the diagnosis is difficult and may require a biopsy.

Modern treatment for TB is effective with standard combination of anti-TB drug: isoniazid, rifampicin, ethambutol, and pyrazinamide. When only the epididymis is involved, it may be removed, but often the testicle is also involved, making an orchidectomy necessary.

#### 37.3.2 Granulomatous Epididymitis

In cases of recurrent epididymitis, when the source of infection is clearly from the urinary tract, it may help to stop the succession of attacks by dividing the vasa. Unfortunately, this is not always successful; even after vasectomy, the inflammation of the epididymis may grumble on and require epididymectomy.

In the postvasectomy setting, extravasation of spermatozoa into the epididymis can provoke a chronic granuloma with features suggestive of TB, probably because the acid-fast helmet of the spermatozoon – the galea capitis – is antigenically similar to the envelope of the tubercle bacillus [40]. Around these acid-fast particles, there are foreign body giant cells and macrophages but no caseation.

Granulomatous epididymitis has also been described following intravesical bacillus Calmette-Guérin therapy [41].

#### 37.3.3 Granulomatous Orchitis

The seminal granuloma is different from chronic granuloma in the testis, which follows repeated urinary infections. It forms a firm mass in the testicle, which cannot
be distinguished from cancer and requires orchidectomy. Histologically, there is chronic inflammatory tissue and fibrosis [42, 43].

37.3.4 Bilharzial Epididymitis

Chronic granulomatous inflammation of the vas and testicle can be caused by infection with Schistosoma. The vas deferens and seminal vesicles may be outlined in the plain abdominal X-ray with thin lines of calcification. Inflammation of the testis is complicated by vascular obstruction by the worms and ova leading to ischaemia as part of the pathological process [44]. The mass may be indistinguishable from a tumour [45–47]. Gonadal schistosomiasis is exceptionally rare but should be considered in areas where Schistosomiasis is endemic [48].

37.3.5 Candidial Epididymo-Orchitis

This can arise as a rare but reported consequence of candidal urine infection. Patients who are immuno-suppressed pare particularly at risk, as are those with indwelling catheters. Changes can be unilateral or bilateral and can develop over months. Such cases are may be complicated with local abscess formation, requiring drainage, or in advanced cases, orchidectomy. If detected early, patients may respond to oral anti-fungal medicines, such as fluconazole, for up to six weeks [49].

37.3.6 Malacoplakia

Malacoplakia is a chronic granuloma in which histiocytes contain specific calcified and laminated microspheres, the Michaelis–Guttmann bodies. In the testicle, it gives rise to a hard mass indistinguishable from cancer [50–52].

37.3.7 Actinomycosis

Actinomycosis of the testicle produces a complex of sinuses leading down to the chronically inflamed mass. The characteristic ‘sulphur grains’ formed by the fungal mycelia may help in the diagnosis of this exceptionally rare disease. The treatment is orchidectomy along with all the sinuses under tetracycline cover [53].

37.3.8 Brucellosis

Brucellosis is equally rare, except in the Middle East. Approximately 1 in 10 men with brucellosis may develop epididymo-orchitis. It forms a hard mass in the testicle, and only when the testicle has been removed on suspicion of cancer is the diagnosis questioned, and then confirmed by immunological tests [54–56].

37.3.9 Behçet’s Disease

Up to 6% of patients with Behçet disease have involvement of the epididymis [57].

37.3.10 Syphilis

Gumma of the testis was common during the nineteenth-century epidemic of syphilis and much was made of the clinical distinction between gumma and cancer. Syphilis has shown resurgence of late, and testicular gumma is still reported. It is impossible to distinguish from cancer, and as a consequence, it is often confirmed only after orchidectomy [58]. In a recent reported case, a patient presented with a penile and testicular gumma. Although the ultrasound was unable to exclude tumour, the patient was treated conservatively with four weeks of antibiotics due to the positive syphilis serology (doxycycline as penicillin allergic). He responded well and the follow-up scan showed complete resolution of the lesion by 10 months. This is the only reported case of conservative management of a testicular gumma [59].

37.3.11 Other Causes of Epididymo-Orchitis

These include coccidioidomycosis [60], cytomegalovirus [61] (after immunosuppression), sarcoidosis [62, 63], and filariasis, which causes acute inflammation at first before it goes on to elephantiasis of the scrotum and hydrocele with a chronic granuloma in the testicle. Perhaps the rarest of all causes of epididymitis is leprosy [64]. Drug-induced epididymitis (e.g. amiodarone) is also a well-recognised entity and cessation of the drug and switching to an alternative anti-arrhythmic medication is usually sufficient [65].

37.4 Treatment

37.4.1 Conservative Therapy

Reassuring patients is often the most important part of management. Armed with the knowledge that there is nothing sinister, patients are more able to manage their symptoms effectively. A scrotal support, simple analgesics, local heat therapies, and avoiding aggravating activities may also be helpful.

37.4.2 Medical Therapy

There is no clearly definitive method of treating chronic epididymitis. Symptomatic control of the ensuing pain and discomfort forms the mainstay of medical therapy. Strategies include anti-inflammatory agents, analgesics, narcotic analgesics, and injection therapy with steroid or anaesthetic in the form of cord blocks, all with
variable success. The poor response to such approaches often results in the need for a surgical approach by epididymectomy.

37.4.3 Surgical Therapy

37.4.3.1 Epididymectomy

Epididymectomy may have a role to play in carefully selected cases. This can be an effective strategy in the rare situation where inflammatory changes are solely localised to the epididymis.

The surgery is performed through a midline scrotal incision. The cord is identified and the vas traced down to the epididymis. The epididymis is separated at the hilum of the testis. Bipolar diathermy should be used to achieve haemostasis, with special care needed when dissecting at head of the epididymis. The blood supply to the epididymis comes from a small branch of the testicular artery near the caput epididymis (Figure 37.2). It is important to secure this vessel without injuring the main artery of the testis (Figure 37.3). By pulling the epididymal head laterally, the main testicular artery can be preserved.

There is limited clinical data with regards to epididymectomy, with most data available reporting on surgery for post vasectomy pain.

Mittemeyer’s study [24] showed that out of 89 patients identified with chronic or recurrent epididymitis, 61 patients underwent epididymectomy and eventually returned to active duty.

Davis et al. reported on 45 patients seen with chronic unilateral or bilateral orchialgia [66]. Orchidectomies were performed with the inguinal approach achieving 73% complete relief of pain and the scrotal route attaining 55% complete relief of pain. Epididymectomies were less successful with the majority of patients proceeding to have an orchidectomy. They concluded that inguinal orchietomy was the procedure of choice for the management of chronic testicular pain when conservative measures were unsuccessful.

However, post-vasectomy, chronic pain has been shown to be cured in 50% of patients with simple epididymectomy [67] and reported patient satisfaction as high as 43% following epididymectomy for chronic epididymitis [68]. The benefit from epididymectomy for postvasectomy pain has also shown to be long-lasting when patients have been reviewed at five years [69].

Epididymectomy for postvasectomy pain has been shown to be more successful than epididymectomy.
performed for other nonvasectomy causes with 93% of patients having less or no pain postoperatively compared to 75%, respectively [70]. Therefore, with good patient satisfaction and a favourable long-term outcome, epididymectomy appears to be an effective treatment option particularly for post-vasectomy chronic epididymal pain which cannot be managed conservatively. Calleary [71] suggested that epididymectomy for structural abnormalities had excellent results, but for those with chronic pain a 55% chance of improvement at best was achievable; therefore, this group should be counselled about the low risk of success.

It is important when counselling such patients that the surgery may not improve their pain, especially because this is the sole symptom they wish to be free from. From our experience, patients with localised structural changes and tenderness which isolates specifically to the epididymis are those most likely to benefit from its removal. In those where the pain is more diffuse, or not accompanied with structural epididymal change, the outcome is less assured, and alternative strategies should be considered. In those with diffuse pain who respond well to cord blocks, a microsurgical cord denervation can provide more effective symptomatic relief [72, 73].

**Expert Opinion**

Scrotal and testicular ailments can cause a significant alteration to a patient’s life. Prompt and appropriate diagnosis is vital. When in doubt about a torsion, exploration is always the safest option. Treating infections promptly can prevent chronic testicular pain. Therefore, basic knowledge of the differential diagnosis of testicular pain is vital.

**References**

References


38

Testes Benign Swelling
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Abstract
Benign testicular swellings tend to be asymptomatic the majority of the time, and good counselling and reassurance might be all that is needed. More often than not, the diagnosis of a hydrocele, epididymal cysts, and varicoceles can be reached by a clinical examination; however, an ultrasound can confirm the diagnosis as well as rule out a sinister cause such as a cancer. Symptomatic hydroceles or epididymal cysts are easily surgically treated, and a testicular torsion warrants emergency scrotal exploration and 'untwisting' followed by fixation. Symptomatic varicoceles can be embolised or surgically corrected by ligating the testicular vein.

Keywords hydrocele; epididymal cysts; varicocele; testicular torsion; testicular pain; orchialgia

Key Points
- Symptomatic hydroceles are best treated surgically with caution taken for meticulous haemostasis.
- Epididymal cysts are conservatively managed unless cause significant distress to the patient.
- Testicular torsion is a urological emergency, and surgical exploration must not be delayed.
- The majority of varicoceles require no treatment, unless they become large and symptomatic. Its role in infertility is a matter for debate.

38.1 Hydrocele

Hydrocele is an abnormal collection of fluid between the two layers of tunica vaginalis, which surrounds the testis. It comes from the Greek words \textit{hydro} and \textit{kele}, meaning 'water' and 'mass', respectively.

38.1.1 Aetiology

Depending on the cause of increase fluid in the sac, hydroceles can be divided into congenital, primary, or secondary.

38.1.1.1 Congenital Hydrocele

This is secondary to incomplete closure of the processus vaginalis leading to accumulation of fluid around the testis which is continuous with the peritoneal cavity.

The processus may close above and below a short segment, giving rise to a 'hydrocele of the cord'; it is a rare condition and an equivalent lesion exists in the female called hydrocele of the canal of Nuck where the cyst lies in relation to the round ligament. A hydrocele may be associated with a hernial sac, with obliteration of the
intervening processus. Rarely, a hydrocele may extend through the internal ring to cause a retroperitoneal swelling (Figure 38.1).

38.1.1.2 Primary or Idiopathic Hydrocele
The fluid in primary hydrocele is lymph and is caused by either obstruction of drainage or decreased absorption of fluid. The lymphatic drainage of the testis is of great interest because the testicular tubules are immunologically deprived sites, keeping the haploid gametes safe from the immune defences of the body. Between the tubules, the lymphatic capillaries drain into the lymphatics of the cord, when these are obstructed, the intertubular spaces expand not the lumina of the tubules. There is always a little fluid between the layers of the tunica vaginalis in the adult; if the absorption is decreased, a hydrocele forms, however it is unknown why this occurs.

38.1.1.3 Secondary Hydrocele
Excessive production and accumulation of exudate fluid secondary to inflammation or malignancy within the sac is analogous to the secondary pleural or peritoneal effusion seen diseases in the pleural or peritoneal cavities. It can occur with epididymitis, orchitis, trauma, and can be a presenting symptom of cancer. Obstruction of the lymphatics of the cord by the filarial worm *Wuchereria*
bancrofti can give rise to hydroceles, sometimes of prodigious size, endemic in countries like India and Myanmar [1].

Hydrocele can be seen in ascites and heart failure, and in men who have undergone radical retroperitoneal node dissection or radical removal of the kidney for cancer.

38.1.2 Clinical Features

An asymptomatic swelling in the scrotum which is translucent, fluctuant in two planes, if large enough difficult to palpate the testes encapsulated by the sac, and can more often palpate above the swelling.

Symptoms can arise if the hydrocele ruptures or bleeds, forming a haematocoele, usually secondary to trauma, or increases in size where it can cause pressure effects and cause the patient discomfort.

38.1.3 Investigations

Clinical examination is usually conclusive of the diagnosis, however, can be difficult to distinguish from a hernia, especially in children. The swelling is trans-illuminable when a torch is shined behind it. An ultrasound can accurately establish the diagnosis, as well as determine if an underlying testicular cancer is present (Figure 38.2). If doubt remains, the fluid can be aspirated to allow the testis to be carefully palpated and if the findings are still inconclusive, then the testicle should be explored.

38.1.4 Treatment

The majority of hydroceles do not need treatment unless symptomatic. An old rule is to advise treatment if a man’s wife or his tailor complain. In the paediatric population, hydrocele repair is indicated for both congenital hydrocele and hydrocele of the cord [2–4]. However, it is recommended to monitoring vaginal hydroceles in infants because of its tendency to spontaneously resolve and on vaginal hydrocele which have shown decrease in size over a period of time. While in adults, surgery repair is the mainstay of treatment. Aspiration of a hydrocele is only advised for symptomatic relief of an elderly man unfit for surgery [2]. While injection of a hydrocele with a scleroscant can be painful and might not resolve the swelling, it can cause multiple smaller hydrocele saculations or an infection leading to a complex hydrocele (Figure 38.3).

38.1.5 Operations for Hydrocele

Incisions for scrotal exploration is done through either a midline scrotal incision or a transverse incision. After the incision, the hydrocele is delivered out of the scrotum in its entirety. The sac is emptied of its fluid content through a small incision opposite the testis (to avoid injuring it), followed by lengthening of the sac incision and delivering the testis. The redundant tunica vaginalis can then be everted and closed behind the testicle (Jaboulay’s procedure) (Figure 38.4) or plicated with a series of interrupted absorbable sutures (Lord’s Procedure) (Figure 38.5). In long-standing hydroceles, the sac is thick and stiff and needs to be cut away leaving a frill around the epididymis, which must be over sewn to achieve perfect haemostasis (Figure 38.6).

38.1.6 Complications

Haematoma is the main complication in the repair of hydrocele and perfect haemostasis must be achieved in every step of the procedure to prevent this from
Figure 38.3 Ultrasound of complex hydrocele showing multiple large septate masses.

Figure 38.4 Jaboulay’s ‘bottle’ operation for hydrocele.

Figure 38.5 Lord’s plication for hydrocele.
38.2 Epididymal Cyst

Epididymal cysts arise as diverticula of the vasa efferentia and contain clear fluid (Figure 38.7). If the cyst contains spermatozoa, it is called a spermatocele. The pathophysiology is unknown, however, are more commonly multiply occurring.

The diagnosis is often clinical with a palpable cystic trans-illuminable mass arising on the epididymis separate from the testes (above and behind the testis) and can be multilocular. It may be difficult to distinguish a hydrocele from a collection of cysts, especially when both are present in the same patient. An ultrasound can accurately make the diagnosis (Figure 38.8).

Treatment with an epididymal cyst excision is only indicated if they become bulky and bothersome with pain and discomfort. Alternative needle aspiration of the fluid can be done; however, they tend to recur.

38.2.1 Operative Technique

The testis is delivered through a transverse scrotal incision and the intact cyst is dissected from the rest of the epididymis. Good haemostasis along the way will help prevent the common complication of haematoma.
38.3 Benign Testicular Cyst

Benign testicular cysts are uncommon and alternative diagnosis such as testicular malignancy should be excluded before making a benign diagnosis. They are of two varieties: simple cysts and epidermoid cysts. Simple cysts contain clear fluid, while epidermoid cysts are well circumscribed lesions filled with keratinized debris. Ultrasounds can accurately diagnose the lesions and distinguish it from malignant masses. Treatment is unnecessary unless they become symptomatic with pain or discomfort due to size, and in which case, enucleation or partial orchiectomy can be done.

38.4 Testicular Torsion

A urological emergency, testicular torsion was first described by Delasiauve in 1840 [5]. The twisting of the spermatic cord causes vascular compromise to the respective testis, initially with venous congestion and ultimately leading to arterial ischaemia and infarction. It has a bimodal distribution with the first year of life and around the pubertal age. It is thought to be more commonly occurring in cold weather [6].

There are two types of torsion, extravaginal and intravaginal.

38.4.1 Extravaginal

Seen in neonates and often occurs at the time of birth, the incomplete fixation of the gubernaculums to the scrotal wall causes the spermatic cord to twist, noticed as a firm mass in the scrotum but can also be diagnosed in utero with an ultrasound (Figure 38.9) [7–9].

