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John Reynard

Consultant Urological Surgeon
Nuffield Department of Surgical Sciences
Oxford University Hospitals
Oxford, UK and
Honorary Consultant Urologist to the
National Spinal Injuries Centre
Stoke Mandeville Hospital
Aylesbury, UK

Simon Brewster

Consultant Urological Surgeon
Nuffield Department of Surgical Sciences
Oxford University Hospitals
Oxford, UK

Suzanne Biers

Consultant Urological Surgeon
Addenbrooke's Hospital
Cambridge University Hospitals
Cambridge, UK

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Symbols and Abbreviations

®	registered trademark
>	more than
<	less than
≥	equal to or greater than
≤	equal to or less than
%	percent
°C	degree Celsius
↓	decreased
↑	increased
📖	cross-reference
~	approximately
α	alpha
β	beta
AAA	abdominal aortic aneurysm
AAOS	American Academy of Orthopaedic Surgeons
AAST	American Association for the Surgery of Trauma
AAT	androgen ablation therapy
ACCP	American College of Chest Physicians
ACE	angiotensin-converting enzyme
ACh	acetylcholine
ACR	albumin:creatinine ratio *or* acute cellular rejection
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
ADT	androgen deprivation therapy
ADPKD	autosomal dominant polycystic kidney disease
AFP	alpha-fetoprotein
AHR	acute humoral rejection
AI	androgen-independent
AID	artificial insemination donor
AIDS	acquired immunodeficiency syndrome
a.m.	*ante meridiem* (before noon)
AMACR	α-methylacyl CoA racemase
AML	angiomyolipoma
amp	ampere
AMS	American Medical Systems
ANP	atrial natriuretic peptide

a-NVH	asymptomatic non-visible haematuria
APD	automated peritoneal dialysis
APF	antiproliferative factor
5AR	5α-reductase
ARCD	acquired renal cystic disease
5ARI	5α-reductase inhibitor
ARPKD	autosomal recessive polycystic kidney disease
ART	assisted reproductive techniques
AS	active surveillance
ASAP	atypical small acinar proliferation
ASTRO	American Society of Therapeutic Radiation Oncologists
ATG	antithymocyte globulin
ATN	acute tubular necrosis
ATP	adenosine triphosphate
AUA	American Urological Association
AUA-SI	American Urological Association Symptom Index
AUR	acute urinary retention
AUS	artificial urinary sphincter
AVM	arteriovenous malformation
BAUS	British Association of Urological Surgeons
BCG	bacillus Calmette–Guérin
BCR	bulbocavernosus reflex
bd	*bis die* (twice daily)
bFGF	basic fibroblastic growth factor
BHCG	beta human chorionic gonadotrophin
BLI	beta-lactamase inhibitor
BMI	body mass index
BMSFI	Brief Male Sexual Function Inventory
BNI	bladder neck incision
BOO	bladder outlet obstruction
BP	blood pressure
BPE	benign prostatic enlargement
bPFS	biochemical progression-free survival
BPH	benign prostatic hyperplasia
BPLND	bilateral pelvic lymphadenectomy
BPO	benign prostatic obstruction
BPS	bladder pain syndrome
BSE	bovine spongiform encephalopathy
BT	brachytherapy
BTA	bladder tumour antigen
BTX-A	botulinum toxin-A

BUO	bilateral ureteric obstruction
BXO	balanitis xerotica obliterans
CAA	Civil Aviation Authority
CABG	coronary artery bypass graft
CAH	congenital adrenal hyperplasia
CAIS	complete androgen insensitivity syndrome
cAMP	cyclic adenosine monophosphate
CAPD	continuous ambulatory peritoneal dialysis
CBAVD	complete bilateral absence of vas deferens
CCF	congestive cardiac failure
C_{Cr}	creatinine clearance
CD	collecting duct
CEULDCT	contrast-enhanced ultra-low dose computed tomography
CFU	colony-forming unit
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CIRF	clinically insignificant residual fragment
CJD	Creutzfeldt–Jakob disease
CIS	carcinoma *in situ*
CISC	clean intermittent self catheterization
CKD	chronic kidney disease
cm	centimetre
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CNS	central nervous system
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
COPUM	congenital obstructive posterior urethral membrane
CP	chronic prostatitis
CPA	cyproterone acetate
CPB	chronic painful bladder (syndrome)
CPPS	chronic pelvic pain syndrome
CPRE	complete primary repair of bladder exstrophy
Cr	creatinine
CRF	chronic renal failure
CRP	C-reactive protein
CRPC	castrate-resistant prostate cancer
CSS	cancer-specific survival
CT	computed tomography *or* collecting tubule
CTPA	computerized tomography pulmonary angiography
CTU	computed tomography urography

CT-KUB	CT of the kidneys, ureters, and bladder
CVA	cerebrovascular accident
CXR	chest X-ray
Da	Dalton
DCT	distal convoluted tubule
DE	delayed ejaculation
DESD	detrusor-external sphincter dyssynergia
DEXA	dual-energy X-ray absorptiometry (scan)
DGI	disseminated gonococcal infection
DH	detrusor hyperreflexia
DHT	dihyrotestosterone
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
dL	decilitre
DMSA	dimercapto-succinic acid (renogram)
DMSO	dimethyl sulphoxide
DNA	deoxyribonucleic acid
DRE	digital rectal examination
DSD	detrusor sphincter dyssynergia *or* disorders of sex development
DVLA	Drivers Vehicle Licensing Agency
DVT	deep vein thrombosis
EAU	European Association of Urology
EBRT	external beam radiotherapy
EBV	Epstein–Barr virus
ECF	extracellular fluid
ECG	electrocardiogram
ED	erectile dysfunction
EDTA	ethylene diamine tetra-acetic acid
e.g.	*exempli gratia* (for example)
EGF	epidermal growth factor
eGFR	estimated glomerular filtration rate
EHL	electrohydraulic lithotripsy
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbant assay
EMDA	electromotive drug administration
EMG	electromyography
EMU	early morning urine
EPLND	extended pelvic lymphadenectomy
EPN	emphysematous pyelonephritis
EORTC	European Organization for Research and Treatment of Cancer

EPS	expressed prostatic secretions
ER	extended release
ESBL	extended spectrum β-lactamase
ESR	erythrocyte sedimentation rate
ESSIC	European Society for the Study of Bladder Pain Syndrome/Interstitial Cystitis
ESWL	extracorporeal shock wave therapy
etc	*et cetera*
FBC	full blood count
FGSI	Fournier's gangrene severity index
FNA	fine needle aspiration
FSH	follicle stimulating hormone
ft	foot/feet
FVC	frequency volume chart
g	gram
GA	general anaesthetic
GABA	γ-aminobutyric acid
GAG	glycosaminoglycan
GCT	germ cell tumour
GFR	glomerular filtration rate
GI	gastrointestinal
GIFT	gamete intrafallopian transfer
Gk	Greek
GnRH	gonadotrophin-releasing hormone
GP	general practitioner
GTN	glyceryl trinitrate
GU	gonococcal urethritis (or genitourinary)
GUM	genitourinary medicine
Gy	gray
h	hour
H^+	hydrogen ion
HAL	hexaminolevulinic acid
Hb	haemoglobin
HCG	human chorionic gonadotrophin
HCO_3	bicarbonate ion
HDR	high-dose rate
HIFU	high-intensity focused ultrasound
HIF	hypoxia-inducible factor
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA reductase
5-HMT	5-hydroxymethyl tolterodine

HPCR	high pressure chronic retention
HPF	high-powered field
H_2O	water
HO	house officer
HoLAP	holmium laser ablation of the prostate
HoLEP	holmium laser enucleation of the prostate
HoLRP	holmium laser resection of the prostate
HPA	Health Protection Agency
HPO_4^{2-}	phosphate ion
$H_2PO_4^-$	phosphoric acid
HPV	human papilloma virus
HRO	high reliability organization
HRP	horseradish peroxidise
HTLA	human T lymphotropic virus
Hz	Hertz
IC	intermittent catheterization *or* interstitial cystitis
ICD	implantable cardioverter defibrillator
i.e.	*id est* (that is)
IFIS	intraoperative floppy iris syndrome
ISC	intermittent catheterization
ICF	intracellular fluid
ICS	International Continence Society
ICSI	intracytoplasmic sperm injection
ICU	intensive care unit
IDC	indwelling catheter
IDO	idiopathic detrusor overactivity
IELT	intravaginal ejaculatory latency time
IFN	interferon
Ig	immunoglobulin
IGCN	intratubular germ cell neoplasia
IGF	insulin-like growth factor
IIEF	International Index of Erectile Function
IL	interleukin
ILP	interstitial laser prostatectomy
IM	intramuscular
INR	international normalized ratio
IPC	intermittent pneumatic calf compression
IPSS	International Prostate Symptom Score
ISC	intermittent self-catheterization
ISD	intrinsic sphincter deficiency
ISF	interstitial fluid

ISSM	International Society for Sexual Medicine
ITU	intensive treatment unit
IU	international unit
IUI	intrauterine insemination
IV	intravenous
IVC	inferior vena cava
IVF	*in vitro* fertilization
IVP	intravenous pyelography
IVU	intravenous urography
J	Joule
JGA	juxtaglomerular apparatus
K^+	potassium
kcal	kilocalorie
kD/kDa	kilodalton
K_f	formation product
kg	kilogram
KGF	keratinocyte growth factor
kHz	kilohertz
kJ	kilojoule
kPa	kilopascal
K_{sp}	solubility product
KTP	potassium titanyl phosphate (laser)
KUB	Kidneys, ureter and bladder (X-ray)
L	litre
LA	local anaesthetic
LDH	lactate dehydrogenase
LDL	low density lipid
LDR	low-dose rate
LDUH	low-dose unfractionated heparin
LFT	liver function test
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LMWH	low molecular weight heparin
LNI	lymph node invasion
LoH	Loop of Henle
LOH	late-onset hypogonadism
LRP	laparoscopic radical prostatectomy
LSD	lysergic acid diethylamide
LUT	lower urinary tract
LUTS	lower urinary tract symptom
m	metre

mA	milliampere
μA	microampere
MAB	maximal androgen blockade
MAG3	mercaptoacetyl-triglycyine (renogram)
MAGPI	meatal advancement and granuloplasty
MAPP	Multidisciplinary Approach to Pelvic Pain
MAPS	Men After Prostate Surgery (study)
MAR	mixed antiglobulin reaction (test)
MCDK	multicystic dysplastic kidney
mcg	microgram
MCUG	micturating cystourethrography
MDCTU	multidetector CT urography
MDP	methylene diphosphonate
MDRD	modification of diet in renal disease
mEq	milliequivalent
MESA	microsurgical epididymal sperm aspiration
MET	medical expulsive therapy
mg	milligram
mGy	milligray
MHC	major histocompatibility complex
MHz	megahertz
MI	myocardial infarction
MIBG	meta-iodo-benzyl-guanidine
min	minute
MIS	Müllerian inhibiting substance
MIT	minimally invasive treatment
mL	millilitre
MMC	mitomycin C
mmol	millimole
MNE	monosymptomatic nocturnal enuresis
mo	month
mOsm	milliosmole
MPA	mycophenolate
MPOA	medial preoptic area
MPR	multiplanar reformatting
MRCoNS	methicillin-resistant coagulase-negative staphylococci
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRSA	meticillin-resistant staphylococcus aureus
MSMB	microseminoprotein-beta
MRU	magnetic resonance urography