38.4.2 Intravaginal

This is seen in children and adults and is often caused by a congenital abnormality with a capacious tunica with an abnormally higher investment of the tunica vaginalis on the posterior wall of the scrotum, giving it the classical ‘bell clapper’ appearance (Figure 38.10). This will cause the cord to be the only pedicle of the testis which can easily twist. Because of its congenital nature, there is an increased risk of it occurring on both sides; bilateral torsion occurs in about 10% of cases.

38.4.3 Clinical Features

There are two distinct clinical pictures. Intermittent torsion whereby there is a clear history of warning attacks of testicular pain which have resolved spontaneously, possibly indicating a torsion-detorsion episode. The other half has no warning and present with sudden pain and swelling in the testis. Associated symptoms include nausea, vomiting, fever, abdominal pain, and shock.

Present cremasteric reflex and a nontender testis can exclude a testicular torsion. A hydrocele may be present due to the underlying testicular inflammation. The affected testis will be tender, often too tender to palpate properly, high riding, and may lie horizontally on clinical examination. Elevation of the testicle increases the pain, whereas relieves it in epididymo-orchitis. There may also be scrotal erythema.

38.4.4 Investigation

A straightforward testicular torsion is a clinical diagnosis and investigations should not delay testicular exploration if the diagnosis is apparent. Ultrasound colour Doppler is useful in atypical presentations with a good specificity and sensitivity, which confirms the absence of the blood supply (Figure 38.11) [10, 11].
38.4.5 Differential Diagnosis

There are a number of ailments that can mimic torsion (Table 38.1); however, if there is any doubt, then scrotal exploration must not be delayed.

<table>
<thead>
<tr>
<th>Infants</th>
<th>Children and Adults</th>
</tr>
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<tbody>
<tr>
<td>Scrotal haemorrhage</td>
<td>Acute epididymo-orchitis</td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>Incarcerated indirect inguinal hernia</td>
</tr>
<tr>
<td>Acute idiopathic scrotal oedema</td>
<td>Acute idiopathic scrotal oedema</td>
</tr>
<tr>
<td>Mumps and viral orchitis</td>
<td></td>
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</table>

38.4.6 Treatment

If the patient’s pain allows it, then a gentle attempt at detorting the testicle can alleviate the pain and can get the situation out of an emergency state, and then early fixation can be planned more electively.

38.4.6.1 Scrotal Exploration

Through a midline scrotal incision, the affect testicle can be delivered. The tunica is opened to expose the epididymis and testicle. You may find a grossly distended black epididymis and a pale testis or the testicles might be dusky. Untwist the stalk and wait for 5–10 minutes. If the blood supply is re-established, the testicle returns to its natural pink colour; alternatively, you can incise the tunica albuginea, and if it bleeds, it means the blood supply is not entirely thrombosed. Once viability is established, testicular fixation is done with a nonabsorbable suture between the tunica vaginalis and the tunica albuginea. As the most likely cause is a congenital variation that lead to the torsion, it is most likely present on the opposite testicle and therefore should also be fixed. If the testicle is no viable (i.e. infarcted), then it should be removed.

In chronic torsion, where by the testicle has been tortured for some days, there is no benefit from emergency exploring the scrotum because the testis will atrophy and fibrous to a hate nodule; however, fixation of the remaining testicle should be carried out.

38.4.7 Torsion of a Testicular Appendage

The more common appendage to tort is the appendix of the testis (hydatid of Morgagni) (Figure 38.12) [12]. Though it can mimic a testicular torsion, there is often less swelling with tenderness confined to the superior pole. Sometimes, a small area of ischaemia represented by a blue dot is seen at the scrotal skin. Torsion of the hydatid of Morgagni will warrant testicular exploration just like a testicular torsion.

38.5 Polyorchidism

At six weeks of embryonal development, the primordial testis develops from the primitive genital ridge medial to the mesonephric ducts [13]. At around eight weeks, the mesonephric ducts gives rise to the epididymis and vas deferens, and the testes starts taken shape [13]. Division of the genital ridge and duplication of the mesonephric duct will give rise to an extra testicle. Contact of the mesonephric duct with the primitive
This occurs when there is division through the genital ridge where it is attached to the mesonephric duct [14]. In Type III, the testis has its own epididymis and shares a common vas. This is the most common form and may result if the division of the genital ridge and a portion of the mesonephros. In Type IV, there is complete duplication of the testis, epididymis, and vas, resulting from simultaneous duplication of the genital ridge and mesonephric duct [14].

Usually asymptomatic and presenting as a lump, but it can present in association with inguinal hernias in 24%, cryptorchidism in 22%, torsion in 15%, and testicular cancer in 6.4% [13, 15]. Diagnosis can be confirmed with ultrasound (Figure 38.13) or magnetic resonance imaging (MRI). Spermatogenesis is normal in 50% of patients, and in the absence of suspected malignancy or torsion, patients can be left alone [15].

### 38.6 Varicocele

A varicocele is an abnormal dilation and tortuosity of the veins draining the testes and epididymis (Figure 38.14). A varicocele is often caused by absent or incompetent valves in the testicular vein. A more sinister cause should be excluded in new onset varicocele in adults, such as renal malignancy causing extramural obstructive pressure on the left testicular vein and venous obstruction from a retroperitoneal metastases from a cancer of the testis. Dissection of the gonadal vein during radical nephrectomy can also cause a varicocele.

A varicocele is more common on the left testis for various reasons. The left testicular vein is longer than the right, the left testicular vein anastomoses with the left renal vein at a right angle, the left testicular artery can...
Varicocele compress the left testicular vein because of a variant anatomy, the descending colon can compress the left testicular vein, and the nutcracker phenomena caused by compression of the left renal vein by the aorta and superior mesenteric artery or compression of the left iliac vein by the left iliac artery [16].

A varicocele is present in 15% of men and is present in 19–41% of men with primary infertility and 45–81% of men with secondary infertility [16, 17]. Although a varicocele is a well-known confounding factor for male subfertility, the pathophysiology behind this is uncertain. Routine repair of varicocele in subfertile men remains controversial. Some advocate that varicocele repair should not be offered as a form of fertility treatment because it does not improve pregnancy rates [18]. Others recommend a repair for those with a clinical varicocele, oligospermia, infertility for at least two years, and for unexplained infertility in the couple [19]. A recent review on varicocele and fertility have concluded that varicocele repair should be offered in young adults with impairment of seminal parameters because it is associated with a significant improvement of sperm concentration, motility and normal morphology, and is associated with improved pregnancy rates [20].

38.6.1 Clinical Features

The majority of varicoceles are asymptomatic; however, some patients may complain of a swelling or a dragging heaviness discomfort in the scrotum or of pain or aching in the testicle. Physical examination can reveal a collection of dilated vein (Figure 38.15); however, on palpation, the classical ‘bag of worms’ is appreciated with a cough impulse and disappears when the patient lies flat owing to the emptying of the vein. In chronic cases the ipsilateral testis can be smaller due to atrophy. Table 38.2 depicts the standard grading system used.
38.6.2 Investigations

Investigations are not required in the majority of cases; however, a Doppler ultrasound can accurately make the diagnosis (Figure 38.16). Where embolisation is considered or in recurrent varicocele post-treatment, a venogram can be obtained.

38.6.3 Treatment

Reserved for symptomatic patients, such as those with pain, large varicoceles, and delayed testicular growth compared to contralateral side if not affected.

There are numerous modalities for the treatment of varicocele.

38.6.3.1 Embolisation

Gaining access via the femoral veins, the testicular vein can be embolised injecting them with coils or a sclerosing agent.

38.6.3.2 Surgical Ligation

The testicular vein is isolated from the artery in the retroperitoneum and ligated during laparoscopic ligation (Figure 38.17).

38.6.3.3 Retroperitoneal Ligation

For an inguinal ligation, the external oblique is slit open through a small crease incision over the internal ring and the internal oblique and transversus are split in the line of their fibres giving access to the retroperitoneal fat. The testicular vessels are seen just as they curl round the inferior epigastric artery. The testicular artery is carefully dissected from the veins, which are divided between ligatures (Figure 38.18).

38.6.3.4 Subinguinal ligation

The spermatic cord is isolated as it emerges from the external ring, and all the veins are ligated outside the internal spermatic fascia, sparing the testicular artery (Figure 38.19).

38.7 Orchialgia

Chronic testicular pain can give patients great grief. Causes for orchialgia such as a previous testicular injury, infection, torsion, and surgical operations (on the testicle or a vasectomy) are conservatively managed with pain relief measures. An ultrasound can exclude a cancer, a missed testicular injury or torsion, referred pain from a renal calculus, or a leaking aortic aneurysm.

A small number of patients have a pain of unknown origin, which could be attributed to a deep-seated psychological disorder, and surgical intervention only makes things worse. Orchiectomy in this situation is usually followed by a return of the pain on the other side [21].

38.8 Nux Amatoris

This painful condition is sometimes seen in young men who become sexually excited without the opportunity to orgasm. The pathophysiology is unclear. On examination, the veins of the cord are tender and distended. The condition may be accompanied by so much pain radiated to the iliac fossa that can lead to a misdiagnosis of an appendicitis. The venous congestion is relieved by a warm bath.
Figure 38.16 Doppler ultrasound showing a varices.

Figure 38.17 Laparoscopic clipping of testicular veins for varicocele.
Figure 38.18 High ligation of testicular veins through the inguinal approach.

Figure 38.19 Low ligation of testicular veins at the external ring.

Expert Opinion

Regarding testicular torsion, when in doubt, exploration is the route. The majority of benign conditions can be treated conservatively and usually the explanation of the pathophysiology is sufficient to allow the patient to cope with the condition. Alternatively, weighing out the risks versus the complications of surgery should be carefully explained.
References


Testes Neoplasm

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Abstract

Primary testicular neoplasms are the most common solid tumour affecting men ages 20–45, representing 5% of urological tumours and 1–1.5% of male neoplasms in the western world. The widespread use of serum tumour markers, sensitive ultrasound, and accurate computed tomography staging has meant that patients can undergo a radical orchiectomy in a timely manner, which is a curative procedure in up to 75% of cases. Adjuvant chemotherapy, radiotherapy, and radical lymph node dissection forms the basis of management following radical orchiectomy and techniques are improving year on year. With such advances in knowledge and accuracy of relapse prediction testicular neoplasms have become one of the most curative cancers if managed early. This chapter outlines the diagnosis, management options, and prognosis for germ cell and non-germ cell testicular neoplasms.

Keywords testicular cancer; germ cell tumours; seminoma; non-seminoma; orchiectomy; retroperitoneal lymph node dissection (RPLND); paratesticular cancer; epididymal cancer

Key Points

- Primary testicular neoplasm is the most common solid tumour affecting men ages 20–45 with 90–95% of cancers being germ cell tumours (GCTs).
- Risk factors for testicular neoplasm include cryptorchidism or undescended testis, Caucasian race, genetic predisposition (HLA associations), and intratubular germ cell neoplasia.
- Often presentation is with a painless isolated scrotal lump.
- Timely imaging with an ultrasound is the gold standard; measurement of tumour markers (alpha-fetoprotein [AFP] and human chorionic gonadotropin [hCG]) and radical inguinal orchiectomy in case of a suspicious ultrasound complete the initial diagnosis. Additional imaging, usually limited to the chest and abdomen, will allow for a tailored management plan.
- The UK and US traditionally follow the international tumour, node, and metastasis (TNM) classification for staging, whereas many European countries follow the Royal Marsden staging system. The International Germ Cell Consensus Classification is an important system which enables prognostic grouping.
  - Stage I is localised disease, which can be managed by orchiectomy and surveillance. A minority of patients will go onto the have adjuvant therapy.
  - Stage II seminoma is metastatic disease and will require radiotherapy or chemotherapy.
  - Stage II and III non-seminomas and stage III seminomas will require chemotherapy.
- Patients should be offered fertility counselling and sperm banking before chemotherapy or radiotherapy.
39.1 History

The distinction between solid tumours of the testicle (lethal) and cystic (innocent) ones was known to the Romans. William Harvey advised ligature of the testicular artery as a safer alternative to castration, and Astley Cooper researched the lymphatic drainage of the testicle and the method of tumour spread [1]. The crucial biological difference between the two main histological types of testicular tumours was discovered by Chevassu who coined the terms ‘seminoma’ and ‘teratoma’ [2].

Kocher was the first to attempt to cure testicular cancer by radical node dissection; however both his patients had advanced disease and died [2]. In 1926, Cairns reviewed these attempts and concluded that they were futile [3]. Within a few years, radiotherapy replaced surgery for lymph node disease in some centres, but in others, the morbidity caused by overdoses of radiation discredited it. For the next 50 years, a contest began between radical node dissection and radiation [1]. The conflict became meaningless because advocates of either method were always comparing tumours that were classified by different systems and staged by different criteria. Eventually, the argument was overtaken by the introduction of tumour markers, combination chemotherapy, and a better understanding of the natural history of these tumours.

39.2 Incidence

Primary testicular neoplasm is the most common solid tumour affecting men ages 20–45 in the Western world and is increasing in incidence, representing 1–1.5% of all male neoplasms and 5% of urological tumours [4–7]. The incidence has been rising over the last century in Europe and North America with data from the Surveillance Epidemiology and End Results (SEER) programme showing a continuing increased risk of seminoma in Caucasian men in the United States [8, 9]. Nearly all testicular cancers (TCa) (90–95%) are germ cell tumours (GCTs) and have a peak incidences in the third decade for non-seminomas and fourth decade for seminomas [6, 7].

The introduction of tumour markers and combination chemotherapy has enhanced patient care and increased survival rates. Survival rates are at their highest, and it is now recognised as the most curable cancer. Public health campaigns aimed at young men to encourage them to self-examine have played a large part in making early diagnosis and treatment possible, leading to a decrease in the average time from diagnosis to treatment [10].

39.3 Basic Embryology

Germ cells from the yolk sac cross the coelom to the gonadal ridge where they differentiate into Leydig, Sertoli, and more germ cells. The germ cells continue to divide to form diploid primary spermatocytes, haploid secondary spermatocytes, and finally spermatooza from which every cell that may occur in the foetus, yolk sac, or placenta, in benign or malignant variations, may arise.

Germ cells have clear cytoplasm full of glycogen and stain for placental alkaline phosphatase (PLAP). If held up in their journey from yolk sac to gonadal ridge, they may give rise to extragonadal CGTs in the para-aortic region, mediastinum, or pineal gland. If they arise in streak gonads in intersex, they are called dysgerminomas. The primordial germ cells, the atypical cells found in seminiferous tubules, and seminoma cells are probably identical.

39.4 Aetiology and Risk Factors

- **Age:** The incidence occurs in any age, increasing post-puberty with a maximum onset in the 20s and 30s, and rarely occurring in infants, prepubertal boys, and men older than 60 years of age [11].
- **Race:** Caucasians are up to three times more likely to develop testicular cancer than other races [12]. It is rare in non-European origin populations, except for the Maori population of New Zealand [11].
- **Genetic:** There have been associations found with the human leucocyte antigens (HLAs) and first-degree relatives (i.e. fathers and brothers) are at a higher risk of being affected [13]. Gene expression analysis and genome-wide screening studies suggest that cancer-specific gene mutations are found on chromosomes 4, 5, 6, 12, 18, and X [11, 12]. The isochromosome of the short arm of chromosome 12 (i12p) is described in all GCT types [14]. Patients with Klinefelter syndrome are at a higher risk, but the exact mechanism for this is unclear.
- **Cryptorchidism or undescended testis:** Is associated with three- to fivelfold increased risk of developing GCTs [11]. One in every 10 cases of testicular tumour occurs in men with an undescended testicle. The higher the undescended testicle, the more likely it is to become malignant [15]. Stilboestrol ingestion during pregnancy has been linked to the increase risk of cryptorchidism, and it is also suggested that high levels of natural oestrogens may be equally important [16]. Cryptorchidism is associated with a 2.2-fold increased risk of TCa in men who underwent orchidopexy before 13 years of age as opposed to a 5.4-fold increased risk for those who underwent orchidopexy after 13 years of age, therefore advocating early fixation [17]. Standard practice is to perform the surgery before two years of age.
- **Intratubular germ cell neoplasia (ITGCN) (testicular intraepithelial neoplasia [TIN]):** Incidence of ITGCN is rare but present in 4% of patients with a history of cryptorchidism, 5% of patients with contralateral TCa, and in 1% of patients with oligospermia. The disease arises from malignant change in spermatogonia where 50% develop invasive germ cell testicular cancer within five years and 90% in seven years [11]. Nearly 66% of cases have chromosomal alteration in p53 locus [18]. The presence of a contralateral TCa or TIN has also been shown to have an increased risk of developing TCa on the nonaffected side [7].

- **Risk factors for TIN:** Older than 30 years of age, <12 ml testes, cryptorchidism, atrophic contralateral testis, previous or contralateral testicular cancer, 45 XO, Klineflelter syndrome, and infertility. Biopsy can be offered to high-risk groups.

- **Treatment:** If unilateral involvement and contralateral testis is normal, is either by conservative observation or radical orchiectomy. If contralateral testis is involved or has established TCa, then treatment is by radiotherapy. Infertility counselling should be discussed with potential sperm storage.

- **Trauma:** Although not a known risk factor, occasionally a history of trauma can predispose to a testicular mass presenting. It can be difficult to decipher whether the lump was from the trauma or whether the injury has brought an unnoticed lump to the attention of the patient. If there is any doubt an ultrasound should be performed.

- **Infections:** HIV sufferers develop seminomas more frequently than expected; however, HIV in itself has not been proven to cause TCa [11]. In up to 10% of cases, a testicular tumour mimics epididymo-orchitis so caution is advised particularly in recurrent or refractive epididymo-orchitis. If there is any doubt of the diagnosis, an ultrasound should be performed.

- **Others:** Men with subfertility or infertile, patients who are immunosuppressed with renal transplants, low birth weight and small-for-gestational-age have been weakly implicated with risk of developing TCa [11]. There is no link between testicular microlithiasis and cancer in healthy men.

### 39.5 Clinical Features

Often presentation is with a painless isolated scrotal lump incidentally identified. Occasionally patients have with a nonspecific ache in the testicle, and in nearly 20% of cases, the first symptom will be scrotal pain, with 27% of patients with TCa having local pain [6]. TCa can present with physical signs of inflammation with the testicle swollen, red, and warm, suggesting epididymo-orchitis or possibly neglected torsion. The pathophysiology of this inflammation is unclear, but it is speculated that haemorrhage into the tumour can contribute. Inflammation in an abdominal cryptorchid testicle may present as an acute abdomen.

It is wise to have a low index for suspicion in the young man with vague discomfort in the testicle or the sensation of a lump. Do not be reassured with the finding of a mere varicocele or dismiss discomfort as adolescent neurosis until the testicle has been carefully examined. Similarly, when a young man complains of vague backache, be sure to exclude metastases from a testicular tumour, even when the testes appear normal.

Trauma to the testicles may reveal the presence of a mass. A small secondary hydrocele can be present, and very rarely it may be the presenting feature. Larger tumours may be concealed by a thick-walled hydrocele containing turbid fluid through which light will not shine. A hydrocele in a young male always calls for confirmation of the diagnosis by ultrasound, tumour markers, and when in doubt, exploration (Figure 39.1).

Gynecomastia from release of chorionic gonadotrophin is reported in up to 7% of cases as the first symptom of a testicular tumour. Therefore, every young man with signs of gynecomastia must have their testicles examined and tumour markers measured [6]. A point-of-care pregnancy test can give an instant diagnosis.

Sometimes the tumour erodes through the testis, leaving behind a scar that shrinks as it heals. The patient will often notice that the testicle is getting smaller. A small primary tumour may be entirely replaced by a scar, leaving a normal testicle, even though the tumour has metastasized widely.

Bilateral testicular cancer occurs in 1–2% of cases [14]. Therefore, it is always advisable to examine both the affected and nonaffected side, in addition to a complete general physical examination looking for possible distant metastasis (e.g. supraclavicular lymph nodes), gynaeomastia, or a palpable abdominal mass. Lower limb oedema may suggest lymph node compression obstructing the venous drainage of the limb.

Delayed presentations can lead to symptoms of weight loss, lumps in the neck, chest symptoms, or bone pain; this suggests advanced disease, which is seen in 10% of cases.

### 39.6 Diagnosis

Imaging and tumour markers should be carried out as a matter of urgency if a testicular neoplasm is suspected. Once confirmed, surgical excision is done to establish a pathological diagnosis.
39.6.1 Imaging

Ultrasound is the gold standard for exploring a testicular mass because its detection rate for picking up testicular masses is nearly 100%. It can differentiate between an intra- or extratesticular mass and allows assessment of the contralateral testis (Figure 39.2) [19]. It is also an inexpensive test that can be carried out readily to avoid delays in management.

An abdominopelvic computed tomography (CT) should be performed on all patients for staging the disease (Figure 39.3). Its sensitivity for detecting enlarged lymph nodes is 70–80%, but the accuracy depends on the size of the nodes [20]. Be aware that at lower stages, there can be a degree of understaging. Magnetic resonance imaging (MRI) produces similar results in detecting nodal disease in the retroperitoneum (Figure 39.4). It can be helpful in those patients who have a contraindication to contrast use or where there is concern about radiation dose. However, its high cost, lack of availability, and similar sensitivity rate mean that CT remains the first-line imaging modality for staging.

A chest CT is recommended in all patients because of its high sensitivity for mediastinal and thoracic lymph nodes. Up to 10% of patients with TCa's have small subpleural nodes that will only be diagnosed on chest CT [21]. Other imaging modalities (such as bone scanning, CT of the head or spine, and abdominal ultrasound) should only be used if there is strong clinical suspicion of metastasis or if the patient is in a high-risk category (see later).

39.6.2 Serum Tumor Markers

Tumor markers contribute to the diagnosis and risk classification of testicular neoplasms and are an important prognostic factors [22]. Tumor markers that should be measured at presentation are the oncofoetal proteins: alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG); and cellular enzymes: lactate dehydrogenase (LDH) and PLAP (Table 39.1).

It is estimated that 90% of patients with non-seminomas (i.e. AFP or HCG mainly) and up to 30% of seminomas (i.e. HCG and LDH) will have an elevated tumor markers. Baseline levels of tumor markers should be taken at presentation, one to two weeks after radical orchiectomy, then as monitoring during follow-up to assess treatment response. A negative tumor marker does not exclude the diagnosis of a TCa or the presence of metastatic disease; however, their persistence after radical orchiectomy may indicate the presence of metastases.

39.6.3 Surgical Excision

Radical inguinal orchiectomy is the gold standard because it is not only part of the initial pathological diagnosis and staging, but it can be curative in nearly 75% of patients. The testis, spermatic cord, and epididymis and their coverings should be excised through a groin incision.

39.6.3.1 The Surgical Approach to Radical Orchiectomy

Through an inguinal incision, open the external oblique and place a vascular clamp across the cord at the internal ring to prevent tumour cells escaping as the testicle is separated from the scrotum (Figure 39.5). If a patient has a large tumour, it is better to carry the inguinal incision into the neck of the scrotum rather than risk bursting the tumour. If there is doubt in the diagnosis, an excisional biopsy by complete enucleation of the intraparenchymal...
mass is taken for a fresh-frozen section pathological examination. If the lump proves benign, the tunica albuginea may be closed. After six months, it will be impossible to tell which side has been operated on.

If the testicle is obviously the seat of a cancer, transfix and ligate the cord above the clamp (Figure 39.6). Haemostasis must be perfect before closing the wound because infection in a haematoma may postpone adjuvant radiotherapy or chemotherapy.

In select patients where there is synchronous bilateral TCa, metachronous contralateral TCa, or TCa in a solitary testis, organ-sparing surgery can be performed if the tumour is less than 30% of the testicular volume. Surgery should be done in a centre with experience in treating these patients. All must have adjuvant radiotherapy [7, 23]. There is a higher risk of infertility in these cases as well as a risk of long-term Leydig cell insufficiency.

Figure 39.2 Ultrasound images of the testicle (a) large solid lesion representing a testicular tumour (b) Doppler showing a well-perfused testicular tumour (c) multiple hypoechoic areas consistent with multiple testicular tumours, microlithiasis present throughout testicle, secondary hydrocele (d) a scrotal lump indistinguishable clinical from the testicle found to be a large epididymal lipoma. (e and f) Testicular microlithiasis.
Figure 39.3  Computed tomography (CT) scans (a-e) showing large para-aortic lymph node metastases. Source: Photographs courtesy of Dr. Neil Collins Southmead Hospital.

Figure 39.4  Magnetic resonance imaging (MRI) scans showing large para-aortic lymph node metastases. Source: Photographs courtesy of Dr. Neil Collins Southmead Hospital.
Retroperitoneal lymph node dissection (RPLND) is an accurate method of staging the tumour because it can detect microscopic metastases in lymph nodes that are less than 1 cm in diameter. Staging node dissection is not only diagnostic, but it will suffice to cure patients who only have microscopic metastases without the need for chemotherapy, but at the risks of major abdominal surgery.

When comparing different methods of treatment, it is necessary to take account of the way the tumour was staged. Where retroperitoneal node dissection is the

### Table 39.1 Table of the common onco-foetal proteins detected in the serum of patients with a testicular neoplasm.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Detail</th>
<th>Seminoma</th>
<th>Non-seminomas</th>
<th>Serum half-life</th>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>Produced by trophoblastic elements in foetal life, AFP is the second-most common protein after albumen</td>
<td>Not usually but if present strongly suggests a non-seminomatous element</td>
<td>Present in 50–70%</td>
<td>3–5 days</td>
<td>&lt;10 ng ml⁻¹</td>
</tr>
<tr>
<td>hCG</td>
<td>Produced by Syncytiotrophoblastic element</td>
<td>Elevated in 10–30%</td>
<td>40–60% teratoma, 100% choriocarcinomas</td>
<td>24–36 hours</td>
<td>&lt;5 ml U ml⁻¹</td>
</tr>
<tr>
<td>LDH</td>
<td>Enzyme marker of cellular turnover therefore non-specific, but its concentration is proportional to tumour volume and can be elevated in up to 80% of advanced disease.</td>
<td>Elevated in 10–20% most useful to monitor treatment response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLAP</td>
<td>Foetal isoenzyme. May be elevated in smokers. It is non-specific so not widely used. Its measurement is considered more optional as opposed to the other three.</td>
<td>Up to 40% with advanced disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AFP, alpha fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; PLAP, placental alkaline phosphatase.

Figure 39.5 Orchiectomy for testicular tumour. A clamp is placed on the cord before delivering the testis.
routine practice, then lymph node metastases will be detected that would have been missed in the CT scan and so invalidate the comparison. However, with improved imaging, the frequency of primary RPLND to confirm the presence or absence of metastasis in normal sized nodes, is decreasing gradually.

### 39.6.4.1 Pathological Classification

In 2004, the World Health Organisation (WHO) split testicular neoplasms into GCTs, sex cord/gonadal stromal tumours, and miscellaneous nonspecific stromal tumours (Table 39.2) [11]. Any tissue in the testicle may undergo malignant change, but most neoplasms arise from germ cells (i.e. gonadocytes) and as a group are referred to as germ-cell tumours (Figure 39.7). There may be only one kind of tissue in the tumour or a mixture, and therefore, the prognosis depends on the level of malignancy of each type of tissue present and the overall percentage composition of each type of tissue [19].

It is vital that the surgeon has an understanding of the requirements for the pathological specimen. Mandatory pathological requirements for diagnosis are a sample of 1 cm² section for every centimetre of maximum tumour diameter, including normal parenchyma if present. At least one distal and one proximal section of the spermatic cord should be analysed. Microscopic features and diagnosis should include the presence or absence of peritumoural venous or lymphatic invasion, albignea, rete testis, epididymis, or spermatic cord invasion and presence or absence of intratubular germ cell neoplasia in nontumour parenchyma intratubular germ cell neoplasia. Immunochemical markers can be useful in cases of doubt.

**Table 39.2 The World Health Organisation histopathological classification of the more common testicular tumours.**

<table>
<thead>
<tr>
<th>Germ cell tumours:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminomas</td>
</tr>
<tr>
<td>Spermatocytic</td>
</tr>
<tr>
<td>Classical</td>
</tr>
<tr>
<td>Anaplastic</td>
</tr>
<tr>
<td>Mixed with nonseminomatous germ cell tumours</td>
</tr>
<tr>
<td>Nonseminomatous germ cell tumours</td>
</tr>
<tr>
<td>Teratoma</td>
</tr>
<tr>
<td>Yolk sac tumours</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Mixed</td>
</tr>
</tbody>
</table>

**Mixed germ cell tumours**

- Sex cord or gonadal stromal tumours
- Leydig cell tumours
- Sertoli cell tumours
- Granulosa cell tumours
- Albuginea or fibroma group tumours
- Mixed germ cell and sex cord or gonadal stromal tumours

**Others:**

- Carcinoid
- Haematopoietic (lymphoma)
- Adenomatoid tumour
- Mesothelioma (benign and malignant types)
- Adenocarcinoma of the epididymis
- Papillary cystadenoma of the epididymis
- Melanotic neuroectodermal tumour
- Metastatic from other sites

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**Figure 39.6** The cord is transfixed and ligated above the clamp.

**Figure 39.7** Cellular origin of germ cell tumours.
39.6.4.1.1 Main CGTs

- **Seminoma**
  There is a peak age incidence at about ages 30–40, which is a decade later than other GCTs. Macroscopically, it forms a pinky-grey lobulated swelling. Microscopically, sheets of glycogen-filled cells, staining for PLAP, are interspersed with lymphocytes. Seminomas are part of a continuum. At one extreme is the well-differentiated spermatocytic seminoma of older men, whose cells resemble spermatocytes. They rarely metastasize and are highly chemosensitive. At the other extreme is the anaplastic seminoma with nuclear pleomorphism, scanty lymphocytes and giant cells resembling syncytiotrophoblast which stain for beta-HCG and raise the serum HCG, verging with embryonal carcinoma.

- **Nonseminomatous germ cell tumour (NSGCT)**
  These tumours are often made up of more than one type of cell and are therefore identified according to the cell types seen.
  - Embryonal carcinoma
    In embryonal carcinoma, the macroscopic appearance is even blotchier. Microscopically, amongst sheets of cells and embryoid bodies there are areas with papillary and pseudoglandular patterns arranged in single or double layers of cells which stain for AFP, betraying their yolk sac origin.
  - Yolk sac tumours
    Pure yolk sac tumours are found in infants. In adults, yolk sac tissue is often found in mixed tumours. AFP can be detected in the tissue by immunoperoxidase staining and in the serum is a useful marker of response to treatment.
  - Teratocarcinoma
    In teratoma, the tissues are similar to those of the developing foetus and can be benign or malignant. When only mature tissue is present, the tumour is referred to as ‘mature teratoma’. Of the malignant tissues the worst is choriocarcinoma; it may be the only tissue present, but it is more often present as part of a mixture.

39.6.4.1.2 Nongerm Cell Tumours

In addition to CGTs, benign and malignant tumours can arise in any of the other tissues present in the testis, epididymis, or their coverings.

- **Leydig cell tumours**
  These are composed of normal-looking interstitial cells and secrete testosterone. Before puberty, they give rise to precocious sexual development, and after puberty, they cause feminization with gynaecomastia.

- **Sertoli cell tumours**
  These are rare. They occasionally metastasize and occasionally cause gynaecomastia.

- **Connective tissue tumours**
  Connective tissue tumours from the tissues in and around the testis can give rise to various tumours, (e.g. tunica albuginea often forms benign fibromatous nodules) and rarely it may form mesothelioma or even fibrosarcoma, most often in children.

39.7 Staging

The staging is based on the tumour, node, and metastasis (TNM) classification (Table 39.3) and grouped according to stage (Table 39.4). It is the predominant system used for testicular neoplasm staging in the US and UK. However, the Royal Marsden system (Table 39.5) is used in many European countries.

The Royal Marsden system stage I equates to T1N0M0 because it is disease confined to the testis. Stage II is subdivided into IIa where the nodes detected by CT below the diaphragm are less than 2 cm in diameter, IIb where they are more between 2 and 5 cm, and IIc more than 5 cm in diameter. Stage III includes those in the mediastinum (N2) and stage IV haematogenous metastases. For metastatic CGTs in particular, it is important that patients are staged in accordance with the International Germ Cell Consensus Classification (IGCCC) which gives prognostic grouping (Table 39.6).

39.8 Method of Spread

GCTs spread by direct invasion from the testicular tubules into the surrounding interstitial spaces, through the rete testis into the epididymis, and finally through the tunica albuginea into the scrotum. They invade the connective tissue and veins of the spermatic cord (Figure 39.8).