MS	multiple sclerosis
MSA	multisystem atrophy
MSK	medullary sponge kidney
MSU	mid-stream urine
mSV	milliSevert
MUCP	maximal urethral closure pressure
MUI	mixed urinary incontinence
MUSE	Medicated Urethral System for Erection
MVAC	methotrexate, vinblastine, adriamycin, cisplatin
Na^+	sodium
NA	noradrenaline
NAAT	nucleic acid amplification test
NaCl	sodium chloride
NAION	non-arteritic anterior ischaemic optic nerve neuropathy
NB	*nota bene* (take note)
NBI	narrow-band imaging
NDO	neurogenic detrusor overactivity
NE	nocturnal enuresis
ng	nanogram
NGU	non-gonococcal urethritis
NICE	National Institute for Health and Clinical Excellence
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institute of Health
NIH-CPSI	National Institute of Health Chronic Prostatitis Symptom Index
nm	nanometre
NMNE	non-monosymptomatic nocturnal enuresis
nmol	nanomole
NMP	nuclear matrix protein
NND	number needed to detect
NNT	number needed to treat
NO	nitric oxide
NP	nocturnal polyuria
NSAID	non-steroidal anti-inflammatory drug
NSGCT	non-seminomatous germ cell tumours
NSU	non-specific urethritis
NVH	non-visible haematuria
od	*omni die* (once daily)
OAB	overactive bladder
OAT	oligoasthenoteratospermia
OIF	onlay island flap

OLND	obturator lymphadenectomy
OP	open prostatectomy
OSA	obstructive sleep apnoea
Pabd	intra-abdominal pressure
PAOD	peripheral artery occlusive disease
P_aCO_2	partial pressure of carbon dioxide (in arterial blood)
P_aO_2	partial pressure of oxygen (in arterial blood)
PAG	periaqueductal grey matter
PAIS	Partial androgen insensitivity syndrome
PBS/IC	painful bladder syndrome/interstitial cystitis
PC	prostate cancer
PCNL	percutaneous nephrolithotomy
PCO_2	carbon dioxide tension
PCR	polymerase chain reaction
PCT	proximal convoluted tubule
PD	Parkinson's disease
PDD	photodynamic detection
PDE5	phosphodiesterase type-5
Pdet	detrusor pressure
PDGF	platelet-derived growth factor
PDT	photodynamic therapy
PE	premature ejaculation *or* pulmonary embolism
PEC	perivascular epithelioid cell
PEP	post-exposure prophylaxis
PESA	percutaneous epididymal sperm aspiration
PET	positron emission tomography
PFMT	pelvic floor muscle training
PFS	pressure flow studies
PGE1	prostaglandin E1
PGF2	prostaglandin F2
PIN	prostatic intraepithelial neoplasia
PLAP	placental alkaline phosphatase
PLESS	Proscar Long-term Efficacy Safety Study
PMC	pontine micturition center
PMNL	polymorphonuclear leukocytes
PN	partial nephrectomy
PNE	peripheral nerve evaluation
PO	orally *(per os)*
PO_2	oxygen tension
POP	pelvic organ prolapse
POPQ	pelvic organ prolapse quantification
PPS	pentosan polysulphate sodium

PR	pulse rate
PREDICT	Prospective European Doxazosin and Combination Therapy
PRP	prion protein
PSA	prostate specific antigen
PTFE	polytetrafluoroethylene
PTH	parathyroid hormone levels
PTN	posterior tibial nerve
PTTI	parenchymal transit time index
PTNS	posterior tibial nerve stimulation
PUJ	pelviureteric junction
PUJO	pelviureteric junction obstruction
PUNLMP	papillary urothelial neoplasm of low malignant potential
PUV	posterior urethral valves
PVD	peripheral vascular disease
Pves	intravesical pressuer
PVN	paraventricular nucleus
PVN	peripheral vascular disease
PVP	photoselective vaporization of the prostate
PVR	post-void residual
QALY	quality-adjusted life year
qds	*quarter die sumendus* (to be taken 4 times per day)
Qmax	maximal flow rate
QoL	quality of life
RBC	red blood count
RBF	renal blood flow
RCC	renal cell carcinoma
RCT	randomized control trial
RFA	radiofrequency ablation
RI	resistive index
RNA	ribonucleic acid
RP	radical prostatectomy
RPD	renal pelvis diameter
RPF	retroperitoneal fibrosis *or* renal plasma flow
RPLND	retroperitoneal lymph node dissection
RPR	rapid plasma regain
RR	respiratory rate
RT	radiotherapy
RTA	renal tubular acidosis
RTK	receptor tyrosine kinase
s	second
SARS	sacral anterior root stimulator
SC	subcutaneous

SCC	squamous cell carcinoma
SCI	spinal cord injury
S_{Cr}	serum creatinine
SEM	standard error of the mean
SHBG	sex hormone binding globulin
SHIM	Sexual Health Inventory for Men
SHO	senior house officer
SIRS	systemic inflammatory response syndrome
SL	sublingual
SLE	systemic lupus erythematosus
SNAP	synaptosomal associated protein
SNM	sacral nerve modulation
SNS	sacral nerve stimulation
s-NVH	symptomatic non-visible haematuria
SOP	standard operating procedures
SPC	suprapubic catheter
SpR	specialist registrar
SRE	skeletal-related events
SSRI	serotonin reuptake inhibitor
ssRNA	single-stranded ribonucleic acid
STD	sexually transmitted disease
STI	sexually transmitted infection
SUI	stress urinary incontinence
TAL	thick ascending limb (of Loop of Henle)
TB	tuberculosis
TBW	total body water
TC	testicular cancer
TCC	transitional cell carcinoma
tds	*ter die sumendus* (to be taken 3 times per day)
TEAP	transurethral ethanol ablation of the prostate
TEDs	thromboembolic deterrent stockings
TENS	transcutaneous electrical nerve stimulation
TESA	testicular exploration and sperm aspiration
TESE	testicular exploration and sperm extraction
TET	tubal embryo transfer
TGF	transforming growth factor
TIN	testicular intratubular neoplasia (synonymous with IGCN)
TIP	tubularized incised plate
TNF	tumour necrosis factor
TNM	tumour, node, metastasis
TOT	transobturator tape

TOV	trial of void
TPIF	transverse preputial island flap
TRUS	transrectal ultrasonography
TS	tuberous sclerosis
TSE	testicular self-examination
TUIP	transurethral incision in the prostate
TULIP	transuretheral ultrasound-guided laser-induced prostatectomy
TUMT	transurethal microwave thermotherapy
TUNA	transurethal radiofrequency needle ablation
TUR	transurethral resection
TURBT	transurethral resection of bladder tumour
TURED	transurethral resection of the ejaculatory ducts
TURP	transurethral resection of prostate
TURS	transurethral resection syndrome
TUU	transureteroureterostomy
TUVP	transurethral electrovaporization of the prostate
TUVRP	transurethral vaporization resection of the prostate
tvl	total vaginal length
TVT	tension-free vaginal tape
TVTO	tension-free vaginal tape obturator route
TWOC	trial without catheter
TZ	transition zone
U	(international) unit
UD	urethral diverticulum
UDT	undescended testis
U & E	urea and electrolytes
UI	urinary incontinence
UK	United Kingdom
ULDCT	ultra-low dose computed tomography
UPJO	ureteropelvic junction obstruction
USA	United States (of America)
USS	ultrasound scan
UTI	urinary tract infection
UUI	urge urinary incontinence
UUO	unilateral ureteric obstruction
UUT-TCC	upper urinary tract transitional cell carcinoma
V	volt
VB_3	post-prostatic massage urine
vCJD	variant Creutzfeldt–Jakob disease
VCUG	voiding cystourethrography

VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VH	visible haematuria
VHL	von Hippel–Lindau
VLAP	visual laser ablation of the prostate
VQ	ventilation/perfusion (scan)
VRE	vancomycin-resistant enterococci
vs	versus
VTE	venous thromboembolism
VUJ	vesicoureteric junction
VUJO	vesicoureteric junction obstruction
VUR	vesicoureteric reflux
VURD	vesicoureteric reflux with renal dysplasia
VVF	vesicovaginal fistula
W	watt
WBC	white blood cell
WCC	white cell count
WHO	World Health Organization
wk	week
WW	watchful waiting
XGP	xanthogranulomatous pyelonephritis
y	year
YAG	ytrium-aluminium-garnet (laser)
ZIFT	zygote intrafallopian transfer

Chapter 1

General principles of management of patients

Communication skills

Communication is the imparting of knowledge and understanding. Good communication is crucial for the surgeon in his or her daily interaction with patients. The nature of any interaction between surgeon and patient will depend very much on the context of the 'interview', whether you know the patient already, and on the quantity and type of information that needs to be imparted. As a general rule, the basis of good communication requires the following:

- **Introduction.**

Give your name, explain who you are, greet the patient/relative appropriately (e.g. handshake), check you are talking to the correct person.