The lymphatics of the testis arise between the tubules and drain along the spermatic cord to the primary regional lymph nodes around the origin of the testicular arteries, the renal hilus, the first lymph nodes to be involved in TCAs. Secondary lymph node spread occurs upwards from the para-aortic nodes to the mediastinum enters the systemic circulation via the thoracic duct. There may also be secondary spread downwards to the lymph nodes of the pelvis (Figure 39.9).

TCAs with trophoblastic elements erode veins and spread via the bloodstream at an early stage. Choriocarcinoma is notorious for this with haemoptysis from lung metastases being a classic presenting symptom.
### Table 39.3 The international TNM staging for testicular neoplasm.

<table>
<thead>
<tr>
<th>T (Primary Tumour)</th>
<th>pTis - Primary tumour cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT0 - no evidence of primary tumour</td>
<td></td>
</tr>
<tr>
<td>Tis - intratubular germ cell neoplasia</td>
<td></td>
</tr>
<tr>
<td>T1 - tumour limited to testis and epididymis without vascular/lymphatic invasion. May invade albuginea but not vaginalis</td>
<td></td>
</tr>
<tr>
<td>T2 - tumour limited to testis and epididymis with vascular/lymphatic invasion or extending through tunica albuginea with involvement of tunica vaginalis</td>
<td></td>
</tr>
<tr>
<td>T3 - tumour invades spermatic cord with or without vascular/lymph invasion</td>
<td></td>
</tr>
<tr>
<td>T4 - tumour invades scrotum with or without vascular/lymph invasion.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N (Regional lymph nodes clinical)</th>
<th>N0 - No regional lymph nodes affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 - Metastasis with lymph node mass &lt;2 cm or multiple lymph nodes none more than 2 cm in greatest diameter</td>
<td></td>
</tr>
<tr>
<td>N2 - metastasis with lymph node mass &gt;2 cm but not more than 5 cm or multiple lymph nodes</td>
<td></td>
</tr>
<tr>
<td>N3 - Metastasis with lymph node mass more than 5 cm in greatest diameter</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pN (pathological-RPLND staging)</th>
<th>pN0 - no regional lymph node affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN1 - metastasis with lymph node mass &lt;2 cm and 5 or fewer positive nodes, none of which are greater than 2 cm</td>
<td></td>
</tr>
<tr>
<td>pN2 - metastasis with lymph node mass of &gt;2 cm but not more than 5 cm or more than 5 nodes positive, none more than 5 cm. Or evidence of extranodal extension of tumour.</td>
<td></td>
</tr>
<tr>
<td>pN3 - metastasis with lymph node mass more than 5 cm in greatest dimension.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M (Distant Metastasis)</th>
<th>M0 - no distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 - distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1a - non-regional lymph nodes or lung</td>
<td></td>
</tr>
<tr>
<td>M1b - other sites</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S (Serum Tumour Markers)</th>
<th>Sx - serum marker studies not performed/not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0 - serum markers study level within normal limits</td>
<td></td>
</tr>
<tr>
<td>S1 - LDH &lt;1.5 X N AND hCG &lt;5000 AND AFP &lt;1000</td>
<td></td>
</tr>
<tr>
<td>S2 - LDH 1.5–10 X N OR hCG 5000–50000 OR AFP 1000–10000</td>
<td></td>
</tr>
<tr>
<td>S2 - LDH &gt;10 X N OR hCG &gt;50000 OR AFP &gt;10000</td>
<td></td>
</tr>
</tbody>
</table>

LDH measured in U\(^{-1}\), hCG in mIU\(ml^{-1}\) and AFP measured in ng\(ml^{-1}\).

AFP, alpha fetoprotein; LDH, lactate dehydrogenase; hCG, human chorionic gonadotropin; RLPND, retroperitoneal lymph node dissection; TNM, tumour, node, metastasis.

### Table 39.4 Stage grouping for testicular cancer.

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>pTis</td>
<td>N0</td>
<td>M0</td>
<td>S0, SX</td>
</tr>
<tr>
<td>Stage I</td>
<td>pT1-4</td>
<td>N0</td>
<td>M0</td>
<td>SX</td>
</tr>
<tr>
<td>la</td>
<td>pT1</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
</tr>
<tr>
<td>lb</td>
<td>pT2-4</td>
<td>N0</td>
<td>M0</td>
<td>S1–3</td>
</tr>
<tr>
<td>ls</td>
<td>Any patient/TX</td>
<td>N1–3</td>
<td>M0</td>
<td>S0–1, SX</td>
</tr>
<tr>
<td>Stage II</td>
<td>Any patient/TX</td>
<td>N1</td>
<td>M1</td>
<td>SX</td>
</tr>
<tr>
<td>Ila</td>
<td>N1</td>
<td>N1</td>
<td>M1a</td>
<td>S0–1</td>
</tr>
<tr>
<td>IIb</td>
<td>N2</td>
<td>N1–3</td>
<td>M0</td>
<td>S2</td>
</tr>
<tr>
<td>IIIC</td>
<td>N3</td>
<td>Any N</td>
<td>M1a</td>
<td>S3</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any patient/TX</td>
<td>Any N</td>
<td>M1</td>
<td>SX</td>
</tr>
<tr>
<td>IIIa</td>
<td>Any N</td>
<td>N1–3</td>
<td>M0</td>
<td>S3</td>
</tr>
<tr>
<td>IIIb</td>
<td>Any N</td>
<td>Any N</td>
<td>M1a</td>
<td>S3</td>
</tr>
<tr>
<td>IIIc</td>
<td>Any N</td>
<td>Any N</td>
<td>M1b</td>
<td>Any S</td>
</tr>
</tbody>
</table>
39.9 Prognosis

If a patient presents early and adequate measures ensure he proceeds to orchiectomy in a timely manner, the prognosis for these patients is very good. Those who present late or have a delay in their treatment do not have such a good prognosis [24]. The International Germ Cell Cancer Collaborative Group have provided a prognostic-based system for metastatic germ cell cancer (Table 39.6).

High risk for relapse of seminomas stage I are patients with tumours >4 cm or rete testis invasion, whereas those with <4 cm and no rete testis invasion are low-risk group patients.

High-risk group for NSGCT stage I include lymphovascular invasion of primary tumour (most important factor), a proliferation rate >70%, and the presence of >50% embryonal carcinoma [25–27]. For those with metastatic disease, relapse rates depend on elevated tumour marker levels, the presence of nonpulmonary visceral metastasis, and the primary location.

Table 39.5 The Royal Marsden staging system.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disease confined to testis</td>
</tr>
<tr>
<td>IM</td>
<td>Rising tumour markers post orchiectomy</td>
</tr>
<tr>
<td>II</td>
<td>Abdominal lymphadenopathy</td>
</tr>
<tr>
<td>III</td>
<td>Supra-diaphragmatic disease</td>
</tr>
<tr>
<td>IV</td>
<td>Extra-lymphatic metastasis</td>
</tr>
<tr>
<td>L1</td>
<td>&lt;3 lung metastasis</td>
</tr>
<tr>
<td>L2</td>
<td>&gt;3 lung metastasis</td>
</tr>
<tr>
<td>L3</td>
<td>&gt;3 lung metastasis with 1 or more &gt;2 cm</td>
</tr>
<tr>
<td>H+</td>
<td>Liver involvement</td>
</tr>
</tbody>
</table>

Table 39.6 Prognostic-based staging system for metastatic germ cell cancer.

<table>
<thead>
<tr>
<th>Good prognosis group</th>
<th>Intermediate prognosis group</th>
<th>Poor prognosis group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-seminomas (56%)</td>
<td>Seminomas (90%)</td>
<td>Non-seminomas (28%)</td>
</tr>
<tr>
<td>Non-seminomas (90%)</td>
<td>Seminomas (10%)</td>
<td>Non-seminomas (16%)</td>
</tr>
<tr>
<td>5 y- PFS 89%</td>
<td>5 y-PFS 82%</td>
<td>5 y-PFS 75%</td>
</tr>
<tr>
<td>5 y- S 92%</td>
<td>5 y-S 86%</td>
<td>5 y-S 80%</td>
</tr>
<tr>
<td>Plus all of the following criteria:</td>
<td></td>
<td>Plus all of the following criteria:</td>
</tr>
<tr>
<td>- Tests or retroperitoneal primary</td>
<td></td>
<td>- any primary site</td>
</tr>
<tr>
<td>- no non-pulmonary visceral metastasis</td>
<td></td>
<td>- any non-pulmonary visceral metastases</td>
</tr>
<tr>
<td>- hCG &lt;5000IU\textsuperscript{-1}</td>
<td></td>
<td>- Normal AFP</td>
</tr>
<tr>
<td>- LDH &lt;1.5 x ULN</td>
<td></td>
<td>- Any LDH</td>
</tr>
<tr>
<td>- AFP &lt;1000 ng\textsuperscript{-1}</td>
<td></td>
<td>- Any hCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- any hCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- any LDH</td>
</tr>
</tbody>
</table>

* 5 y-PFS year progression free survival. Y-S year survival.
AFP alpha-fetoprotein; hCG human chorionic gonadotrophin; LDH lactate dehydrogenase.

Source: From International Germ Cell Cancer Collaborative Group.
surveillance is feasible in these patients [7, 28]. Surveillance is only possible in a well-equipped unit with ready access to CT scanning and prompt measurement of tumour markers. The patient must be compliant and understand the need for strict cooperation and repeated follow-up to allow timely treatment of any tumour that appears during surveillance.

Nearly 15–20% have subclinical metastatic disease, not detectable with current radiological modalities, which will relapse within five years. The remaining 5% will present with distant metastatic disease. Use of adjuvant carboplatin or radiotherapy reduces relapse to <1% [29, 30]. With no difference between disease relapse with use of single course carboplatin therapy or radiotherapy treatment, recommendations are for adjuvant carboplatin use because it avoids toxic complications of radiotherapy [7]. Carboplatin treatment of patients who have high risk of disease relapse (tumour >4 cm or rete testis invasion) reduces recurrence to 1.4% [31].

To summarise, low risk should be observed, and high risk should be observed or be treated with chemotherapy instead of radiotherapy.
39.10.1.2 How Chemotherapy Works
A simplistic explanation for the sensitivity of CGTs to chemotherapy is that there is a high level of p53 tumour suppressor gene in normal germ cells, located on chromosome 17p. It has a key role in the control of DNA replication, regulation of apoptosis, and inhibits angiogenesis. Therefore, it can suppress cell proliferation and transformation. In tumour cells, there is an absence of p53 mutations and p53 is overexpressed when exposed to chemotherapy, leading to apoptosis of the tumour cells [32]. Furthermore, possibly under p53 control, TCa express high levels of the apoptosis-promoting protein Bax and have little or no expression of the suppressor of apoptosis Bcl-2. Bcl-2 is important in determining if the tumor cell is resistant to chemotherapy, leading to apoptosis of the tumour cell [32].

39.10.1.3 NSGCTs
Radical orchiectomy cures approximately 70–75% of patients. Continual management options include surveillance, chemotherapy, or RPLND.

Surveillance: Suitable for compliant patients with low risk of relapse (pT1 with no lymphovascular invasion). Risk of relapse is quoted at 80% in the first year, 12% in second year, 6% in third year, and 1% in fourth and fifth years, necessitating close regular follow-up for at least five years.

Patients who are unwilling or unable to be managed with surveillance or have high risk of relapse (pT2-pT4 or pT1 with lymphovascular invasion), can receive two courses of chemotherapy with bleomycin (B), etoposide (E), and cisplatin (P) (PEB). Reducing recurrence rates to as low as 2.7% [7].

RPLND: The oncologist will often manage the patient after radical orchiectomy, but the urologist may be involved in the RPLND. Nearly 30% of patients are found to have lymph node metastasis on RPLND (upgrading their staging to stage II disease), and if no lymph nodes are found, nearly 10% will relapse with distant metastasis [7].

Patients with low-risk disease who are not willing or suitable for surveillance can either have chemotherapy or nerve-sparing RPLND; however, if lymph nodes metastasis was found, two course BEP should be considered. Nearly 30% (pathologically stage I) and 50% (clinically stage I) of patients with vascular invasion relapse; however, two courses of BEP reduce the incidence to <2% [7].

RPLND involves taking para-aortic nodes, and one must be cautious of damage to the sympathetic chain, which will lead to ejaculatory failure. Careful preservation of the sympathetic chain (at least one and its preaortic fibres) can reduce the chances of ejaculatory failure. In the US, RPLND is the gold standard for staging investigation following radical orchiectomy, whereas in the UK it is only performed on select cases for debulking post-chemotherapy.

39.10.2 Metastatic Disease (Stages II and III)

39.10.2.1 Seminomas
- Stage Ila (any pTN1MO50–1): Radiotherapy; long-term relapse-free survival 92–95% [33, 34].
- Stage IIb (any pTN2M0S0–1): Radiotherapy (only in small volume stage 2b because of the toxicity to the bowel); long-term relapse-free survival 89–90% [33, 34]. Chemotherapy with four cycles of EP (indications to leave out B: smoking, age older than 50, chronic obstructive pulmonary disease, and top athletes) or three cycles of BEP achieve similar long-term relapse free rates (87%) to radiotherapy [35].
- Stage ≥III: Chemotherapy with BEP with or without RPLND if residual lymph nodes >3 cm

39.10.2.2 NSGCTs
- Dependent on the prognostic grouping (Table 39.6).
  – Chemotherapy with three cycles of BEP or four cycles of EP if bleomycin indicated for the good prognosis group and four cycles of BEP for intermediate and poor prognostic group [7]. Nerve-sparing RPLND for residual or recurrent mass or for patients unwilling to undergo primary chemotherapy. Cure rate for either is nearly 98% [7].

39.10.2.3 Residual or Refractory Disease or Relapse after Primary Treatment
For seminomas: if HCG is elevated, the patient must undergo salvage chemotherapy. Salvage radiotherapy in small volume disease is an alternative. If HCG is negative, patients should undergo histological verification with either biopsy or surgical excision or positron emission tomography (PET) scanning before salvage chemotherapy [7].

NSGCTs: Residual disease (masses >1 cm) should be completely resected within four to six weeks of completion of chemotherapy [7]. After chemotherapy, only 10% of residual masses will contain viable cancer, 50% will contain mature teratoma, and 40% will contain necrotic-fibrotic tissue [7].

Salvage chemotherapy after first-line chemotherapy can give up to 54% of patients long-term remission [36]. The recommended regime is four cycles of etoposide, ifosfamide, and cisplatin (PE1/VIP), our cycles of paclitaxel, ifosfamide, cisplatin (TIP), or four cycles of vinblastine, ifosfamide, and cisplatin (VeIP) [7].

Late relapse, occurring >2 years after chemotherapy for metastatic disease of NSGCTs, should undergo immediate radical surgery and excision of all lesions [7]. If it is not possible to resect all the lesions, then salvage chemotherapy should be given.

Postprimary chemotherapy surgical excision should be carried out in specialised centres with appropriate interdisciplinary specialities in case hepatic resection, vessel replacement, spinal neurosurgery, or thoracic
surgery are needed. These centres are capable of reducing perioperative mortality from 6 to <1%, in addition to reducing local recurrence rates from 16 to 3% [7]. If completely excised, no further treatment is required, otherwise two cycles of chemotherapy should be given [7].

Salvage surgery, carried out after salvage chemotherapy of all residual masses, can provide up to 25% long-term survival [7].

39.10.3 Other Considerations in the Treatment of These Patients

It is advised that consideration is given to performing fertility investigations before commencing chemo- or radiotherapy. Sperm abnormalities are often found in patients with testis tumours, and subsequent chemo- or radiotherapy can further impair fertility. These tests include total testosterone, luteinising hormone (LH), follicle-stimulating hormone (FSH), and semen analysis. It is important to discuss the use of sperm banking with your patient and their partner if necessary. This should be considered before orchietomy or if not possible at least before commencement of chemotherapy. Patients should be offered a testicular prosthesis which can occur at time of initial orchietomy or at a later date. In cases of bilateral orchietomy, lifelong testosterone treatment may be necessary.

39.10.4 Follow-Up

As recurrence or relapse can occur at any time, strict follow-up regimes were recommended by the European Association of Urology to ensure detection and subsequent treatment is carried out promptly, allowing for a higher chance of survival and cure rate (Table 39.7).

Table 39.7 European Association of Urology recommended follow up regimes.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3–5</th>
<th>Year 6–10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a) Stage I NSGCT under surveillance management</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>4 times</td>
<td>4 times</td>
<td>Once a year</td>
<td>Once a year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>4 times</td>
<td>4 times</td>
<td>Once a year</td>
<td>Once a year</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>2 times</td>
<td>2 times</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AbdoPelvic CT scan</td>
<td>2 times (at 3 and 12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>b) Stage I NSGCT after RPLND</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>Year 1</td>
<td>Year 2</td>
<td>Year 3–5</td>
<td>Year 6–10</td>
</tr>
<tr>
<td>Physical examination</td>
<td>4 times</td>
<td>4 times</td>
<td>Once a year</td>
<td>Once a year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>4 times</td>
<td>4 times</td>
<td>Once a year</td>
<td>Once a year</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>2 times</td>
<td>2 times</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AbdoPelvic CT scan</td>
<td>1 time</td>
<td>1 time</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>c) Stage I Seminomas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>Year 1</td>
<td>Year 2</td>
<td>Year 3–5</td>
<td>Year 6–10</td>
</tr>
<tr>
<td>Physical examination</td>
<td>3 times</td>
<td>3 times</td>
<td>Once a year</td>
<td>Once a year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>3 times</td>
<td>3 times</td>
<td>Once a year</td>
<td>Once a year</td>
</tr>
<tr>
<td>AbdoPelvic CT scan</td>
<td>2 times</td>
<td>2 times</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>d) Stage II and Metastatic disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>Year 1</td>
<td>Year 2</td>
<td>Year 3–5</td>
<td>After 5 years</td>
</tr>
<tr>
<td>Physical examination</td>
<td>4 times</td>
<td>4 times</td>
<td>Twice a year</td>
<td>Once a year</td>
</tr>
<tr>
<td>Tumour markers</td>
<td>4 times</td>
<td>4 times</td>
<td>Twice a year</td>
<td>Once a year</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>4 times</td>
<td>4 times</td>
<td>Twice a year</td>
<td>Once a year</td>
</tr>
<tr>
<td>AbdoPelvic CT scan</td>
<td>2 times</td>
<td>2 times</td>
<td>As Indicated</td>
<td>As Indicated</td>
</tr>
<tr>
<td>Chest CT scan</td>
<td>As Indicated</td>
<td>As Indicated</td>
<td>As Indicated</td>
<td>As Indicated</td>
</tr>
<tr>
<td>Brain CT scan</td>
<td>As Indicated</td>
<td>As Indicated</td>
<td>As Indicated</td>
<td>As Indicated</td>
</tr>
</tbody>
</table>

* An abdominal CT must be performed at least annually if teratoma is found in the retroperitoneum.
* If the postchemotherapy evaluation in a seminoma patient shows any mass >3 cm, the appropriate CT should be repeated two and four months later to ensure that the mass is continuing to regress. If available, FDG-PET/CT can be performed.
* A chest CT is indicated if abnormality is detected on a plain radiography chest and after pulmonary resection.
* In patients with headaches, focal neurological findings, or any central nervous system symptoms.
CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; NSGCT, nonseminomas germ cell tumour; RLPND, retroperitoneal lymph node dissection.
39.11 Nongerm Cell Tumours

The majority of this chapter is devoted to GCTs because they are by far the most common. Often testicular masses are treated as GCTs until the histology proves otherwise. It is important for the urologist to know the main nongerm cell tumours such as Leydig, Sertoli tumours, and granulosa cell tumours. It is also important to be aware of other tumours such as sarcoma or lymphoma that can affect the testis.

39.11.1 Sex Cord or Gonadal Stromal Tumours

Rare tumours accounting for 2–4% of all testicular tumours.

39.11.2 Leydig Cell Tumours

Incidence: Leydig cell tumours (LCTs) account for 1–3% of all adult testicular tumours, more commonly in the third to sixth decades of life and 3% of infant and children testicular tumours, between three and nine years of age [11]. Nearly 5–10% of patients have a history of cryptorchidism, and there have been occasional cases in patients with Klinefelter syndrome [11]. Nearly 10% are malignant and rarely occurring bilaterally (3%) [7, 11].

Asymptomatic or painless testicular mass or lump is the most common presentation. Gynecomastia is seen in about 30% of patients [11]. Other features such as loss of libido and potency in adults or precocious puberty in adolescents are not uncommon.

Investigations: Comprise of hormone levels, tumour markers, and imaging.

- Hormone levels: these tumours produce steroids, particularly testosterone, androstenedione, and dehydroepiandrosterone [11]. Serum oestrogen and estradiol levels can be elevated and may be associated with low testosterone and high LH and FSH levels.
- Tumour markers: to distinguish between LCT (negative) and GCTs.
- Ultrasound: as this will provide a diagnosis of a mass in the body of the testis but might not distinguish between LCTs and GCTs.
- Malignant LCT are large sized (>5 cm), cytological atypia, have increased mitotic activity (>3 per 10 high power field), have increased MIB-1 expression (18.6% vs 1.2% in benign), necrosis, vascular invasion, infiltrative margins, extension beyond the testicular parenchyma, and DNA aneuploidy [7, 11].

It is likely that these tumours will be treated as GCTs and radical orchiectomy performed. Organ-sparing procedures in small intraparenchymal lesions are sent of pathological confirmation sometimes. Immediate orchiectomy can be avoided in patients with gynecomastia and hormonal imbalances as suspicion will lie with a LCT instead of a GCT [7]. Fresh-frozen sections can be carried out if any doubt, and if CGT is confirmed the surgeon can proceed to orchiectomy.

Malignant LCT are managed by radical orchiectomy followed by retroperitoneal lymphadenectomy [7]. These tumours respond poorly to radiotherapy or chemotherapy and metastases invariably leads to death [11].

39.11.3 Sertoli Cell Tumours (SCT)

Account for <1% of testicular tumours with a mean age of presentation of 45 years [11]. SCTs can be associated with genetic disorders such as androgen insensitivity syndrome, Carney syndrome, and Peutz-Jeghers syndrome [11].

Clinical features: A slowly enlarging testicular mass; it can be bilateral in 44% of patients [7].

Pathological classification:

- Classic SCTs
- Large cell calcifying form
- Sclerosing form

Ultrasound cannot safely distinguish between SCTs and GCTs. However, large cell calcifying form SCTs have a characteristic brightly echogenic foci due to calcification [11]. Tumour markers are negative.

Malignant SCTs range from 10 to 22% and typically are large (>5 cm), pleomorphic nuclei with nucleoli, increased mitotic activity (>5 per 10 high power field), necrosis, and vascular invasion [7, 11].

Similar to LCTs where small masses are misdiagnosed as GCTs and radical orchectomy performed. For small lesions, organ-sparing surgery is performed, or fresh-frozen section, and only on histological confirmation of GCT, is orchectomy performed.

Malignant SCT are managed by radical orchectomy followed by retroperitoneal lymphadenectomy [7]. These tumours respond poorly to radiotherapy or chemotherapy and metastases invariably leads to death [11].

39.11.4 Granulosa Cell Tumours (GrCT)

There are two types of GrCT, an adult and a juvenile form. Adult GrCTs are rare and are limited to case reports in the literature. The average age of presentation is 44 years [11]. A quarter present with gynecomastia. Patients have a high serum inhibin and müllerian-inhibiting hormone levels. Nearly 20% of GrCTs are malignant and are large (>7 cm) with vascular invasion and necrosis [7].

Juvenile GrCTs are benign and represent 6.6% of prepubertal testicular tumours [11]. Clinical features are of an asymptomatic scrotal or abdominal mass and 30% are associated with an abdominally located cryptorchidism [11]. Nearly 20% of patients have ambiguous genitalia (with 45X/46XY mosaicism or structural anomalies of Y chromosome), with mixed gonadal dysgenesis being most frequent followed by hypospadias [11]. These tumours are cystic on ultrasonography. Treatment is conservative.
39.12 Tumours Containing Both Germ Cell and Sex Cord or Gonadal Stromal Elements: Gonadoblastoma

Composed of large germ cells (seminomas) and small cells (Sertoli and granulosa), most commonly seen in 15–25% of mixed gonadal dysgenesis associated with ambiguous genitalia and 45,X karyotype and Y chromosome material [11]. Bilateral in 40% of cases. Prognosis is based on the germ cell component [7].

39.13 Other Tumours of the Testis

39.13.1 Sarcomas

Testicular and paratesticular adnexal sarcomas are the most common urinary tract sarcomas. Liposarcoma is the most common in adults with rhabdomyosarcoma occurring more commonly in the younger (<30 years of age) age groups. Others include leiomyoma, malignant fibrous histiocystoma, and fibrosarcoma.

Clinical features include an asymptomatic scrotal swelling or lump which can be large (>5 cm).

Ultrasound demonstrate a solid mass, however cannot distinguish between benign and malignant tumours. An MRI scan can be useful. Otherwise, surgical exploration and biopsy is advocated.

Radical orchiectomy with or without RPLND is the treatment of choice. Chemotherapy reserved for patients with regional or distant metastasis.

39.13.2 Lymphoma

Testicular lymphoma (TL) comprises of 2% of TCa, 2% of all high-grade lymphomas and 5% of all extranodal lymphomas [11]. Primary TL comprises of 40–60% of TLs and most patients are between 60 and 80 years of age, whereas in children TL is rare, occurring between 3 and 10 years of age. Paratesticular lymphoma (PTL) alone is rare and usually present with TL, with 25–60% of TL showing local spread to paratesticular tissue [11].

Scrotal swelling, with bilateral involvement is rare. However, lymphoma recurrence in the contralateral side is more common (10–40%) [11]. Ultrasound of TL is often indistinguishable from GCTs; those of PTL, appear as multiple nodules or as a diffuse infiltration of the epididymis or spermatic cord with or without testicular involvement. Lymphoma should be suspected when these features are seen and involve both testicular and paratesticular tissue.

Prognosis tends to be poor, with a median survival 32–53 months, with a 5- and 10-year overall survival rates of 37–48% and 19–27%, respectively [11]. In children with primary TL, prognosis is excellent with orchiectomy and chemotherapy, whereas in secondary TL, chemotherapy alone can be curative without the need for orchiectomy [11].

39.14 Tumours of the Paratesticular Structures

These are extremely rare and limited to case reports or series in the literature (Table 39.8).

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BENIGN</strong></td>
<td>Ultrasound-smooth, round, well circumscribed hyperechoic homogeneous mass that arises from the epididymis, spermatic cord, or tunica albuginea all of which extra-testicular.</td>
<td>Conservative management, however if become symptomatic surgical excision can be offered.</td>
</tr>
<tr>
<td>Adenomatoid tumour</td>
<td>Comprising 60% of all benign tumours of the paratesticular tumours [11].</td>
<td></td>
</tr>
<tr>
<td>Cystadenoma</td>
<td>Benign papillary epithelial hyperplasia of the epididymal ducts, Seen in one-third of patients with Hippel-Lindau syndrome.</td>
<td>They are usually small, asymptomatic nodules, however some have been implicated as causing azoospermic infertility.</td>
</tr>
<tr>
<td>Nodular mesothelial hyperplasia</td>
<td>Benign nodules found either attached or unattached in hernia sacs, caused by reaction of the hernia sac during incarceration and inflammation. Patient presents with an inguinal hernia.</td>
<td>Clinically defined hernia</td>
</tr>
</tbody>
</table>

Table 39.8 Tumours of the paratesticular structures.
Table 39.8 (Continued)

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALIGNANT</strong></td>
<td></td>
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</tr>
</tbody>
</table>

### Malignant mesothelioma
- Arise from the tunica vaginalis or albuginea
- Peak incidence between 55 and 75 years of age.
- Strong associated risk factor is asbestos exposure with incidences ranging from 23 to 50% [37, 38].

### Adenocarcinoma of the epididymis
- Rare malignant condition occurring in men from 27 to 82 years of age.
- Clinical features are of a painful or painless scrotal mass, can present with testicular pain or a hydrocele.

### Melanotic neuroectodermal tumour of the epididymis
- Children ages 1–8 years
- Rare tumour
- Clinically presents with firm scrotal mass often with a hydrocele

### Desmoplastic small round cell tumour
- Rare; patients from 5 to 37 years of age.
- These tumours have been implicated with specific genetic abnormalities in the Ewing sarcoma gene on 22q12 and the Wilms' tumour gene, WT1 on 11p13.

### Expert Opinion

Testicular tumours are the most common solid tumour in men ages 20–45, and incidence is rising. 90–95% are of germ cell origin. The most important risk factor for testicular germ cell tumours is cryptorchidism or undescended testis. Diagnosis of testicular cancer requires a combination of scrotal and laboratory examination, scrotal ultrasound, followed by a radical inguinal orchietomy. Risk group classification of patients with GCTs of the testis depends on histology of the tumour, tumour markers and staging, usually a CT scan of the chest and abdomen.

Additional treatment of patients with testicular tumours is very well defined, dependent on the risk group, and can be (a combination of): (i) active surveillance in a subset of compliant patients without signs of metastatic disease; (ii) radiotherapy in low stages of seminoma; (iii) chemotherapy in higher stages of GCTs; (iv) surgery (i.e. RPLND of residual disease after chemotherapy). Patients should be offered fertility counselling and sperm banking before chemo- or radiotherapy.

Patient prognosis depends on the risk group to which they belong. Patients in the low-risk group, for example, have a chance of cure above 95% if they are treated according to current recommendations. Apart from improving therapeutic outcome of patients with testicular tumours, reducing toxicity of current treatment and attention for late toxicity in long-term survivors is a major focus of research.

### References


40

Male Infertility

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Abstract

Fertility is vital to the majority of couples in this modern era. With infertility affecting 15% of couples, knowledge of the causes, diagnosis, and treatment is essential to help in conceiving. This chapter gives an overview of the aetiology, investigations, and treatment modalities available to help couples suffering from infertility.

Keywords  fertility; infertility; reproduction; azoospermia; assisted reproduction

Key Points

- History and examination are key to determine aetiology and also to guide treatment.
- Semen analysis and hormonal profile are essential to aid the diagnosis.
- Differentiation between obstructive and nonobstructive causes is important.
- The use of assisted reproductive techniques has improved pregnancy rates, and various techniques exist depending on the diagnosis required.

40.1 Incidence

Infertility is defined as the failure to conceive after regular, unprotected intercourse for at least 12 months. Infertility affects up to 15% of couples.

A male factor is solely responsible in about 20% of infertile couples and contributory in 30–40% of cases; thus it may be estimated that 7% of men have fertility problems. Female factors alone are responsible for 30%, and idio­pathic infertility accounts for 10–20% of the cases [1].

The chances of natural conception are at their highest in the first three ovulatory cycles with unprotected intercourse, with a natural conception rate of 20–25% per cycle, but this rate gradually decreases with time. After one year, it drops to less than 5% per cycle.

The age of the female partner is a crucial point in determining the fertility of a couple and the success of any fertility treatment. A woman’s fertility is its peak in her 20s and this gradually declines especially older than the age of 35 years. In women 40 years and older, natural conception rate is less than 5% per cycle.

The understanding of infertility starts with understanding the normal male reproductive physiology, see Chapter 36.

40.2 Definitions

Let’s start with some definitions.

- Aspermia: lack of semen
- Asthenozoospermia: reduced sperm motility
- Azoospermia: Absence of sperm from the ejaculate after centrifugation of the sample; it is found in 15–20% of the infertile male population, and in 10% the sperm density below 1 million ml^-1 [2]. Azoospermia can be obstructive or non-obstructive.
40 Male Infertility

- Oligospermia: a low sperm concentration < $15 \times 10^6$ per mil of ejaculate.
- Necrozoospermia: dead sperm
- Teratospermia: sperm have an abnormal morphology.

40.3 History and Examination

History and examination are vital to help determine the aetiological factor(s) and prognosis as well as plan further investigation and treatment.

A full medical history is taken, including previous reproductive history, sexual history, developmental history, general medical and surgical history, and drug history. An emphasis is made on lifestyle factors such as alcohol, tobacco, the use of recreational drugs, scrotal heat exposure, and the frequency of intercourse.

The examination of the male should be conducted by a urologist. The focus of the male examination is assessment of the scrotal contents (Table 40.1).

40.4 Aetiology

40.4.1 Functional Causes of Male Infertility

40.4.1.1 Genetic Causes

40.4.1.1.1 Chromosomal Abnormalities

Chromosomal abnormalities are found in 4–15% of infertile men compared to 0.4% of the general population. The lower the sperm count the higher the prevalence [3].