- **Establish the purpose of the interview.**

Explain the purpose of the interview from the patient's perspective and yours and the desired outcome of the interview.

- **Establish the patient's baseline knowledge and understanding.**

Use open questions, let the patient talk, and confirm what they know.

- **Listen actively.**

Make it clear to the patient that they have your undivided attention—that you are focusing on them. This involves appropriate body language (keep eye contact—don't look out of the window!).

- **Pick up on and respond to cues.**

The patient/relative may offer verbal or non-verbal indications about their thoughts or feelings.

- **Elicit the patient's main concern(s).**

What you think should be the patient's main concerns may not be. Try to find out exactly what the patient is worried about.

- **Chunks and checks.**

Give information in small quantities and check that this has been understood. A good way of doing this is to ask the patient to explain what they think you have said.

- **Show empathy.**

Let the patient know you understand their feelings.

- Be non-judgemental

Don't express your personal views or beliefs.

- **Alternate control of the interview between the patient and yourself.**

Allow the patient to take the lead where appropriate.

- **Signpost changes in direction.**

State clearly when you move onto a new subject.

- **Avoid the use of jargon.**

Use language the patient will understand, rather than medical terminology.

- **Body language.**

Use body language that shows the patient that you are interested in their problem and that you understand what they are going through. Respect cultural differences; in some cultures, eye contact is regarded as a sign of aggression.

- **Summarize and indicate the next steps.**

Summarize what you understand to be the patient's problem and what the next steps are going to be.

Documentation and note keeping

The Royal College of Surgeons' guidelines state that each clinical history sheet should include the patient's name, date of birth, and record number. Each entry should be timed, dated, and signed, and your name and position (e.g. SHO for 'senior house officer' or SPR for 'specialist registrar') should be clearly written in capital letters below each entry. You should also document which other medical staff were present with you on ward rounds or when seeing a patient (e.g. 'ward round—SPR (Mr X)/SHO/HO').

Contemporaneous note keeping is an important part of good clinical practice. Medical notes document the patient's problems, the investigations they have undergone, the diagnosis, and the treatment and its outcome. The notes also provide a channel of communication between doctors and nurses on the ward and between different medical teams. In order for this communication to be effective and safe, medical notes must be clearly written. They will also be scrutinized in cases of complaint and litigation. Failure to keep accurate, meaningful notes which are timed, dated, and signed, with your name written in capital letters below, exposes you to the potential for criticism in such cases. The standard of note keeping is seen as an indirect measure of the standard of care you have given your patients. Sloppy notes can be construed as evidence of sloppy care, quite apart from the fact that such notes do not allow you to provide evidence of your actions! Unfortunately, the defence of not having sufficient time to write the notes is not an adequate one, and the courts will regard absence of documentation of your actions as indicating that you did not do what you said you did.

Do not write anything that might later be construed as a personal comment about a patient or colleague (e.g. do not comment on an individual's character or manner). Do not make jokes in the patient's notes. Such comments are unlikely to be helpful and may cause you embarrassment in the future when you are asked to interpret them.

Try to make the notes relevant to the situation so, e.g. in a patient with suspected bleeding, a record of blood pressure and pulse rate is important, but a record of a detailed neurological history and examination is less relevant (unless, e.g. a neurological basis for the patient's problem is suspected).

The results of investigations should be clearly documented in the notes, preferably in red ink, with a note of the time and date when the investigation was performed.

Avoid the use of abbreviations. In particular, always write LEFT or RIGHT in capital letters, rather than Lt/Rt or L/R. A handwritten L can sometimes be mistaken for an R and vice versa.

Operation notes

We include the following information on operation notes:

- Patient name, number, and date of birth.
- Date of operation.
- Surgeon, assistants.
- Patient position (e.g. supine, prone, lithotomy, Lloyd–Davies).
- Type of deep vein thrombosis (DVT) prophylaxis (AK–TEDS, flowtrons, heparin, etc.).
- Type, time of administration, and doses of antibiotic prophylaxis.
- Presence of image intensifier, if appropriate.
- Type and size of endoscopes used.
- Your signature and your name in capitals.
- Post-operative instructions and follow-up, if appropriate.

If a consultant is supervising you, but is not scrubbed, you must clearly state that the 'consultant (named) was in attendance'.

Patient safety in surgical practice

The aviation, nuclear, and petrochemical industries are termed 'high reliability organizations' (HROs) because they have adopted a variety of core safety principles that have enabled them to achieve safety success, despite 'operating' in high-risk environments. Surgeons can learn much from HROs and can adopt some of these safety principles in surgical practice in order to improve safety in the non-technical aspects of care.

Foremost amongst the safety principles of HROs are:

- **Team working.**
- **Use of standard operating procedures (SOPs):** day-to-day tasks are carried out according to a set of rules and in a way that is standardized across the organization.
- **Cross-checking:** members of the team check that a procedure, drug, or action has been done or administered by 'verbalizing' that action to another team member. This is most familiar when aircraft cabin crew are asked by the pilot to check that the doors of the plane are locked shut ('doors to cross-check') and crew members cross to the opposite door to confirm this has been done. In surgical practice, an example of cross-checking could be 'antibiotic given?', confirmed by a specific reply such as '240mg IV gentamicin given'.
- **Regular audit and feedback of audit data:** performance data (both good and bad) are collected regularly and crucially, team members are notified (e.g. in audit meetings) of where they are performing well or badly.
- **Establishment of variable hierarchies:** development of a working environment where junior staff are encouraged to 'speak up' if they believe an error is about to occur, without fear of criticism.
- **Cyclical training:** frequent and regular training sessions to reinforce safe practice methods.

Chapter 2

Significance and preliminary investigation of urological symptoms and signs

Haematuria I: definition and types

The presence of blood in the urine.

The Joint Consensus Statement on the Initial Assessment of Haematuria (The Renal Association and British Association of Urological Surgeons, July 2008) now terms macroscopic or gross haematuria as 'visible' haematuria (VH)—the patient or doctor has seen blood in the urine or describes the urine as red or pink (or 'cola'-coloured—occasionally seen in acute glomerulonephritis).

Microscopic or dipstick haematuria is 'non-visible' haematuria (NVH). Non-visible haematuria is categorized as symptomatic (s-NVH, i.e. LUTS such as frequency, urgency, urethral pain on voiding, suprapubic pain) or asymptomatic (a-NVH).

Non-visible haematuria (microscopic or dipstick haematuria). Blood is identified by urine microscopy or by dipstick testing. Microscopic haematuria has been variably defined as 3 or more, 5 or more, or 10 or more red blood cells (RBCs) per high-power field. Samples sent from the community by GPs to hospital labs have a significant false negative rate (due to red cell lysis in transit).

The sensitivity of urine dipstick testing of a freshly voided urine sample is now good enough for detecting haematuria that routine confirmatory microscopy is no longer considered necessary. Dipstick haematuria is considered to be significant if 1+ or more. 'Trace' haematuria is considered negative. No distinction is made between haemolysed and non-haemolysed dipstick-positive urine; as long as 1+ or more of blood is detected, it is considered significant haematuria.

Urine dipsticks test for haem (i.e. they test for the presence of haemoglobin and myoglobin in urine). Haem catalyses oxidation of orthotolidine by an organic peroxidase, producing a blue-coloured compound. Dipsticks are capable of detecting the presence of haemoglobin from one or two RBCs.

- **False-positive urine dipstick:** occurs in the presence of myoglobinuria, bacterial peroxidases, povidone, hypochlorite.
- **False-negative urine dipstick (rare):** occurs in the presence of reducing agents (e.g. ascorbic acid—prevents the oxidation of orthotolidine).

Is microscopic or dipstick haematuria abnormal?

A few RBCs can be found in the urine of normal people. The upper limit of normal for RBC excretion is 1 million per 24h (as seen in healthy medical students). In healthy male soldiers undergoing yearly urine examination over a 12y period, 40% had microscopic haematuria on at least one occasion, and 15% on two or more occasions. Transient microscopic haematuria may occur following rigorous exercise, sexual intercourse, or from menstrual contamination.

The fact that the presence of RBCs in the urine can be a perfectly normal finding explains why in approximately 70% of 'patients' with microscopic or dipstick haematuria, no abnormality is found despite full conventional urological investigation (urine cytology, cystoscopy, renal ultrasonography, and intravenous urogram (IVU)).[2] That said, a substantial proportion

with visible and a smaller, but significant, proportion with NVH will have serious underlying disease and since there is no way, other than by further investigation, of distinguishing the dipstick-positive patient without significant disease from the dipstick-positive patient without significant disease, the recommendation is to investigate all patients with dipstick haematuria.

What is significant haematuria?

- Any single episode of VH.
- Any single episode of s-NVH (in absence of urinary tract infection (UTI) or other transient causes).
- Persistent a-NVH—defined as two out of three dipsticks positive for NVH (in absence of UTI or other transient causes).

Transient (non-significant haematuria) is caused by:

- UTI. Treat the UTI and repeat dipstick testing to confirm the absence of haematuria. UTI is most easily excluded by a negative dipstick result for both leucocytes and nitrites. If dipstick haematuria positive with a negative dipstick result for both leucocytes and nitrites, investigate the haematuria further.
- Exercise-induced haematuria or rarely myoglobinuria (VH and NVH). Repeat dipstick testing after a period of abstention from exercise.
- Menstruation.

Initial investigation for s-NVH and persistent a-NVH?

- Exclude UTI or other transient causes.
- Plasma creatinine/eGFR.
- Measure proteinuria on a random sample (24h urine collections for protein are rarely required).*
- Blood pressure (BP).

When is urological referral warranted?

- All patients with VH.
- All patients with s-NVH.
- a-NVH in patients aged 40y or more.
- Persistent a-NVH (defined as two out of three positives for NVH).

For the patient <40y with a-NVH, if eGFR is >60mL/min, BP <140/90, and no proteinuria (PCR <50mg/mmol or ACR <30mg/mmol), then while the a-NVH persists, it is recommended that the patient has an annual eGFR, BP check, and proteinuria check. If VH or s-NVH develops, referral to urology for a cystoscopy and imaging is indicated. If eGFR is <60mL/min, BP >140/90, or there is proteinuria (PCR >50mg/mmol or ACR >30mg/mmol), nephrological referral is indicated.

* Protein assessment on a single urine sample. Protein:creatinine ratio (PCR) or albumin:creatinine ratio (ACR). Significant proteinuria is a PCR >50mg/mmol or an ACR >30mg/mmol.

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Haematuria II: causes and investigation

Urological and other causes of haematuria

Non-visible haematuria (microscopic or dipstick haematuria) is common (20% of men >60y old). Bear in mind that most patients (70%—and some studies say almost 90%)[1,2] with NVH have no urological pathology. Conversely, a significant proportion of patients have glomerular disease despite having normal bp, a normal serum creatinine, and in the absence of proteinuria[3,4] (although it is fair to say that most do not develop progressive renal disease and those that do usually develop proteinuria and hypertension as impending signs of deteriorating renal function). The management algorithm for patients with negative urological haematuria investigations is shown on 📖 p. 14.

Causes of haematuria

- **Cancer:** bladder (transitional cell carcinoma (TCC), squamous cell carcinoma (SCC)), kidney (adenocarcinoma), renal pelvis, and ureter (TCC), prostate.
- **Stones:** kidney, ureteric, bladder.
- Infection: bacterial, mycobacterial (tuberculosis (TB)), parasitic (schistosomiasis), infective urethritis.
- **Inflammation:** cyclophosphamide cystitis, interstitial cystitis.
- **Trauma:** kidney, bladder, urethra (e.g. traumatic catheterization), pelvic fracture causing urethral rupture.
- **Renal cystic disease** (e.g. medullary sponge kidney).
- **Other urological causes:** benign prostatic hyperplasia (BPH, the large, vascular prostate), loin pain haematuria syndrome, vascular malformations.
- **Nephrological causes of haematuria:** tend to occur in children oryoung adults and include, commonly, IgA nephropathy, post-infectious glomerulonephritis; less commonly, membrano-proliferative glomerulonephritis, Henoch–Schönlein purpura, vasculitis, Alport's syndrome, thin basement membrane disease, Fabry's disease, etc.
- **Other 'medical' causes of haematuria:** include coagulation disorders—congenital (e.g. haemophilia), anticoagulation therapy (e.g. warfarin), sickle cell trait or disease, renal papillary necrosis, vascular disease (e.g. emboli to the kidney cause infarction and haematuria).
- **Nephrological causes:** more likely in the following situations—children andyoung adults; proteinuria; RBC casts.

What percentage of patients with haematuria have urological cancers?

- **Microscopic:** about 5–10%.
- **Macroscopic:** about 20–25%.[5]

Urological investigation of haematuria—VH, s-NVH, a-NVH aged >40y, persistent (2 out of 3 dipsticks) a-NVH

Modern urological investigation involves urine culture (where, on the basis of associated 'cystitis' symptoms, urinary infection is suspected), urine cytology, cystoscopy, renal ultrasonography, and CT urography (CTU).

Diagnostic cystoscopy

Nowadays, this is carried out using a flexible, fibre optic cystoscope, unless radiological investigation demonstrates a bladder cancer, in which case one may forego the flexible cystoscopy and proceed immediately to rigid cystoscopy and biopsy under anaesthetic (transurethral resection of bladder tumour—TURBT).

What is the role of multidetector CT urography (MDCTU) in the investigation of haematuria?

This is a rapid acquisition CT done following intravenous contrast administration with high spatial resolution. Overlapping thin sections can be 'reconstructed' into images in multiple planes (multiplanar reformatting—MPR) so lesions can be imaged in multiple planes. It has the advantage of a single investigation which potentially could obviate the need for the traditional '4-test' approach to haematuria (IVU, renal ultrasound, flexible cystoscopy, urine cytology), although at the cost of a higher radiation dose (a 7-film IVU = 5–10mSV, 3-phase MDCTU = 20–25mSV).

There is evidence suggesting that MDCTU has reasonable sensitivity and high specificity for diagnosing bladder tumours[6] (in patients with macroscopic haematuria 93% sensitivity, 99% specificity) and that it has equivalent diagnostic accuracy to retrograde uretero-pyelography (the retrograde administration of contrast via a catheter inserted in the lower ureter to outline the ureter and renal collecting system).[7] Overall, for patients with haematuria and no prior history of urological malignancy, for the detection of all urological tumours, it has approximately 65% sensitivity and 98% specificity[8]—so it only rarely calls a lesion a tumour when, in fact, the lesion is benign, but it still fails to diagnose a significant proportion of urinary neoplasms (sensitivity for upper tract neoplasms 80%, for bladder tumours 60%).

The role of MDCTU (described by some as the 'ultimate' imaging modality) in the investigation of haematuria remains controversial. MDCTU in all patients with haematuria (microscopic, macroscopic), when most will have no identifiable cause for the haematuria, has a cost (high radiation dose, financial). A targeted approach, aimed at those with risk factors for urothelial malignancy (age >40y, macroscopic as opposed to microscopic haematuria, smoking history, occupational exposure to benzenes and aromatic amines), might be a better use of this resource, rather than using MDCTU as the first imaging test for both high- and low-risk patients. Thus, the 'best' imaging probably depends on the context of the patient.

Should cystoscopy be performed in patients with a-NVH?

The American Urological Association (AUA)'s *Best Practice Policy on Asymptomatic Microscopic Hematuria*[1] (in the process of being revised at the time this 3rd edition went to press) recommends cystoscopy in all high-risk patients (high risk for development of TCC) with microscopic haematuria (the AUA still uses the term 'microscopic' haematuria) (see risk factors 📖 pp. 12–13).[9]

- **Patients at high risk for TCC:** positive smoking history, occupational exposure to chemicals or dyes (benzenes or aromatic amines), analgesic abuse (phenacetin), history of pelvic irradiation, previous cyclophosphamide treatment.

In asymptomatic, low-risk patients <40y, it states that 'it may be appropriate to defer cystoscopy', but if this is done, urine should be sent for cytology. However, the AUA also states that 'the decision as to when to proceed with cystoscopy in low-risk patients with persistent microscopic haematuria must be made on an individual basis after a careful discussion between the patient and physician'. It is our policy to inform such patients that the likelihood of finding a bladder cancer is low, but nevertheless we recommend flexible cystoscopy. The patient then makes a decision as to whether or not to proceed with cystoscopy based on their interpretation of 'low risk'.

If no cause for haematuria (VH or NVH) is found with cystoscopy and CT urography, is further investigation necessary?

Some say yes, quoting studies that show serious disease can be identified in a small number of patients where, in addition, retrograde ureterography, endoscopic examination of the ureters, and renal pelvis (ureteroscopy) and renal angiography were done. Others say no, citing the absence of development of overt urological cancer during 2–4y follow-up in patients originally presenting with microscopic or macroscopic haematuria (although without further investigations).[10]

For patients with negative initial investigations, the AUA's *Best Practice Policy on Asymptomatic Microscopic Hematuria*[9] advises repeat urinalysis, urine cytology, and BP measurement at 6, 12, 24, and 36 months, with repeat imaging and cystoscopy where dipstick or microscopic haematuria persists (in the process of being revised at the time of this 3rd edition went to press). The diagnostic yield from repeat testing where initial tests are normal remains to be identified with certainty. There is evidence that unless a patient represents with visible haematuria, repeat urologic investigation in those with persistent dipstick or microscopic haematuria will not identify any additional significant urologic pathology and nephrological investigation only in a very small number of patients with IgA nephropathy.[11]

The EAU currently has no policy for the management or follow-up of patients with persistent dipstick or microscopic haematuria.

If no cause for NVH is found, is there a risk of subsequent urological cancer developing (i.e. do normal initial haematuria investigations fail to identify urologic cancer in some patients)?

Over 10–13y of follow-up, two studies have revealed that where initial investigations in those patients with asymptomatic dipstick haematuria are negative and repeat dipstick analysis after full urologic investigation reveals no haematuria, no patient developed urological cancer.[11,12]

If NVH persists after initial negative investigation, should the patient undergo repeat investigation?

Where dipstick haematuria persists after initial renal imaging and cystoscopy reveal no cause, the diagnostic yield of repeat investigation is very low. Nephrologic and repeat urological investigation reveal no urological malignancies, IgA nephropathy in 12%, and UTI in 24%.[11]

The recommendation from these studies is that repeat urological investigation is not necessary unless a patient become symptomatic or develops visible haematuria.

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Haemospermia

Definition The presence of blood in the semen.
Usually intermittent, benign, self-limiting, and no cause identified.

Causes

Age <40y: usually inflammatory (e.g. prostatitis, epididymo-orchitis, urethritis); infective, including sexually transmitted diseases (STDs) (e.g. gonococcus), non-STD infection (e.g. *Enterococcus faecalis*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*), or viral infection (e.g. *Herpes simplex*), urethral warts or idiopathic (though to an extent, this reflects the limited investigation that is usually carried out in this age group). Rarely, testicular tumour; perineal or testicular trauma. Tumours are found in 2.4%.

Age >40y: as for men aged <40—commonest cause is now post-transrectal ultrasound (TRUS) biopsy of prostate; prostate cancer; bladder cancer; testicular cancer; BPH; dilated veins in the prostatic urethra; prostatic or seminal vesicle calculi; hypertension; carcinoma of the seminal vesicles; post-external beam radiotherapy or brachytherapy for prostate cancer. Tumours are found in 3.5% (mostly prostatic, rarely testis, seminal vesicle, epididymal).

Rare causes at any age: bleeding diathesis (von Willebrand's disease, haemophilia, acquired coagulation defects); utricular, Müllerian or seminal vesicle cysts—which may cause ductal obstruction, dilatation, distension, and rupture of blood vessels; TB; schistosomiasis; amyloid of prostate or seminal vesicles; post-injection of haemorrhoids. Very rarely, haemospermia may be confused with melanospermia from urinary tract melanoma.
NB. Abnormalities detected on TRUS or MRI may not necessarily be the cause of the haemospermia.

Examination

Examine the testes, epididymis, prostate, and seminal vesicles (DRE). Measure BP.