Klinefelter syndrome (KS) is the most common numerical abnormality; it occurs in 1 in 500–1 in 1000 live male births and in up to 10% of men with nonobstructive azoospermia. Most cases are of the nonmosaic form, 47XXY. KS is associated with primary testicular failure. Patients present with azoospermia, hypogonadism, gynaecomastia, reduced testicular size, and some may have learning difficulties. The severity of symptoms depends on the extent of Leydig cell dysfunction [4, 5].

47XYY male syndrome is another numerical disorder occurring in 1 in 1000 births and is associated with subfertility and tall stature. Patients may also have reduced intelligence, antisocial behaviour, and a higher risk of developing leukaemia [6].

46,XX male syndrome involves abnormal translocation of the SRY gene from the Y chromosome to the X chromosome or an autosome during meiotic division of paternal spermatogenesis. An SRY negative form involves activation of genes down the SRY cascade. Thus the gonads will develop into testes and the müllerian duct structures will regress. The testes are small however, and there is no spermatogenesis due to the absence of the azoospermia factor (AZF) region. There may also be a degree of hypogonadism, gynaecomastia, ambiguous genitalia, and undescended testes due to lack of virilisation.

Structural chromosomal defects include balanced Robertsonian and reciprocal translocations which are a cause of infertility and repeated abortion [7]. Because there is no loss of genetic material, patients will have normal phenotype; however, some of the sperm will lack or have excess genetic material. Abnormal sperm undergoes apoptosis, which explains why these patients present with azoospermia or oligozoospermia. During in vitro fertilisation (IVF) treatment, prenatal genetic diagnosis (PGD) is a must to avoid the transfer of embryos with unbalanced karyotype.

40.4.1.1.2 Y Chromosome Microdeletions

The AZF gene is found on the long arm of the Y chromosome. Microdeletions of this gene are associated with impaired spermatogenesis. AZF microdeletions are found in 5–10% of infertile men, especially those with counts less than 2 million sperm per ml [3]. An AZFc microdeletion reduces spermatogenesis but does not stop it completely. Men with an AZFc microdeletion may be oligozoospermic and may even father children naturally. Those who are azoospermic may still have a chance of fathering children via surgical sperm retrieval and intracytoplasmic sperm injection (ICSI) [8]. However, they will pass this microdeletion to their male offspring who will therefore be infertile. AZFa and AZFb microdeletions completely inhibit spermatogenesis. Patients with such deletions will be azoospermic and will not have any intratesticular spermatogenesis; thus surgical sperm retrieval should not be offered [9].
40.4.1.3  Androgen Receptor Gene Mutations
Minimal androgen insensitivity may be suspected in an infertile male from the clinical signs of hypogonadism accompanied by elevated testosterone and luteinising hormone (LH). This confirmed by genetic studies of the androgen receptor gene which is located on the X chromosome [10].

40.4.1.4  Genetic Sperm Disorders
Globozoospermia is a rare condition characterised by absence of the acrosomal cap. Sperm characteristically have a round head [11].

Primary ciliary dyskinesia includes several autosomal recessive syndromes resulting in a defect in the axoneme of ciliated cells in the respiratory tract or in the tail of sperm. Kartagener syndrome is seen in 50% of cases and consists of a triad of chronic sinusitis and bronchiectasis, dextrocardia, and infertility [11].


40.4.1.5  Other Genetic Factors
There are numerous other genes not yet identified that regulate sperm production, hormone production, and hormone receptors. Any defect in such genes will impair fertility. These defects are probably responsible for the idiopathic causes of infertility [12].

40.4.1.2  Hormonal Causes
40.4.1.2.1  Hypogonadotropic Hypogonadism
This is caused by hypothalamic–pituitary axis disorders and is characterised by low testosterone level secondary to low LH level which is usually associated with low follicle-stimulating hormone (FSH) level. It may occur in congenital disorders or in acquired conditions such as brain tumours, head injuries, and following radiotherapy or may be idiopathic.

Congenital, idiopathic, or isolated hypogonadotropic hypogonadism (IHH) has prevalence from 1 in 10000 to 1 in 86 000 [13]. IHH occurs due to a variety of gene defects which either prevent the migration of gonadotropin-releasing hormone (GnRH) neurones during embryonic development or prevent the activation of these neurones. Kallmann syndrome occurs in 50–60% of IHH cases and is an X-linked recessive disorder, which, in addition to the hypogonadism, is associated with anosmia and may be associated with midline facial defects, neurologic abnormalities, and unilateral renal agenesis [14, 15].

IHH is usually diagnosed earlier in life because patients present with delayed puberty; however, IHH has different phenotypes, and in some cases the hypoandrogenisation is mild, and patients may only present with infertility and mild hypogonadism. Furthermore, some cases of IHH present in adulthood [3].

Hormonal therapy with LH/FSH preparations can induce spermatogenesis in such cases.

40.4.1.2.2  Other Hormonal Abnormalities
Endocrinopathies such as thyroid gland disorders, hyperprolactinaemia, and primary hypogonadism will also impair sperm production.

40.4.1.3  Varicocele
Varicocele is found in 11.7% of men with normal semen parameters and in 25.4% of men with abnormal semen parameters [16]. Varicocele disrupts spermatogenesis by impairing the venous drainage and interfering with the countercurrent exchange of heat mechanism from the spermatic cord which causes elevation of the scrotal temperature. Varicocele also causes hypoxia and interferes with the drainage of toxins from the testes [17]. Varicocele may be associated with progressive testicular atrophy, impaired semen parameters, and Leydig cell dysfunction [18].

40.4.1.4  Undescended Testes
Cryptorchidism occurs due to genetic, environmental, and hormonal factors which impair spontaneous testicular descent. It has an incidence of 2–5% at birth, making it the most common congenital abnormality of the male genital tract; however, spontaneous descent occurs in many cases by the age of three months, and the incidence is reduced to 1–2% [16]. A history of cryptorchidism and orchidopexy is found in 10% of infertile men [19].

Cryptorchidism is also associated with impaired spermatogenesis due to degeneration of the germ cells [20]. In men with bilateral cryptorchidism, oligozoospermia is found in 31% and azoospermia in 42% of cases. In men with bilateral cryptorchidism, paternity is only 35–53% [21]. Unilateral cryptorchidism is also associated with reduced fertility; however, paternity in men with a history of unilateral cryptorchidism is almost equal to that in the general male population (89.7 and 93.7%, respectively) [22].

In addition to subfertility, the risk of developing germ cell tumours in men with history of undescended testes is 2–6% compared to 0.001–0.01% in the general male population, and there is a history of cryptorchidism in 5–10% of testicular tumours [16, 23].

40.4.1.5  Testicular Tumours
Testicular cancer occurs in 0.5–1% of infertile men compared to an incidence of 0.001–0.01% in the male general population [24]. A genetically determined testicular
dysgenesis may be the cause of both conditions [25]. Testicular tumours lead to infertility by destroying and compressing the healthy testicular tissue. In addition, treatment of testicular cancer whether orchiectomy, chemotherapy, or radiotherapy impairs fertility.

40.4.1.6 Exposure to Gonadotoxins
Several agents may affect spermatogenesis by disruption of the hypothalamo-pituitary-gonadal axis including heat, ionising radiation, alkylating agents, heavy metals, recreational drugs, tobacco, alcohol, insecticides, pesticide, and synthetic oestrogens.

40.4.1.7 Systemic Diseases
Systemic diseases whether acute such as fever, burns, and viraemia or chronic such as liver cirrhosis, renal failure, haematological disease, and endocrinopathies affect fertility by disruption of the hypothalamo-pituitary-gonadal axis [26].

40.4.1.8 Iatrogenic Factors
Several drugs may have a negative impact on fertility such as anti-androgens, steroids, radiotherapy, and chemotherapy, especially alkylating agents.

40.4.1.9 Orchitis
Inflammation mainly affecting the testes damages the parenchyma causing nonobstructive infertility as in mumps orchitis, while inflammation of the epididymis causes obstructive infertility such as postgonococcal and chlamydial infections.

40.4.1.10 Infection of the Accessory Glands
Infection of the urethra, prostate, seminal vesicles, and epididymis may affect fertility by the direct effect of bacterial toxins, elevated reactive oxygen species (ROS) levels, DNA fragmentation, accessory gland dysfunction, and secondary obstruction.

40.4.1.11 Testicular Torsion
Testicular torsion affects 1 in 4000 males younger than age of 25. Untreated torsion causes ischaemic necrosis of the seminiferous tubules and shrinking of the testis on the affected side [27]. Furthermore, disruption of the blood-testis barrier may be followed by the production of anti-sperm antibodies which affect the other testis.

40.4.1.12 Testicular Trauma
Blunt scrotal trauma can damage the testicular parenchyma and cause intratesticular haematomas, which lead to pressure atrophy of the surrounding seminiferous tubules and scarring. Testicular trauma may also lead to the disruption of the blood-testis barrier and the production of anti-sperm antibodies.

40.4.1.13 Autoimmune Infertility
The blood-testis barrier, which is formed by Sertoli cells, separates germ cells from the immune system. Disruption of this barrier by trauma, orchitis, torsion, varicocele, and surgery causes the production of anti-sperm antibodies which impair sperm motility and sperm-ovum interactions [28].

40.4.2 Genital Tract Obstruction

40.4.2.1 Intratesticular Obstruction
Intratesticular obstruction occurs in 15% of obstructive azoospermia (OA). It may be congenital due to disconnection between rete testis and efferent ductules or acquired due trauma and inflammation [29]. This blockage is not amenable to surgical reconstruction.

40.4.2.2 Epididymal Obstruction
The most common cause of obstructive infertility is epididymal obstruction which accounts for 30–67% of OA [29]. Epididymal obstruction is mostly caused by epididymitis which is secondary to chlamydial or gonococcal urethritis or urinary tract infections. It may also result from scrotal trauma, surgery, or occur congenitally as in disconnection of the epididymal head and body, atresia, agenesis, and Young syndrome, which consists of a triad of chronic sinusitis, bronchiectasis, and azoosperma due to epididymal obstruction by viscid secretions.

40.4.2.3 Congenital Absence of the Vas Deferens
Congenital absence of the vas deferens (CBAVD) may be unilateral be or bilateral and occurs due to two types of genetic defects. CBAVD affects 1–2% of the infertile male population and 6% of men with obstructive azoosperma [30]. Men with CBAVD will have low semen volume azosperma with an acid PH.

Cystic fibrosis is an autosomal recessive disease which affects 1 in 2500 people of Caucasian descent with a carrier frequency of 1 in 25 [30]. The cystic fibrosis gene encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein and is located on chromosome 7. Mutations in both alleles of the CFTR gene causes cystic fibrosis disease due the deficiency of CFTR protein which regulates the sodium and chloride balance in epithelial secretions and regulates their viscosity; the CFTR protein also influences the formation of the ejaculatory duct, seminal vesicles, the vas, and the distal two-thirds of the epididymis. All men with cystic fibrosis disease have vasal aplasia in addition to obstructive pulmonary disease and pancreatic exocrine failure due to high viscosity of the epithelial secretions. Men who only present with vasal aplasia represent a mild form of cystic fibrosis disease due to milder mutations [11].
Another form of vasal aplasia found in 10–20% of cases is due to other gene mutations (non-CFTR). This type may be associated with unilateral renal aplasia [31].

Vasal aplasia cannot be surgically corrected; however, affected men may father children via surgical sperm retrieval and ICSI. Men who test positive for CFTR gene mutations should have their female partners screened. If the female partner is a carrier for one of the CFTR gene mutations, preimplantation genetic diagnosis before embryo transfer is a must because the couple would have a 25% chance of having an offspring with full-blown cystic fibrosis disease.

### 40.4.2.4 Vasal Obstruction

Vasectomy is a popular and effective form of male contraception; however, 2–6% of those men request a reversal [32]. Vasal obstruction not due to vasectomy occurs secondary to surgeries in the region of the inguinal canal or pelvis, such as hernia repair, bowel surgery, ureteric surgery, and orchidopexy.

### 40.4.2.5 Ejaculatory Duct Obstruction

Ejaculatory duct obstruction (EDO), either complete or partial, can be found in 5% of infertile men.

Causes of EDO are congenital and acquired.

**Congenital causes:**
- Congenital midline prostatic cysts: müllerian and wolffian duct cysts.
- Atresia or stenosis of the ejaculatory ducts.
- Agenesis of the ejaculatory ducts.

**Acquired causes:**
- Post traumatic: after pull through operations for imperforate anus, perineal surgeries, prostate biopsy, or urethral instrumentation.
- Post inflammatory: Gonorrhea, nonspecific urethritis, and prolonged catheterization are the most common causes; however, chronic prostatitis, prostatic calcifications, prostatic abscess, tuberculosis, and schistosomiasis have also been implicated in EDO.
- Neoplasia.
- Ejaculatory duct calculi.
- Acquired prostatic cysts.
- Functional obstruction due to neuropathy where there is either atony or hypertony.

In addition to infertility, patients may also present with painful ejaculation and reduced force and volume of ejaculate, haemospermia, dysuria, pelvic pain, and scrotal pain [33].

Men with complete bilateral EDO will have low volume azoospermia with an acid PH.

### 40.4.3 Coital Infertility

Sexual dysfunction may interfere with deposition of the semen in the vagina.

#### 40.4.3.1 Erectile Dysfunction

Men with severe erectile dysfunction may be unable to penetrate the vagina.

#### 40.4.3.2 Premature Ejaculation

In severe cases, ejaculation occurs before intromission.

#### 40.4.3.3 Penile Deformities

Men with severe penile curvature whether congenital or secondary to Peyronie disease may have problems in vaginal penetration. Men with abnormal position of the urethral meatus, as in hypospadias, may have problems in sperm deposition.

#### 40.4.3.4 Anejaculation

Anejaculation may occur secondary to injury of the sympathetic chain during pelvic or abdominal surgery or as a consequence of autonomic neuropathy as in diabetes or drugs such as antidepressants and alpha-blockers. Primary anejaculation may occur due to psychosexual factors or decreased sensitivity of the genital organs or high threshold of the ejaculatory reflex [34].

#### 40.4.3.5 Retrograde Ejaculation

Retrograde ejaculation is diagnosed by the presence of sperm in postorgasmic urine. It occurs due the same causes as anejaculation but represents a milder pathology in which there is emission but the bladder neck fails to contract. It can also occur after transurethral resection of the prostate and with alpha-blockers [34].

### 40.5 Investigations for Male Infertility

#### 40.5.1 Semen Analysis

This is the first and arguably the most direct guide is semen analysis.

The results of semen analysis provide a guide to whether other investigations are needed or not (Tables 40.2 and 40.3). The results may provide a diagnostic clue for certain conditions (e.g., the presence of low volume, azoospermia, negative fructose, and an acid pH are pathognomonic of EDO or CBAVD). A second test is indicated if the first test is abnormal. A two- to seven-day abstinence period is needed before collection.

There are other specialised semen tests as well.
40.5.1.1 Antisperm Antibodies
This is now part of the routine semen analysis. The presence of more than 50% of sperm is bound to antibodies is a significant result and indicates immunological infertility. Found in 10% of men with infertility, antisperm antibodies form if the blood-testes barrier is breached. The barrier is formed by tight junctions between the Sertoli cells separating the developing spermatozoa from the immune system. Any traumatic or inflammatory condition to the testes can disrupt the blood-testes barrier, including obstruction as seen post vasectomy and in patients with CBAVD. Antibodies are either from the genital tract mucosal surface (IgA) or most likely the blood (IgG) and are only seen on mixed agglutination tests. Assisted reproductive technology (ART) is now the treatment of choice for such cases rather than the use of steroids for immunosuppression.

40.5.2 Male Reproductive Hormonal Profile
The basic hormones that are tested are FSH, LH, prolactin, and testosterone, especially when the sperm density is <10^6 ml⁻¹ (Table 40.4). Other hormone and blood tests may be tested if there is a clinical indication such as thyroid hormones and cortisol. Men who are obese should also be tested for estradiol.

40.5.3 Male Reproductive Genetic Profile
Genetic profiling includes karyotype, Y chromosome microdeletions, and cystic fibrosis gene mutations (CFTR gene). Karyotyping is indicated in men with sperm counts <10^6 ml⁻¹, nearly 5% of oligozoospermia and 15% of azoospermia will have an abnormal karyotype; Y chromosome microdeletion testing is indicated when the sperm density is <5 x 10^6 cc⁻¹ with a frequency of up to 5 and 10% in oligozoospermic and azoospermic patients, respectively. CFTR gene mutation tests are indicated for both patient and partner in cases of vasal aplasia and other forms of congenital obstruction of the genital tract [37–39].
40.5.4 Postorgasmic Urine Analysis

Postorgasmic urine (POU) analysis is indicated in low semen volume, and dry ejaculate to diagnose retrograde ejaculation by detecting sperm in the postorgasmic urine sample.