Investigation

Send urine for culture. If risk of exposure to STDs, refer to local STD clinic for STD screen. If the haemospermia resolves after a single episode, an argument can be made for doing nothing else. If it recurs or persists, then even in young men (2.4% risk of finding cancer if <40y old), arrange tests for PSA, FBC, LFTs and clotting, TRUS, flexible cystoscopy (look for urethral polyps, urethritis, prostatic cysts, urethral foreign bodies, stones, and vascular abnormalities) and renal ultrasound, pelvic MRI (MRI angiography can identify rare vascular abnormalities). The author has a low threshold for flexible cystoscopy given the simplicity of doing this test. If haematuria coexists, investigate this as described.

Treatment

This is directed at the underlying abnormality, if found. If no cause is found, reassure the patient that most cases are self-limiting.

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Lower urinary tract symptoms (LUTS)

A plethora of terms have been coined to describe the symptom complex traditionally associated with prostatic obstruction due to BPH. The 'classic' prostatic symptoms of hesitancy, poor flow, frequency, urgency, nocturia, and terminal dribbling have, in the past, been termed 'prostatism' or simply 'BPH symptoms'. One sometimes hears these symptoms being described as due to 'BPO' (benign prostatic obstruction) or benign prostatic enlargement ('BPE'; benign prostatic enlargement) or, more recently, 'LUTS/BPH'. However, these 'classic' symptoms of prostatic disease bear little relationship to prostate size, urinary flow rate, residual urine volume or indeed, urodynamic evidence of bladder outlet obstruction.[1,2] Furthermore, age-matched men and women have similar 'prostate' symptom scores,[3,4] but women obviously have no prostate. We, therefore, no longer use the expression 'prostatism' to describe the symptom complex of hesitancy, poor flow, etc. Instead, we call such symptoms 'lower urinary tract symptoms' (LUTS), which is purely a descriptive term avoiding any implication about the possible underlying cause of these symptoms.[5]

The new terminology 'LUTS' is useful because it reminds the urologist to consider possible alternative causes of symptoms which may have absolutely nothing to do with prostatic obstruction and it reminds us to avoid operating on an organ, such as the prostate, when the cause of the symptoms may lie elsewhere.

Baseline symptoms can be 'measured' using a symptom index. The most widely used is the International Prostate Symptom Score (IPSS) which, in addition to the seven symptoms of the American Urological Association-Symptom Index (AUA-SI), includes a question for the patient to assess the 'bothersomeness' of their LUTS[6], the AUA-SI.

Other causes of LUTS

In broad terms, LUTS can be due to pathology in the prostate, the bladder, the urethra, other pelvic organs (uterus, rectum), or due to neurological disease affecting the nerves that innervate the bladder. These pathologies can include BPE causing bladder outflow obstruction (BOO), and infective, inflammatory, and neoplastic conditions of the bladder, prostate, or urethra. While LUTS are, in general, relatively non-specific for particular pathologies, the *context* in which they occur (i.e. associated symptoms) can indicate their cause. For example:

- LUTS in association with macroscopic haematuria or with dipstick or microscopic haematuria suggests a possibility of bladder cancer. This is more likely if urinary frequency, urgency, and 'bladder' pain (suprapubic pain) are prominent. Carcinoma *in situ* of the bladder—a non-invasive, but potentially very aggressive, form of bladder cancer which very often progresses to muscle-invasive or metastatic cancer—classically presents in this way.
- Recent onset of bedwetting in an elderly man is often due to high-pressure chronic retention. Visual inspection of the abdomen may show marked distension due to a grossly enlarged bladder. The diagnosis of chronic retention is confirmed by palpating the enlarged,

tense bladder which is dull to percussion and by drainage of a large volume (often well in excess of 2L) following catheterization

- Rarely, LUTS can be due to neurological disease causing spinal cord or cauda equina compression or to pelvic or sacral tumours. Associated symptoms include back pain, sciatica, ejaculatory disturbances, and sensory disturbances in the legs, feet, and perineum. In these rare cases, loss of pericoccygeal or perineal sensation (sacral nerve roots 2–4) indicates an interruption to the sensory innervation of the bladder and an MRI scan will confirm the clinical suspicion that there is a neurological problem.

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Nocturia and nocturnal polyuria

- Nocturia ≥2 is common and bothersome (sleep disturbance).
- Prevalence of nocturia ≥2:[1,2] men—40% aged 60–70y, 55% aged >70y; women—10% aged 20–40y, 50% aged >80y.
- Nocturia ≥2 is associated with a 2-fold increased risk of falls and injury in the ambulant elderly.
- Men who void more than twice at night have a 2-fold increased risk of death (possibly due to the associations of nocturia with endocrine and cardiovascular disease).[3]

The diagnostic approach to the patient with nocturia

Nocturia can be due to urological disease, but more often than not, is non-urological in origin. Therefore, 'approach the lower urinary tract last' (Neil Resnick, Professor of Gerontology, Pittsburgh[4]).

Causes of nocturia

- **Urological:** BPO, overactive bladder, incomplete bladder emptying.
- **Non-urological:** renal failure, idiopathic nocturnal polyuria, diabetes mellitus, central diabetes insipidus (DI), nephrogenic DI, primary polydipsia, hypercalcaemia, drugs, autonomic failure, obstructive sleep apnoea.

Assessment of the nocturic patient

Ask the patient to complete a frequency volume chart (FVC)—a voiding diary that records time and volume of each void over a 24h period for 7 days. This establishes:

- If the patient is polyuric or non-polyuric?
- If polyuric, is the polyuria present throughout 24h or is it confined to night time (nocturnal polyuria)?

Polyuria is defined empirically as >3L of urine output per 24h (Standardization Committee of the International Continence Society (ICS), 2002).

Nocturnal polyuria is empirically defined as the production of more than one-third of 24h urine output between midnight and 8 a.m. (It is a normal physiological mechanism to reduce urine output at night. Urine output between midnight and 8 a.m.—one-third of the 24h clock—should certainly be no more than one-third of 24h total urine output and in most people, will be considerably less than one-third.)

Polyuria (urine output of >3L per 24h) is due either to a solute diuresis or a water diuresis. Measure urine osmolality: <250mOsm/kg = water diuresis, >300mOsm/kg = solute diuresis. Excess levels of various solutes in the urine, such as glucose in the poorly controlled diabetic, lead to a solute diuresis. A water diuresis occurs in patients with primary polydipsia (an appropriate physiological response to high water intake) and DI (antidiuretic hormone (ADH) deficiency or resistance). Patients on lithium have renal resistance to ADH (nephrogenic DI).

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Loin (flank) pain

This can present suddenly as severe pain in the flank reaching a peak within minutes or hours (acute loin pain). Alternatively, it may have a slower course of onset (chronic loin pain), developing over weeks or months. Loin pain is frequently presumed to be urological in origin on the simplistic basis that the kidneys are located in the loins. However, other organs are located in this region, pathology within which may be the source of the pain and pain arising from extra-abdominal organs may radiate to the loins ('referred' pain). So when faced with a patient with loin pain, think laterally—the list of differential diagnoses is long!

The speed of onset of loin pain gives some, although not an absolute, indication of the cause of urological loin pain. Acute loin pain is more likely to be due to something obstructing the ureter, such as a stone. Loin pain of more chronic onset suggests disease within the kidney or renal pelvis.

Acute loin pain

The most common cause of sudden onset of severe pain in the flank is the passage of a stone formed in the kidney down through the ureter. Ureteric stone pain characteristically starts very suddenly (within minutes), is colicky in nature (waves of increasing severity are followed by a reduction in severity, although seldom going away completely), and it radiates to the groin as the stone passes into the lower ureter. The pain may change in location, from flank to groin, but its location does not provide a good indication of the position of the stone, except where the patient has pain or discomfort in the penis and a strong desire to void which suggests that the stone has moved into the intramural part of the ureter (the segment within the bladder). The patient cannot get comfortable. They often roll around in agony.

Fifty percent of patients with these classic symptoms of ureteric colic do not have a stone confirmed on subsequent imaging studies nor do they physically ever pass a stone.[1,2] They have some other cause for their pain (see 🕮 pp. 20–22). A ureteric stone is only very rarely life-threatening, but many of these differential diagnoses may be life-threatening. Acute loin pain is less likely to be due to a ureteric stone in women and in patients at the extremes of age. It tends to be a disease of men (and to a lesser extent, women) between the ages of 720 and 60y, although it can occur in younger and older individuals.

Acute loin pain—non-stone, urological causes

- **Clot or tumour colic:** a clot may form from a bleeding source within the kidney (e.g. renal cell cancer or transitional cell cancer of the renal pelvis). Similarly, a ureteric TCC may cause ureteric obstruction and acute loin pain. Loin pain and haematuria are often assumed to be due to a stone, but it is important to approach investigation of such patients from the perspective of haematuria (i.e. look to exclude cancer).
- **Pelviureteric junction obstruction (PUJO), also known as ureteropelvic junction obstruction (UPJO):** may present acutely with flank pain severe enough to mimic a ureteric stone. A CT scan will

demonstrate hydronephrosis, with a normal calibre ureter below the PUJ and no stone. MAG3 renography confirms the diagnosis.

- **Infection:** e.g. acute pyelonephritis, pyonephrosis, emphysematous pyelonephritis, xanthogranulomatous pyelonephritis. These patients have a high fever (>38°C) whereas ureteric stone patients do not (unless there is infection 'behind' the obstructing stone) and are often systemically very unwell. Imaging studies may or may not show a stone and there will be radiological evidence of infection within the kidney and perirenal tissues (oedema).

Acute loin pain—non-urological causes

- Vascular.
  - Leaking abdominal aortic aneurysm (AAA).
- 'Medical'.
  - Pneumonia.
  - Myocardial infarction.
  - Malaria presenting as bilateral loin pain and dark haematuria—black water fever.
- Gynaecological and obstetric.
  - Ovarian pathology (e.g. twisted ovarian cyst).
  - Ectopic pregnancy.
- Gastrointestinal.
  - Acute appendicitis.
  - Inflammatory bowel disease (Crohn's, ulcerative colitis).
  - Diverticulitis.
  - Burst peptic ulcer.
  - Bowel obstruction.
- Testicular torsion.
- Spinal cord disease.
  - Prolapsed intervertebral disc.

Distinguishing urological from non-urological loin pain

History and examination are clearly important. Patients with ureteric colic often move around the bed in agony. Those with peritonitis lie still. Palpate the abdomen for signs of peritonitis (abdominal tenderness and/or guarding) and examine for abdominal masses (pulsatile and expansile = leaking AAA). Examine the patient's back, chest, and testicles. In women, do a pregnancy test.

Chronic loin pain—urological causes

- Renal or ureteric cancer.
  - Renal cell carcinoma.
  - TCC of the renal pelvis or ureter.
- Renal stones.
  - Staghorn calculi.
  - Non-staghorn calculi.
- Renal infection.
  - TB.
- PUJO.

- Testicular pathology (referred pain).
  - Testicular neoplasms.
- Ureteric pathology.
  - Ureteric reflux.
  - Ureteric stone (may drop into the ureter, causing severe pain which then subsides to a lower level of chronic pain).

Chronic loin pain—non-urological causes

- Gastrointestinal.
  - Bowel neoplasms.
  - Liver disease.
- Spinal disease.
  - Prolapsed intervertebral disc.
  - Degenerative disease.
  - Spinal metastases.

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Urinary incontinence

Definitions

Urinary incontinence (UI): the complaint of any involuntary leakage of urine.

Stress urinary incontinence (SUI): the complaint of involuntary leakage of urine on effort or exertion or sneezing or coughing. SUI can also be a sign, the *observation* of involuntary leakage of urine from the urethra that occurs synchronously with exertion, coughing, etc. A diagnosis of *urodynamic* SUI is made during filling cystometry when there is involuntary leakage of urine during a rise in abdominal pressure (induced by coughing) in the absence of a detrusor contraction.

Urge urinary incontinence (UUI): the complaint of any involuntary leakage of urine accompanied by or immediately preceded by urgency.

Mixed urinary incontinence (MUI): a combination of SUI and UUI.

- Both UUI and MUI cannot be a sign as they both require a perception of urgency by the patient.
- 25% of women aged >20y have UI, of whom 50% have SUI, 10–20% pure UUI, and 30–40% MUI.
- UI impacts on psychological health, social functioning, and quality of life.

Significance of SUI and UUI

SUI occurs as a result of bladder neck/urethral hypermobility and/or neuromuscular defects causing intrinsic sphincter deficiency (sphincter weakness incontinence). As a consequence, urine leaks whenever urethral resistance is exceeded by an increased abdominal pressure occurring during exercise or coughing, for example.

UUI may be due to bladder overactivity (formerly known as detrusor instability) or less commonly due to pathology that irritates the bladder (infection, tumour, stone). The correlation between urodynamic evidence of bladder overactivity and the sensation of urgency is poor, particularly in patients with MUI. Symptoms resulting from involuntary detrusor contractions may be difficult to distinguish from those due to sphincter weakness. Furthermore, in some patients, detrusor contractions can be provoked by coughing and, therefore, distinguishing leakage due to SUI from that due to bladder overactivity can be very difficult.

Other types of incontinence

While SUI and especially UUI do not specifically allow identification of the underlying cause, some types of incontinence allow a specific diagnosis to be made.

- **Bedwetting** in an elderly man usually indicates high-pressure chronic retention (HPCR).

- A **constant leak** of urine suggests a fistulous communication between the bladder (usually) and vagina (e.g. due to surgical injury at the time of hysterectomy or Caesarian section) or, rarely, the presence of an ectopic ureter draining into the vagina (in which case the urine leak is usually low in volume, but lifelong).

Further reading

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Genital symptoms

Scrotal pain

- Pathology within the scrotum.
  - Torsion of the testicles.
  - Torsion of testicular appendages.
  - Epididymo-orchitis.
  - Testicular tumour.
- Referred pain.
  - Ureteric colic.

Testicular torsion: ischaemic pain is severe (e.g. myocardial infarction, ischaemic leg, ischaemic testis). Torsion presents with sudden onset of pain in the hemiscrotum, sometimes waking the patient from sleep. May radiate to the groin and/or loin. Five to ten percent of boys report a history of scrotal trauma in the period prior to the acute presentation of testicular torsion.[1,2] Similar episodes may have occurred in the past, with spontaneous resolution of the pain (suggesting torsion/spontaneous detorsion). The testis is very tender. It may be high-riding (lying at a higher than normal position in the testis) and may lie horizontally due to twisting of the cord. There may be scrotal erythema.

Epididymo-orchitis: similar presenting symptoms as testicular torsion. Tenderness is usually localized to the epididymis (absence of testicular tenderness may help to distinguish epididymo-orchitis from testicular torsion, but in many cases, it is difficult to distinguish between the two). See 🕮 p. 522 for advice on attempting to distinguish torsion from epididymo-orchitis.

Testicular tumour: 20% present with testicular pain.

Acute presentations of testicular tumours

- Testicular swelling may occur rapidly (over days or weeks). An associated (secondary) hydrocele is common. A hydrocele in a young person should always be investigated with an ultrasound to determine whether the underlying testis is normal.
- Rapid onset (days) of testicular swelling can occur. Very rarely present with advanced metastatic disease (high-volume disease in the retroperitoneum, chest, and neck causing chest, back, or abdominal pain or shortness of breath).
- Approximately 10–15% of testis tumours present with signs suggesting inflammation (i.e. signs suggesting a diagnosis of epididymo-orchitis—a tender, swollen testis, with redness in the overlying scrotal skin and a fever).

Chronic scrotal pain

Includes:

- Testicular pain syndrome (a cause can be identified in as many as 75% of cases).
  - Testicular tumour.
  - Previous trauma or surgery, e.g. hernia repair, hydrocele repair, epididymal cyst removal, varicocele repair.
  - Post-infection.

  - Diabetic neuropathy.
  - Polyarteritis nodosa.
  - If there is radiation of the pain, consider a primary source in the vertebrae (e.g. prolapsed disc, tumour), ureter (ureteric stone), or a retroperitoneal tumour.
- Post-vasectomy pain syndrome (1–15% of men post-vasectomy; in some men, caused by obstruction to the vas, sperm granuloma, chronic epididymitis).
- Epididymal pain syndrome.
  - Chronic bacterial infection.
  - STDs.
  - Trauma.

Other causes of chronic scrotal pain include post-laparoscopic nephrectomy (55% of men) and radical nephrectomy (20%)—50% of men experiencing resolution of the pain by one month post-surgery (possibly due to ligation of gonadal vein); chronic prostatitis (tender prostate on DRE); pudendal neuralgia.

Management

- **Examination:** examine scrotum for any of the above pathologies; DRE.
- **Investigation:** midstream urine (MSU), scrotal ultrasound scan.
- **Treatment:** having excluded the above causes, antibiotics may be used if chronic epididymitis is suspected; pelvic floor physiotherapy; pain clinic referral; surgery—last resort, partial or total epididymectomy, inguinal orchidectomy, vasectomy reversal, spermatid cord denervation.

Priapism

Painful, persistent, prolonged erection of the penis not related to sexual stimulation (causes summarized in Chapter 13). Two broad categories—low-flow (most common) and high-flow. Low-flow priapism—due to haematological disease, malignant infiltration of the corpora cavernosa with malignant disease, or drugs; painful because the corpora are ischaemic. High-flow priapism—due to perineal trauma which creates an arteriovenous fistula; painless.

Diagnosis is usually obvious from the history and examination of the erect, tender penis (in low-flow priapism). Characteristically, the corpora cavernosa are rigid and the glans is flaccid. Examine the abdomen for evidence of malignant disease and perform a DRE to examine the prostate and check anal tone.

Further reading

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Abdominal examination in urological disease

Because of their retroperitoneal (kidneys, ureters) or pelvic location (bladder and prostate), 'urological' organs are relatively inaccessible to the examining hand when compared with, for example, the spleen, liver, or bowel. For the same reason, for the kidneys and bladder to be palpable implies a fairly advanced disease state.

It is important that the urologist appreciates the characteristics of other intra-abdominal organs when involved with disease so that they may be distinguished from 'urological' organs.

Characteristics and causes of an enlarged kidney

The mass lies in a paracolic gutter, it moves with respiration, is dull to percussion, and can be felt bimanually. It can also be balloted (i.e. bounced like a ball (*balla = ball* (*Italian*)) between your hands, one placed on the anterior abdominal wall and one on the posterior abdominal wall.

Causes of an enlarged kidney: renal carcinoma, hydronephrosis, pyonephrosis, perinephric abscess, polycystic disease, nephroblastoma.

Characteristics and causes of an enlarged liver

The mass descends from underneath the right costal margin, you cannot get above it, it moves with respiration, it is dull to percussion, and has a sharp or rounded edge. The surface may be smooth or irregular.

Causes of an enlarged liver: infection, congestion (heart failure, hepatic vein obstruction—Budd–Chiari syndrome), cellular infiltration (amyloid), cellular proliferation, space-occupying lesion (polycystic disease, metastatic infiltration, primary hepatic cancer, hydatid cyst, abscess), cirrhosis.

Characteristics and causes of an enlarged spleen

The mass appears from underneath the costal margin, enlarges towards the right iliac fossa, is firm and smooth, and may have a palpable notch. It is not possible to get above the spleen, it moves with respiration, is dull to percussion, and it cannot be felt bimanually.

Causes of an enlarged spleen: bacterial infection (typhoid, typhus TB, septicaemia); viral infection (glandular fever); protozoal infection (malaria, kala-azar); spirochaete infection (syphilis, Leptospirosis—Weil's disease); cellular proliferation (myeloid and lymphatic leukaemia, myelosclerosis, spherocystosis, thrombocytopenic purpura, pernicious anaemia); congestion (portal hypertension—cirrhosis, portal vein thrombosis, hepatic vein obstruction, congestive heart failure); cellular infiltration (amyloid, Gaucher's disease); space-occupying lesions (solitary cysts, hydatid cysts, lymphoma, polycystic disease).

Characteristics of an enlarged bladder

Arises out of the pelvis, dull to percussion, pressure of examining hand may cause a desire to void.

Abdominal distension: causes and characteristics

- Foetus—smooth, firm mass, dull to percussion, arising out of the pelvis.
- Flatus—hyperresonant (there may be visible peristalsis if the accumulation of flatus is due to bowel obstruction).
- Faeces—palpable in the flanks and across the epigastrium, firm, and may be indentable; there may be multiple separate masses in the line of the colon.
- Fat.
- Fluid (ascites)—fluid thrill, shifting dullness.
- Large abdominal masses (massive hepatomegaly or splenomegaly, fibroids, polycystic kidneys, retroperitoneal sarcoma).