40.5.5 Imaging

40.5.5.1 Scrotal Ultrasound and Colour Doppler

Scrotal ultrasonography is done to assess the testes and epididymi and to detect their dimensions and exclude the presence of tumours or varicocele. It will also show testicular microlithiasis, which may indicate testicular carcinoma in situ (Figures 40.1 and 40.2) [40].

40.5.5.2 Transrectal Ultrasound Scan

Transrectal ultrasound (TRUS) should be performed in all cases with low semen volume and ejaculatory dysfunction to diagnose anomalies of the distal genital tract such as EDO (Figure 40.3).

TRUS findings suggestive of EDO include:

- Midline cysts which are anechoic and well defined.
- Dilated seminal vesicles (larger than 15 mm in transverse diameter).
- Dilated ejaculatory duct (diameter larger than 2 mm).
- Hyperechoic regions suggestive of calcifications along the course of the ejaculatory ducts.
- Ejaculatory duct calculi which have hyperechoic appearance.

Other imaging tests include:

TRUS-guided seminal vesiculography: To confirm TRUS findings of EDO (Figure 40.4).

Renal ultrasound: to exclude secondary varicocele due to a mass lesion blocking venous return in men with large varicoceles and in men with vassal aplasia to exclude renal anomalies, which may be found in 10–20% of cases.

Magnetic resonance imaging (MRI) of the pelvis: may help in diagnosing obstructions and abnormalities in the distal genital tract. It may also help in locating the testes in cases of undescended testes.

Magnetic resonance imaging of the brain: in cases of hyperprolactinaemia and hypogonadotropic hypogonadism.

40.6 Testis Biopsy

During surgical sperm retrieval, a small piece of tissue is taken to study the testicular architecture and exclude carcinoma in situ. The tissue is kept in Bouin’s solution which is a mixture of formalin, alcohol, and picric acid that prevents cellular distortion and gives a better picture of the seminiferous tubule (Figure 40.5).

Because spermatogenesis does not proceed at a uniform rate in every tubule in the testis, but in waves (i.e. some
actively dividing and others resting) the interpretation of a biopsy makes it necessary that several tubules are present, and the opinion is based on the proportion of tubules in the biopsy which show each stage in spermatogenesis. This is the Johnsen mean score (Table 40.5). At least 10 tubules are examined. Each is assigned a score on a scale of 1–10. The normally fertile man has a mean score of 9.38 ± 0.24. There is a direct correlation to the testicular volume to the Johnsen score (i.e. the smaller the testicles the more likely there will be a smaller score).

Testis biopsy should not be offered as an investigation independent from surgical sperm retrieval because it would still be invasive and if sperm is found it will not be stored which would be a waste, and if sperm was not found, it would not mean that this is the picture in the rest of the testicular tissue as there may be patchy areas with active spermatogenesis.

Table 40.5 The Johnsen Score of testicular biopsy.

<table>
<thead>
<tr>
<th>Score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Complete spermatogenesis, many spermatozoa</td>
</tr>
<tr>
<td>9</td>
<td>Many spermatozoa, disorganised germinal epithelium</td>
</tr>
<tr>
<td>8</td>
<td>Few spermatozoa (&lt;5–10)</td>
</tr>
<tr>
<td>7</td>
<td>No spermatozoa but many spermatids</td>
</tr>
<tr>
<td>6</td>
<td>No spermatozoa and few spermatids (&lt;5–10)</td>
</tr>
<tr>
<td>5</td>
<td>No spermatozoa or spermatids, but many spermatocytes</td>
</tr>
<tr>
<td>4</td>
<td>Few spermatocytes (&lt;5), no spermatozoa or spermatids</td>
</tr>
<tr>
<td>3</td>
<td>Spermatogonia are the only germ cells</td>
</tr>
<tr>
<td>2</td>
<td>Sertoli cells only</td>
</tr>
<tr>
<td>1</td>
<td>No cells in tubules</td>
</tr>
</tbody>
</table>
40.7 Treatment of Male Infertility

40.7.1 Obstructive Azoospermia

40.7.1.1 Ejaculatory Duct Obstruction
It may be possible to relieve an obstruction of the ejaculatory ducts by transurethral resection of the ejaculatory ducts (TURED) (Figure 40.6), particularly if the obstruction is found to be at the level of the prostatic urethra. This is done by injecting methylene blue into the ejaculatory system and resecting at the level of the verumontanum, while taking care not to injure the rectum. If a congenital cyst is the cause, simple deroofing can be done. Alternatively, a transurethral resection of the ejaculatory ducts is done. Patency rates of 65–95% and pregnancy rates 20–30% have been reported [33].

40.7.1.2 Vasal Obstruction
This most often results from vasectomy or rarely accidental damage during inguinoscrotal surgery previously in life. If the obstruction is in an isolated segment, such as after vasectomy, the vasal ends can usually be re-anastomosed (vaso-vasostomy). The outcome of repair is dependent on the time interval since the vasectomy or obstruction. The best outcomes are achieved using a microsurgical technique, and in the largest series, up to 97% of patients regain sperm in the ejaculate if the vaso-vasostomy is done within a three-year interval since vasectomy, with a 76% pregnancy rate [41].

40.7.1.3 Congenital Bilateral Absence of the Vas Deferens
This involves loss of long segments of the vas on both sides and is not reconstructible. However, sperm production is usually normal, and it is easy to palpate and aspirate sperm from the head of the epididymis (see PESA below), for use in assisted conception.

40.7.1.4 Epididymal Obstruction
Where there is spermatogenesis in the presence of an obstructed segment of epididymis, it may be possible to by-pass the obstruction by joining the vas deferens to a single tubule in the body of the epididymis (epididymo-vasostomy) using 10/0 nylon sutures (Figure 40.7). This is technically challenging due to the extremely small diameter of the epididymal tubules (~ 0.2 mm). Patency rates vary from 60 to 87%, with pregnancy rates between 10 and 43% [42].

40.7.1.5 Intratesticular Obstruction
It is not possible to surgically treat obstruction within the testis, and it is therefore necessary to obtain sperm through testicular sperm aspiration (TESA) or biopsy or TESE (see below).

40.7.2 Nonobstructive Azoospermia
Attempted surgical sperm retrieval followed by ICSI is the mainstay of treatment for nonobstructive azoospermia (NOA). Following diagnosis of NOA, it is important to counsel the patient fully risks and benefits of surgical sperm retrieval, including the estimated chances of sperm being found. Although there is no accurate predictive factor, it is possible to give a rough estimate of the odds based on clinical and investigative parameters.

Figure 40.6 Transurethral resection of the ejaculatory ducts using a resectoscope. Methylene blue dye which was inserted just before resection during TRUS-guided seminal vesiculography can be seen coming out through the resected duct indicating adequate resection. TRUS, transurethral ultrasound.

Figure 40.7 Epididymo-vasostomy. Source: Courtesy of Mr. Nim Christopher.
40.7.3 Surgical Sperm Retrieval Techniques

40.7.3.1 PESA
Sperm can be retrieved successfully from most patients with obstruction by percutaneous epididymal sperm aspiration (PESA). This can be done under local anaesthesia.

40.7.3.2 MESA
Microsurgical epididymal sperm aspiration is usually performed in cases of obstruction during microsurgical epididymo-vasostomy.

40.7.3.3 TESA
When sperm cannot be obtained from the epididymis as in cases of intratesticular obstruction or if microsurgical reconstruction is to be performed at a later date, testicular sperm aspiration can be done.

40.7.3.4 TESE
Testicular sperm extraction involves delivery of the testes and taking multiple random biopsies from different quadrants. TESE was previously the technique of choice for surgical sperm retrieval in NOA; however it has now been replaced by Micro-TESE.

Microdissection TESE (Figure 40.8)

The testes are delivered and an equatorial incision involving three-quarters of the circumference is made using the surgical microscope to avoid vascular injury, the testis is bivalved, microdissection is then performed to expose the seminiferous tubules and multiple tiny pieces of testicular tissue are taken from areas that have dilated opaque tubules which are more likely to contain sperm. This technique has been shown to be superior to standard TESE in terms of sperm retrieval rate [43]. Thus, micro-TESE should be offered to all men with NOA.

The surgical sperm retrieval rate is 100% for men with OA. In men with NOA, however, sperm can be found in approximately 50% of the cases, and although clinical and investigative parameters can be used to help with prognosis, there is no single reliable predictive factor. However, the presence of AZFa and AZFb Y chromosome microdeletions is a highly negative predictive factor [44].

40.8 Assisted Conception Techniques

Assisted conception techniques are usually done by the fertility clinic and will require ovarian stimulation with gonadotrophins.

- Intrauterine insemination: sperm is placed into the uterus
- IVF: oocytes are retrieved by transvaginal ultrasound-guided needle aspiration and placed in petri dish with sperm for fertilisation to take place. Once fertilised, embryos are incubated for two to three days then placed into the uterine cavity. Pregnancy rates vary between 20 and 40%
- ICSI and IVF: a single sperm cell (spermatozoa) is injected into the oocyte. Incubated then placed into the uterine cavity. Pregnancy rates are between 10 and 40%, highly dependent on the female age; pregnancy rates of 40% if younger than 35 years of age and drops to 11% if older than 40 years of age.

Malformation rates with assisted reproductive techniques are <6% (6.2% with ICSI and 4.1% with IVF) which is not significantly higher than natural pregnancy, which has a malformation rate of 4.4%.

40.9 Varicocele Repair

There is insufficient evidence to link varicocele repair with improved pregnancy rates [45]. However, up to 70% of patients with repaired varicocele will have improvement in their sperm parameters: on average an increase of 10 million sperms, 10% improvement in sperm motility, and 3% improvement of sperm morphology. This reflects to a 16% increase in paternity rate [45, 46].

A number of treatment options are available for varicocele treatment (Table 40.6). Of the surgical procedures, the lowest recurrence rate is following a microsurgical subinguinal approach [47].

Table 40.6 Treatment options for varicocele repair.

<table>
<thead>
<tr>
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<tr>
<td>High ligation of vein only (Bernandi)</td>
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<tr>
<td>Laparoscopic high ligation</td>
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<tr>
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</tr>
<tr>
<td>Antegrade sclerotherapy (high scrotal incision)</td>
</tr>
<tr>
<td>Retrograde sclerotherapy (embolisation)</td>
</tr>
<tr>
<td>Subinguinal microsurgical ligation</td>
</tr>
</tbody>
</table>
Medical therapy can be effective for some specific causes of male fertility and is also sometimes offered as empirical therapy when there is male infertility of unknown cause.

It is important to realise that the testes are responsible for the production of sperm and testosterone, and although spermatogenesis is dependent on high levels of intratesticular testosterone, exogenous administration of testosterone may inhibit spermatogenesis via a negative feedback effect via the hypothalamic–pituitary system.

### 40.10.1 Endocrine Treatments

#### 40.10.1.1 Gonadotrophin-Releasing Hormone

Deficiency of gonadotrophins (i.e. FSH and LH) such as in Kallman syndrome or idiopathic hypogonadotropic hypogonadism results in reduced intratesticular testosterone and infertility. GnRH therapy is best given in pulsatile doses with a syringe pump and stimulates the anterior pituitary to release FSH and LH, leading to increased spermatogenesis and fertility [48]. However, it may take four months to reach maximum effect. Although there is evidence supporting the use of GnRh in hypogonadotrophic hypogonadism, there is no evidence of benefit in idiopathic infertility.

#### 40.10.1.2 Gonadotrophins

Pituitary insufficiency can be treated with synthetic gonadotrophins such as human chorionic gonadotropin (HCG), recombinant FSH and LH. There is lack of evidence for benefit in idiopathic infertility, but in hypogonadotropic hypogonadism a combination approach using HCG and FSH can achieve pregnancy rates of up to 50% in those previously unsuccessful in achieving pregnancy [49].

#### 40.10.1.3 Dopamine Agonists

Elevated prolactin levels due to a pituitary adenoma will suppress the pulsatile secretion of GnRH, and thus cause hypogonadism and infertility. The infertility can therefore be treated by a dopamine agonist such as cabergoline, which can reduce the size of prolactin-secreting tumours and normalise prolactin levels.

#### 40.10.1.4 Aromatase Inhibitors

Anastrozole and other aromatase inhibitors have been used to increase testosterone levels and decrease oestrogen levels and act by inhibiting the conversion of testosterone to oestrogen by aromatase enzyme especially in patients who are obese because they have increased activity of aromatase enzyme in the adipose tissue. High oestrogen levels (and therefore altered testosterone-to-oestrogen ratio) has been shown to impair spermatogenesis and negatively feedback back to LH and FSH production.

#### 40.10.1.5 Selective Oestrogen Receptor Modulators

Selective oestrogen receptor modulators (SERMs) such as clomiphene citrate and tamoxifen have been used off-label to treat male infertility. Both inhibit the negative feedback of oestrogen on the hypothalamus by blocking oestrogen receptors leading to an increase in the production of LH and FSH, with consequent increase in testosterone production and spermatogenesis. Evidence suggests that using these modulators leads to an increase in sperm concentration and pregnancy rates however, the evidence is scant [50].

#### 40.10.1.6 Treatment of Chronic Prostatovesiculitis

Chronic prostatovesiculitis is associated with impaired semen parameters, elevated ROS and increased DNA fragmentation. It is diagnosed by the finding of white blood cells (WBCs) ≥10⁶ per millilitre of ejaculate. Antimicrobial therapy may be of help in such cases with significant improvement in semen parameters and spontaneous pregnancy rate [51].

#### 40.10.1.7 Treatment with Antioxidants

Antioxidants such as vitamin E, vitamin C, and L-Carnitine have been used empirically to reduce the ROS levels. There is lack adequate data which shows benefit of such treatments.

### Expert Opinion

Management of the infertile male requires specialist care to allow for the identification and treatment of the cause and thus for a spontaneous pregnancy to occur. If treatment fails or no cause is identified (idiopathic cases), the couples are advised to try assisted reproductive techniques. In patients with nonobstructive azoospermia microsurgical testicular sperm extraction (micro-TESE) by a specialist followed by intracytoplasmic sperm injection (ICSI) offers the best chances of fatherhood to these patients.
References

30 Grangea, A., Niel, E., Carvalho, F. et al. (2004). Characterization of cystic fibrosis conductance transmembrane regulator gene mutations and IVS8


Vasectomy and Seminal Vesicle Disorders

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Abstract

The seminal vesicles are about 5 cm long and hold 1–10 ml of fluid. Their secretions comprise 80% of the seminal fluid and all of the fructose content. Joining the vas deferens at the ejaculatory duct, their muscular tubes contract during ejaculation to release the alkaline seminal fluid. Similar to the rest of the body, the seminal vesicles may be afflicted by congenital anomalies, infections, and cancers.

Vasectomy is one of the most common procedures for urology. Thorough counselling is essential before each procedure to warn patients of its potential risks and irreversibility. Only when azoospermia is achieved can the procedure be deemed successful. Vasectomy reversals are possible; however, the chance of pregnancy might be low, necessitating sperm retrieval methods and in vitro fertilisation.

Keywords seminal vesicles; semen analysis; vasectomy; infertility; scrotal pain; vasectomy reversal

Key Points

<table>
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<td>The alkaline section contributes 80% of the volume of the semen.</td>
</tr>
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<td>The seminal vesicles can be afflicted with congenital anomalies, such as agenesis, as well as infections and cancer, albeit extremely rare.</td>
</tr>
<tr>
<td>Transrectal ultrasonography with biopsy is the best method of investigation and differentiating benign and malignant disease.</td>
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<td>Surgical resection is possible if required.</td>
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<table>
<thead>
<tr>
<th>Vasectomy</th>
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<tbody>
<tr>
<td>Vasectomy is one of the most common causes of medico-legal litigation.</td>
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<tr>
<td>Thorough counselling is a must and should address potential irreversibility, complications, and failure rates; no long-term side effects or consequences, such as cancer, exist.</td>
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<tr>
<td>Cauterisation and fascial interposition is the most effective technique.</td>
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<tr>
<td>Complications (on average) include:</td>
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<td>– Haematoma 2%</td>
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<tr>
<td>– Infection 3%</td>
</tr>
<tr>
<td>– Chronic scrotal pain 2–15%</td>
</tr>
<tr>
<td>– Failure: early recanalization 0–2%; late recanalization &lt;1%</td>
</tr>
<tr>
<td>– Death 1 in 1 000 000</td>
</tr>
<tr>
<td>Postoperative semen analysis determines success.</td>
</tr>
<tr>
<td>Vasectomy reversals leading to pregnancy has variable success rates depending on length of time since vasectomy; however, in general, they are disappointing.</td>
</tr>
</tbody>
</table>
41.1 Seminal Vesicles

For many years, the seminal vesicles were something of an enigma to urologists. With the advent of transrectal ultrasound, we have come to appreciate that they may suffer all the disorders that affect all other hollow organs in the body.

Hippocrates noted a paired structure resembling a honeycomb on either side of the base of the bladder. Bold early investigators like Fallopius, de Graaf, and John Hunter all found that their secretions tasted sweet. But their function remained a mystery.

41.1.1 Anatomy and Physiology

The seminal vesicle arises in the third month of foetal life as a diverticulum from the vas deferens (mesonephric ducts) just before it joins the ejaculatory duct. Surrounding mesenchyme clothes it with a muscular coat. It remains small until puberty, when it swells and becomes convoluted.

Blood supply is via the inferior vesical artery and vein and can also receive branches from the superior vesical artery through its umbilical artery branch. Lymphatics follow the blood supply to the internal iliac nodes. The hypogastric nerve via the pelvic plexus supplies the seminal vesicles.

41.1.2 Topographical Anatomy

The seminal vesicles lie in the groove between bladder and prostate, inferior to the ampulla of the vasa efferentia. The ureter passes inferior to the vas deferens en route to the bladder.

In adult life, the vesicle holds from 1.5 to 10 ml of fluid. When unravelled, each vesicle consists of a sac about 15 cm long, with one or two side arms. After the age of 40, its mucosa becomes thinner and flatter, decreasing in size.

The wall, has an external connective tissue layer, a middle bilayered alpha-adrenergic smooth muscle layer (i.e. external longitudinal and internal circular), and an internal mucosal layer. Stimulation of the presacral nerve causes them to contract. This contraction is inhibited by testosterone. Sympathectomy (e.g. during bilateral retroperitoneal node dissection for testicular cancer) is followed by ejaculatory paralysis. If one chain can be preserved, ejaculation is normal, though with a reduced volume.

Contrast medium injected into the seminal tract show that the ampullae of the vasa efferentia empty first, and then the seminal vesicles, which function like a syringe to flush out the first sperm-rich aliquot of semen.

From puberty onwards, the seminal vesicles normally contain live spermatozoa and were considered to be reservoirs, hence the name; but probably the main sperm reservoir is the ampulla of the vasa efferentia and the epididymis. Their secretion makes up about 80% of the ejaculate; it is rich in fructose, citric acid, magnesium, ammonium, ascorbic acid, prostaglandins, and other specific proteins in an alkaline, viscous yellowish fluid.

41.1.3 Congenital Anomalies

The seminal vesicles may be absent on one or both sides, the ureter may enter the vesicle, and the vesicle may have cysts and diverticula (Figures 41.1 and 41.2) [1–3]. Seminal vesical cysts can be very large and may contain up to 51 of fluid, which may become infected and form stones (Figures 41.3 and 41.4) [2, 4]. Cysts of the seminal vesicles must be distinguished from cysts arising from the midline müllerian duct.

Seminal vesical agenesis is associated with a cystic fibrosis gene mutation and can be associated with renal and vas deferens anomalies or agenesis.

41.1.4 Infection

Gonococcal infection of the seminal vesicles was common and serious; however, with antibiotics, this infection is now rarely seen. Rarely, abscesses are seen and are associated with diabetes, long-term catheters, and potentially cystoscopy. All the causes of chronic infection of the urinary tract (e.g. Schistosoma, tuberculosis, amoeba and trichomonas) may involve the seminal vesicles. Patients can present with haematospermia, perineal pain, painful ejaculation, or infertility or a mixture of these. Diagnosis can be made by ultrasound and perineal needle aspiration and treated with appropriate antibiotics.

With the increasing use of transrectal ultrasound, it has become possible to identify seminal vesicle obstruction, which can be complicated by infection or a calculus lodged in the ejaculatory duct [5, 6].

41.1.5 Neoplasms

Benign and malignant tumours may arise in the seminal vesicles, differentiated with a biopsy. The difficulty with the seminal vesicle is that by the time the diagnosis is made, it is almost impossible to be sure that the origin of the cancer was in the vesicle.

Any cavity lined with mucosa may give rise to adenocarcinoma. Sarcomas and choriocarcinomas arising from the connective tissue of the seminal vesicle have been reported (22). However, local spread from prostate cancer is more commonly seen than primary cancer.

Serum carcinoembryonic antigen can be elevated.

Their spread, like the prostate, is by the Batson’s veins to the pelvis and femora, eroding the bone rather than causing sclerosis on imaging, but it seems that these metastases may be hormone sensitive.
Asymptomatic benign lesions can be conservatively managed. Malignant tumours are surgical excised where feasible. The role of radiotherapy and androgen ablation is unclear due to the scarcity of seminal vesical cancers.

41.1.6 Degenerative Diseases
Amyloid is seen in the seminal vesicle as a normal feature in old men, and it occurs at an earlier age in those who have diabetes [7].

41.1.7 Investigations
Clinically the seminal vesicles are impalpable on digital rectal examination (DRE) unless involved in a pathological process.

41.1.8 Imaging
Transrectal ultrasound show the vesicles with great clarity, and when there is an obstructed seminal vesicle, it allows aspiration and biopsy to be performed under ultrasound control. Fluid (cysts) is hypoechoic and a solid mass (cancer) is hyperechoic.

Plain radiographs may show calculi in seminal vesicles and calcification of the vesicles and vasa is commonly seen in bilharziasis and may occur in those with diabetes or hyperparathyroidism.

Injection of contrast medium into the vas gives an outline of the vasa, the ampulla, and the seminal vesicle but the wide range of normal variations makes them difficult to interpret. Computed tomography (CT) and magnetic resonance imaging (MRI) are both useful in imaging of the seminal vesicle and have been particularly useful in showing invasion of the vesicles by cancer of the prostate.

41.1.9 Semen Analysis
The majority of the volume of the semen is derived from the seminal vesicles, as is all the fructose; so semen of small volume with an absence of fructose generally signifies disease of the vesicles. This is common in those with diabetes, but also occurs as a result of inflammation, obstruction, or absence.
41.1.10 Surgical Approach to the Seminal Vesicles

The most simple and direct approach to the vesicles is through an abdominal incision (i.e. open, laparoscopic, or robotic), stripping the peritoneum off the posterior surface of the bladder, and following the vas deferens down on either side. Care must be taken to avoid injury to the ureter which passes under the seminal vesicle.

41.2 Vasectomy

Attempts at male contraceptive methods or male contribution to contraception has been time tested for many years; however there are high failure rates, periodic abstinence 20%, withdrawal 19%, and condoms 3–14% [6]. This led to look to surgery for a relatively more permanent method, vasectomy. It was first described by Sir Astley Cooper in 1827; today it is one of the most commonly performed procedures. It is in danger of being regarded with too little seriousness and yet it is fraught with medicolegal consequence.

41.2.1 Counselling

Consultation with is essential before embarking on vasectomy. The wife may be about to undergo a hysterectomy. One must be cautious of the husband who is being driven to submit to vasectomy to save a failing marriage.

Both partners must understand that the procedure should be considered irreversible, associated with a low complication rate, low but existing failure rate, advice to continue with other effective contraception until clearance is confirmed, and that the procedure is not associated with any serious, long-term, side effects [6].
41.2.2 Examination

Examine the patient carefully before deciding to proceed, it is difficult to do a vasectomy under local anaesthetic in a frightened man with a tight scrotum or when there has been previous scrotal or inguinal surgery, or if the vas is impalpable or absent.

41.2.3 Shaving

Let the patient shave his own scrotum before the procedure to minimise infection; it is much more comfortable for him if he does it in the bath at leisure.

41.2.4 Anaesthesia

Local infiltration with a local anaesthetic provides excellent anaesthesia, which is usually sufficient in the relaxed cooperative patient.

41.2.5 Choice of Incision

The operation may be done through a single transverse, vertical scrotal incision, or through two incisions, one over each vas (Figure 41.5).

41.2.6 Operative Technique

There are many techniques for performing vasectomy. However, the most effective is when the lumen is cauterised and fascia interpositioned between the two ends [6].

The essential steps are that the vas deferens is located by its characteristic feel, like a hard cord (Figure 41.6). The sheath of the vas is incised longitudinally taking care to avoid the artery and veins of the vas. The vas is lifted up out of the sheath. Care is taken not to pull on the vas because this can cause vagal stimulation, bradycardia, fainting, and even cardiac arrest.

The vas is doubly clamped and divided and a small segment of vas from each side resected, carefully labelled in formalin as medico-legal proof that the right organ was removed, should questions arise afterwards. Coagulate the lumen of the vas with diathermy and interpositioning tissue while closing is essential. Another way is to ligate the testicular end of the vas with fine (4–0) suture, curl the end back on itself into a loop, and tie it again (Figure 41.6). The other end is ligated and dropped back into the sheath of the vas, which is then closed with a stitch. The looped-back end is left outside the sheath. It is the intention that the fascia of the sheath will prevent the ends coming together again.

Many urologists now advocate a ‘no-scalpel’ vasectomy where a sharp haemostat is used to puncture the scrotal skin. The incision usually does not require a suture and may decrease the incidence of haematoma and infection rates.

41.2.7 Complications

Every large series of vasectomies records complications, few are severe, but all of them are notoriously apt to generate resentment and litigation [8–15]:

![Figure 41.5 Choice of incision for vasectomy.](image1)

![Figure 41.6 The sheath of the vas deferens is slit open and the vas lifted out. After resecting 1 cm, one end is turned back and ligated. A suture closes the sheath.](image2)
41.2.7.1 Early Complications

- Haematoma is common after vasectomy (average 2%), usually starts about 30 minutes after the end of the operation and is generally thought to be due to arterial or venous spasm, caused by handling the vas, and relaxing spontaneously later on.

When reactionary haemorrhage occurs and leads to a haematoma, it is usual to return the patient to the operating theatre and evacuate the clot under anaesthesia. In practice, it is rare that a single bleeding vessel can be identified, and the blood is usually found between the tissues of the scrotum. After evacuation of the haematoma, the swelling may take several weeks to resolve completely. It is common for the patient to complain of pain in the scrotum for some time afterwards.

- Wound infection, urinary tract infection, and epididymitis can occur on average in 3.4% of patients. Infections can be severe enough to cause Fournier gangrene, albeit rare.

- Injury to surrounding structures can occur in less than 5%.

41.2.7.2 Later Complications

- Sperm granuloma can occur in 10–33% of patients, leading to a painful swelling which can develop either at the site of the divided vasa or in the epididymis. In most cases, it resolves spontaneously, but in others it persists, and the patient demands treatment. However, removal of the epididymis may, but does not always, relieve the pain. Histologically, there is a sperm granuloma, a chronic inflammatory response to extravasated sperm, which can lead to recanalization of the vas (Figure 41.7).

- Chronic testicular or scrotal pain can occur as a result of the sperm granuloma or from congestive epididymitis in 12–52% of patients. However, the majority usually have tolerable and transient, with about 2.2–15% affecting quality of life and seek further treatments.

- Failure, due to inadequate occlusion of one of both vasa which can lead to recanalization (Figure 41.7). Recanalization can occur either early (0–2%; 1 in 200) or even late in <1% (1 in 2000 men). Early recanalization is detected by regular semen analysis, the sperm would never completely disappear. Late recanalization is diagnosed once the wife gets pregnant, often years after the vasectomy.

The mechanism of spontaneous recanalization seems to be that sprouts of the epithelium lining the vas burrow into the granulation tissue filling the gap between the divided ends of the vasa. If the sprouts meet each other, continuity is re-established. It is believed that this recanalization took place in the first few months after vasectomy, when the granuloma was new before scar tissue had contracted to form an impenetrable barrier.

Very occasional cases were reported where the vasa would reunite years later; they were regarded as an extreme rarity. However, whenever spontaneous reunion
of the vas results in an unwanted pregnancy, the surgeon is likely to be accused of negligence; hence, the intense medico-legal interest in the issue of ‘late’ recanalization (i.e. after the semen had been shown to be entirely free from spermatozoa in at least two consecutive specimens).

- Anti-sperm antibodies develop in more than 60% of patients, but they do not have any long-term sequelae.
- Vasectomy-related death occurs in 1 per 100,000 in the developed world; however, it can be as high as 190 per 100,000 in the developing world. The main cause is infections.

Few surgeons would think it necessary to warn of complications so rare, but vasectomy is an exception because of the suspicions and ill feeling that are aroused by an unexpected pregnancy years after vasectomy. It is therefore a wise precaution to warn the patient and his wife that this, however rare, can happen.

Increased risk of prostate cancer or systemic illnesses, like atherosclerosis or cardiovascular disease has not been proven after vasectomy [6].

41.2.8 Postoperative Semen Analysis

After vasectomy, two consecutive semen samples (12 and 16 weeks) must show no sperm to be considered a success. Azoospermia is achieved in 80% of patients after 12 weeks and 20 ejaculations; however, it is recommended that only after 16 weeks and 24 ejaculations that initial assessment for sperm motility be carried out and when examination of a well-mixed, uncentrifuged, fresh postvasectomy sample shows azoospermia or only rare nonmotile sperm (<100,000 nonmotile sperm/ml) can other contraceptive precautions be stopped [15–17].

Clearance to stop contraception can be given to some patients who have very few nonmotile sperm (<10,000 nonmotile sperm/ml) found in a fresh specimen examined at least seven months after vasectomy [6, 12]. However, be cautious; paternity has been proven when not a single sperm can be found [18].

41.2.9 Vasectomy Reversal

Nearly 6% of patients that undergo vasectomy, undergo a reversal [19]. Vasovasostomy and vasoepididymostomy are vasectomy reversal techniques used. Both require patience, time, and adequate anaesthesia. Surgeons should use loupes or the operating microscope and smaller suture material [20]. The divided ends of the vasa are exposed and sectioned until the lumen is revealed (Figure 41.8). The ends are anastomosed, either an end-to-end method, or end-to-side method can be used (Figure 41.9).

The results of reversal of vasectomy are disappointing. Although sperms reappear in the ejaculate in 90%, the pregnancy rate decreases with the increase in the interval from the vasectomy to reversal (Table 41.1) [6, 21]. There are several explanations. First the couples are older and biologically less likely to conceive. Second, while the sperms are retained in the epididymis, they may leak into the tissues and provoke an immunological reaction which will result in death or immobilisation of the sperms.
Ten year post-vasectomy, 25% of men develop epididymal blockages that will require tubulovasostomy during reversal to give patency [6, 22]. If the vasectomy reversal fails, then sperm retrieval methods (i.e. microsurgical epididymal sperm aspiration and testicular sperm extraction) and in vitro fertilisation (i.e. intracytoplasmic sperm injection) can be used however are quite costly [6].

References


Table 41.1 Patency and pregnancy rate with time.

<table>
<thead>
<tr>
<th>Time from vasectomy to reversal (years)</th>
<th>Patency rate (%)</th>
<th>Pregnancy rate (%)</th>
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<tbody>
<tr>
<td>3</td>
<td>97</td>
<td>76</td>
</tr>
<tr>
<td>3–8</td>
<td>88</td>
<td>53</td>
</tr>
<tr>
<td>9–14</td>
<td>79</td>
<td>44</td>
</tr>
<tr>
<td>&gt;15</td>
<td>71</td>
<td>30</td>
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**Expert Opinion**

Disease of the seminal vesicles are rare and can be confused with disease associated with the prostate, including cancer. Nonetheless, ultrasound and biopsy and semen analysis for volume and content can lead to the diagnosis. Surgical resections can be difficult and should be done by those experienced with pelvic oncology surgery.

Vasectomy is a simple surgical procedure; however, complications occur and can cause serious detriment to the patient’s quality of life. Therefore, thorough counselling is vital. Nonetheless, postprocedural failure may still lead to litigation, so postvasectomy semen analysis is a must. More patients are requesting reversals; however, the pregnancy rates are low and decrease with the length of time from the vasectomy. All of this should be carefully explained during counselling as well.
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