The umbilicus and signs and symptoms of associated pathology

The umbilicus represents the location of four fetal structures—the umbilical vein, two umbilical arteries, and the urachus which is a tube extending from the superior aspect of the bladder towards the umbilicus (it represents the obliterated vesicourethral canal).

The urachus may remain open at various points, leading to the following abnormalities.

- **Completely patent urachus:** communicates with the bladder and leaks urine through the umbilicus; usually doesn't present until adulthood (strong contractions of bladder of a child closes the mouth of the fistula).
- **Vesicourachal diverticulum:** a diverticulum in the dome of the bladder; usually symptomless.
- **Umbilical cyst or sinus:** can become infected, forming an abscess or may chronically discharge infected material from the umbilicus. A cyst can present as an immobile, midline swelling between the umbilicus and bladder, deep to the rectus sheath. It may have a small communication with the bladder and, therefore, its size can fluctuate as it can becomes swollen with urine.

Other causes of umbilical masses

Metastatic deposit (from abdominal cancer, metastatic spread occurring via lymphatics in the edge of the falciform ligament, running alongside the obliterated umbilical vein); 'deposit' of endometriosis (becomes painful and discharges blood at the same time as menstruation).

Digital rectal examination (DRE)

The immediate anterior relationship of the rectum in the male is the prostate. The DRE is the mainstay of examination of the prostate.

Explain the need for the examination. Ensure the examination is done in privacy. In the UK, DRE is usually done in the left lateral position—with the patient lying on their left side, and with the hips and knees flexed to 90° or more. Examine the anal region for fistulae and fissures. Apply plenty of lubricating gel to the gloved finger. Lift the tight buttock upwards with your other hand to expose the anus and gently and slowly insert your index finger into the anal canal, then into the rectum.

Palpate anteriorly with the pulp of your finger and feel the surface of the prostate. Note its consistency (normal or firm), its surface (smooth or irregular), and estimate its size. (It can be helpful to relate its size to common objects (e.g. fruit or nuts!) A normal prostate is the size of a walnut, a moderately enlarged prostate that of a tangerine, and a big prostate the size of an apple or orange.) The normal bilobed prostate has a groove (the median sulcus) between the two lobes and in prostate cancer, this groove may be obscured.

Many men find DRE uncomfortable or even painful and the inexperienced doctor may equate this normal discomfort with prostatic tenderness. Prostatic tenderness is best elicited by gentle pressure on the prostate with the examining finger. If the prostate is really involved by some acute, inflammatory condition such as acute, infective prostatitis or a prostatic abscess, it will be very tender.

DRE should be avoided in the profoundly neutropenic patient (risk of septicaemia) and in patients with an anal fissure where DRE would be very painful.

Other features to elicit in the DRE

The integrity of the sacral nerves that innervate the bladder and of the sacral spinal cord can be established by eliciting the bulbocavernosus reflex (the BCR) during a DRE. The sensory side of the reflex is elicited by squeezing the glans of the penis or the clitoris (or in catheterized patients, by gently pulling the balloon of the catheter onto the bladder neck). The motor side of the reflex is tested by feeling for contraction of the anus during this sensory stimulus. Contraction of the anus represents a positive BCR and indicates that the afferent and efferent nerves of the sacral spinal cord (S2–4) and the sacral cord are intact.

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Lumps in the groin

Differential diagnosis

Inguinal hernia, femoral hernia, enlarged lymph nodes, saphena varix, hydrocele of the cord (or of the canal of Nück in women), vaginal hydrocele, undescended testis, lipoma of the cord, femoral aneurysm, psoas abscess.

Determining the diagnosis

Hernia

A hernia (usually) has a cough impulse (i.e. it expands on coughing) and (usually) reduces with direct pressure or on lying down unless, uncommonly, it is incarcerated (i.e. the contents of the hernia are fixed in the hernia sac by their size and by adhesions). *Movement* of the lump is not the same as *expansion*. Many groin lumps have a transmitted impulse on coughing (i.e. they move), but do not expand on coughing. Since inguinal and femoral hernias arise from within the abdomen and *descend* into the groin, it is not possible to 'get above' them. For lumps that arise from within the scrotum, the superior edge can be palpated (i.e. it *is* possible to 'get above' them).

Once a hernia has protruded through the abdominal wall, it can expand in any direction in the subcutaneous tissues and therefore, the position of the unreduced hernia *cannot* be used to establish whether it is inguinal or femoral. The point of *reduction* of the hernia establishes whether it is an inguinal or femoral hernia.

Inguinal: the hernia reduces through the abdominal wall at a point *above and medial* to the pubic tubercle. An indirect inguinal hernia often descends into the scrotum; a direct inguinal hernia rarely does.

Femoral: the hernia reduces through the abdominal wall at a point *below and lateral* to the pubic tubercle.

Enlarged inguinal lymph nodes

A firm, non-compressible, nodular lump in the groin. Look for pathology in the skin of the scrotum and penis, the perianal area and anus, and the skin and superficial tissues of the thigh and leg.

Saphena varix

A dilatation of the proximal end of the saphenous vein. Can be confused with an inguinal or femoral hernia because it has an expansile cough impulse (i.e. expands on coughing) and disappears on lying down. It is easily compressible and has a fluid thrill when the distal saphenous vein is percussed.

Hydrocele of the cord (or of the canal of Nück in women)

A hydrocele is an abnormal quantity of peritoneal fluid between the parietal and visceral layers of the tunica vaginalis, the double layer of peritoneum surrounding the testis, and which was the processus vaginalis in the foetus. Normally, the processus vaginalis becomes obliterated along its entire length, apart from where it surrounds the testis where a potential

space remains between the parietal and visceral layers. If the central part of the processus vaginalis remains patent, fluid secreted by the 'trapped' peritoneum accumulates and forms a hydrocele of the cord (the equivalent in females is known as the canal of Nück). A hydrocele of the cord may, therefore, be present in the groin.

Undescended testis

May be on the correct anatomical path, but may have failed to reach the scrotum (incompletely descended testis) or may have descended away from the normal anatomical path (ectopic testis). The 'lump' is smooth, oval, tender to palpation, non-compressible, and there is no testis in the scrotum.

Lipoma of the cord

A non-compressible lump in the groin, with no cough impulse.

Femoral aneurysm

Usually in the common femoral artery (rather than superficial or profunda femoris branches) and, therefore, located just below the inguinal ligament. Easily confused with a femoral hernia. Like all aneurysms, they are expansile (but unlike hernias, they do not expand on coughing).

Psoas abscess

The scenario is one of a patient who is unwell with a fever and with a soft, fluctuant, compressible mass in the femoral triangle.

Lumps in the scrotum

Differential diagnosis

Inguinal hernia, hydrocele, epididymal cyst, testicular tumour, varicocele, sebaceous cyst, tuberculous epididymo-orchitis, gumma of the testis, carcinoma of scrotal skin.

Determining the diagnosis

Inguinal hernia

An indirect inguinal hernia often extends into the scrotum. It usually has a cough impulse (i.e. it expands on coughing) and usually reduces with direct pressure or on lying down. It is not possible to get above the lump.

Hydrocele

A hydrocele is an abnormal quantity of peritoneal fluid between the parietal and visceral layers of the tunica vaginalis, the double layer of peritoneum surrounding the testis and which was the processus vaginalis in the fetus. Normally, the processus vaginalis becomes obliterated along its entire length, apart from where it surrounds the testis where a potential space remains between the parietal and visceral layers.

Usually painless, unless the underlying testicular disease is painful. A hydrocele has a smooth surface and it is difficult or impossible to feel the testis which is surrounded by the tense, fluid collection (unless, rarely, the hydrocele is very lax). The superior margin can be palpated (i.e. you can get above the lump). It is possible to transilluminate a hydrocele (i.e. the light from a torch applied on one side can be seen on the other side of the hydrocele).

May be primary (idiopathic) or secondary. Primary hydroceles develop slowly (over the course of years usually) and there is no precipitating event such as epididymo-orchitis or trauma, and the underlying testis appears normal on ultrasound (no testicular tumour). Secondary hydroceles (infection, tumour, trauma) represent an effusion between the layers of the tunica vaginalis (the visceral and parietal layers), analogous to a pleural or peritoneal effusion. In filariasis (infection with the filarial worm,*Wuchereria bancrofti*), obstruction of the lymphatics of the spermatic cord give rise to the hydrocele.

Epididymal cyst

(Also known as a spermatocele if there are spermatozoa in the contained fluid.) Derived from the collecting tubules of the epididymis and contains clear fluid. They develop slowly (overy), lie within the scrotum (you can get above them), and usually lie above and behind the testis. They are often multiple (multiloculated).

Orchitis

In the absence of involvement of the epididymitis, due to a viral infection, e.g. mumps. Often occurs with enlargement of the salivary glands.

Tuberculous epididymo-orchitis

Infection of the epididymis (principally) by TB, which has spread from the blood or urinary tract. The *absence* of pain and tenderness is noticeable. The epididymis is hard and has an irregular surface. The spermatic cord is thickened and the vas deferens also feels hard and irregular (a 'string of beads').

Testicular tumour (seminoma, teratoma)

A solid mass, arising from within the scrotum that, if very large, may extend up into the spermatic cord. They may present with symptoms which mimic an acute epididymorchitis (i.e. pain and tenderness in the testis and fever). Not infrequently, the patient reports a history of minor trauma to the testis in the days or weeks preceding the onset of symptoms. They may have undergone an orchidopexy as a child (fixation of the testis in the scrotum for an undescended testis).

The lump is usually firm or hard, and may have a smooth or irregular surface. Examine for abdominal and supraclavicular lymph nodes.

Gumma of the testis

Rare; syphilis of the testis resulting in a round, hard, insensitive mass involving the testis (a so-called 'billiard ball'); difficult to distinguish from a tumour.

Varicocele

Dilatation of the pampiniform plexus—the collection of veins surrounding the testis and extending up into the spermatic cord (essentially varicose veins of the testis and spermatic cord). Small, symptomless varicoceles occur in approximately 20% of normal men and are more common on the left side. They may cause a dragging sensation or ache in the scrotum. Said to feel like a 'bag of worms'. The varicocele disappears when the patient lies down.

Sebaceous cyst

Common in scrotal skin. They are fixed to the skin and have a smooth surface.

Carcinoma of scrotal skin

Appears as an ulcer on the scrotal skin, often with a purulent or bloody discharge.

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Chapter 3

Urological investigations

Assessing kidney function

When we talk about measuring kidney function, what we mean is measurement of glomerular filtration rate (GFR). This is regarded as the best measure of kidney function and we grade the degree of renal impairment and renal failure according to the GFR. Normal GFR in young men is approximately 130mL/min per 1.73m^2 of body surface area. In young women, it is 120mL/min per 1.73m^2 of body surface area. Mean GFR declines with age (Table 3.1).

The ideal filtration marker is excreted by filtration alone. Exogenous markers that can be used to measure include inulin, iothalamate, ethylene diamine tetra-acetic acid (EDTA), diethylene triamine penta-acetic acid, and iohexol. Measurement of GFR using exogenously administered markers is complex and expensive and is difficult to do in routine clinical practice.

Urinary clearance of endogenous markers, such as creatinine, can be used to estimate GFR. Creatinine is a 113D-amino acid derivative that is freely filtered at the glomerulus. A timed urine collection and measurement of serum creatinine concentration allows calculation of GFR according to the formula:

$$\text{Clearance (GFR)} = U \times V/P$$

where U is the concentration of urine in urine, P the concentration in plasma, and V the urine flow.

As an alternative, estimation of GFR can be made from simple measurement of serum creatinine since the main mechanism of creatinine excretion is by glomerular filtration and GFR has a reciprocal relationship with serum creatinine. Thus, as GFR falls (indicating worsening renal function), creatinine rises. However, creatinine is not the ideal filtration marker since it is also excreted by proximal tubular secretion as well as by glomerular filtration and therefore, creatinine clearance exceeds GFR, i.e. creatinine clearance tends to overestimate GFR.

Estimated GFR (eGFR)

Since the endogenous production of creatinine is determined by muscle mass, serum levels of creatinine will not only vary according to renal function (glomerular filtration), but also according to age, body size, ethnic group, and sex. Taking account of these factors can overcome some of the limitations of measurement of serum creatinine alone.

Two equations have been widely used for calculating eGFR—the Cockcroft–Gault formula and the Modification of Diet in Renal Disease (MDRD) equation. Both were developed from populations of patients with chronic kidney disease. They are less accurate estimates of renal function in populations *without* chronic kidney disease.

The ***Cockcroft–Gault formula*** (overestimates GFR because of tubular secretion of creatinine and the value is not adjusted for body surface area).

$$C_{Cr} \text{ in mL/min} = [(140 - \text{age}) \times \text{weight}]/(0.84 \times S_{Cr}) \text{ if male}$$

$$C_{Cr} \text{ in mL/min} = [(140 - \text{age}) \times \text{weight}]/(0.85 \times S_{Cr}) \text{ if female}$$

where S_{Cr} = serum creatinine (mM/L) and C_{Cr} = creatinine clearance.

The ***MDRD equation*** (modified in 2005; adjusts for body surface area).

$$GFR\ (mL/min/1.73m^2) = 30\,849 \times (S_{Cr})^{-1.154} \times (age)^{-0.203}$$

($\times$ 0.742 if female; $\times$ 1.212 if black)

The MDRD is reasonably accurate as an estimate of GFR, the mean difference between eGFR and measured GFR ranging from –5 to 1mL/min/1.73m^2.

The eGFR provides substantial improvements over serum creatinine measurements alone in the clinical assessment of renal function in terms of the detection, evaluation, and management of chronic kidney disease (Table 3.1).

Table 3.1 Chronic kidney disease (CKD) classification

Stage	eGFR (mL/min/1.73m^2)
1 (kidney damage with normal or increased GFR)	>90
2 (mild decrease in GFR)	60–89
3 (moderate decrease in GFR)	30–59
4 (severe decrease in GFR)	15–29
5 (kidney failure)	<15

Urine examination

Dipstick testing

Analysis for pH, blood, protein, glucose, and white cells can be done with dipstick testing.

pH

Urinary pH varies between 4.5 and 8, averaging between 5.5 and 6.5.

Blood

Normal urine contains <3 RBCs per high-powered field (HPF) (1000 erythrocytes/mL of urine; upper limit of 5000–8000 erythrocytes/mL). Positive dipstick for blood indicates the presence of haemoglobin in the urine. Haemoglobin has a peroxidase-like activity and causes oxidation of a chromogen indicator which changes colour when oxidized. Sensitivity of urine dipsticks for identifying haematuria (>3 RBCs/HPF is >90%); specificity is lower (i.e. a higher false positive rate with the dipstick due to contamination with menstrual blood, dehydration (concentrates what RBCs are normally present in urine)).

Haematuria due to a urological cause does not elevate urinary protein. Haematuria of nephrological origin often occurs in association with casts and there is almost always significant proteinuria.

Protein

Normal, healthy adults excrete about 80–150mg of protein per day in their urine (normal protein concentration <20mg/dL). Proteinuria suggests the presence of renal disease (glomerular, tubulo-interstitial, renal vascular) or multiple myeloma, but it can occur following strenuous exercise. Dipstick test is based on a tetrabromophenol blue dye colour change (green colour develops in the presence of protein of >20mg/dL).

White blood cells

Leukocyte esterase activity detects the presence of white blood cells in the urine. Leukocyte esterase is produced by neutrophils and causes a colour change in a chromogen salt on the dipstick. Not all patients with bacteriuria have significant pyuria. False negatives: concentrated urine, glycosuria, presence of urobilinogen, consumption of large amounts of ascorbic acid. False positives: contamination.

Nitrite testing

Nitrites in the urine suggest the possibility of bacteriuria. They are not normally found in the urine. Many species of Gram negative bacteria can convert nitrates to nitrites and these are detected in urine by a reaction with the reagents on the dipstick, which form a red azo dye. The specificity of the nitrite dipstick for detecting bacteriuria is >90% (false positive nitrite testing is contamination). Sensitivity is 35–85% (i.e. lots of false negatives); less accurate in urine containing fewer than 10^5 organisms/mL.

Cloudy urine that is positive for white blood cells and nitrite-positive is very likely to be infected.

Urine microscopy

Red blood cell morphology

Determined by phase contrast microscopy. RBCs derived from the glomerulus are dysmorphic (they have been distorted by their passage through the glomerulus). RBCs derived from tubular bleeding (tubulointerstitial disease) and those from lower down the urinary tract (i.e. urological bleeding from the renal pelvis, ureters, or bladder) have a normal shape. Glomerular bleeding is suggested by the presence of dysmorphic RBCs, RBC casts, and proteinuria.

Casts

A protein coagulum (principally, Tamm–Horsfall mucoprotein derived from tubular epithelial cells) formed in the renal tubule and 'cast' in the shape of the tubule (i.e. long and thin). The protein matrix traps tubular luminal contents. If the cast contains only mucoproteins, it is called a hyaline cast. Seen after exercise, heat exposure, and in pyelonephritis or chronic renal disease. RBC casts contain trapped erythrocytes and are diagnostic of glomerular bleeding, most often due to glomerulonephritis. White blood cell casts are seen in acute glomerulonephritis, acute pyelonephritis, and acute tubulointerstitial nephritis.

Crystals

Specific crystal types may be seen in urine and help diagnose underlying problems (e.g. cystine crystals establish the diagnosis of cystinuria). Calcium oxalate, uric acid, and cystine are precipitated in acidic urine. Crystals precipitated in alkaline urine include calcium phosphate and triple phosphate (struvite).

Urine cytology

- **Urine collection for cytology:** exfoliated cells lying in urine that has been in the bladder for several hours (e.g. early morning specimens) or in a urine specimen that has been allowed to stand for several hours are degenerate. Such urine specimens are not suitable for cytological interpretation. Cytological examination can be performed on bladder washings (using normal saline) obtained from the bladder at cystoscopy (or following catheterization) or from the ureter (via a ureteric catheter or ureteroscope). The urine is centrifuged and the specimen obtained is fixed in alcohol and stained by the Papanicolaou technique.
- Normal urothelial cells are shed into the urine and under the microscope, their nuclei appear regular and monomorphic (diffuse, fine chromatin pattern, single nucleolus).
- Causes of a positive cytology report (i.e. abnormal urothelial cells seen—high nuclear:cytoplasmic ratio, hyperchromatic nuclei, prominent nucleoli):
  - Urothelial malignancy (TCC, SCC, adenocarcinoma).
  - Previous radiotherapy (especially if within the last 12 months).
  - Previous cytotoxic drug treatment (especially if within the last 12 months, e.g. cyclophosphamide, busulfan, ciclosporin).
  - Urinary tract stones.
- Renal adenocarcinoma (clear cell cancer of the kidney) usually does not exfoliate abnormal cells, although occasionally clusters of clear cells may be seen, suggesting the diagnosis.
- High-grade urothelial cancer and carcinoma in situ exfoliate cells which look very abnormal and usually the cytologist is able to indicate that there is a high likelihood of a malignancy. Low-grade bladder TCC exfoliates cells which look very much like normal urothelial cells. The difficulty arises where the cells look abnormal, but not that abnormal—here, the likelihood that the cause of the abnormal cytology is a benign process is greater.
- Sensitivity and specificity of positive urine cytology for detecting TCC of the bladder depends on the definition of 'positive'—if only obviously malignant or highly suspicious samples are considered positive, then the specificity will be high. Urine cytology may be negative in as many as 20% of high-grade cancers. If 'atypical cells' are included in the definition of 'abnormal', the specificity of urine cytology for diagnosing urothelial cancer will be relatively poor (relatively high number of false positives) because many cases will have a benign cause (stones, inflammation).

Prostatic-specific antigen (PSA)

(see also 📖 pp. 318–321)

PSA is a 34kD glycoprotein enzyme produced by the columnar acinar and ductal prostatic epithelial cells. It is a member of the human kallikrein family and its function is to liquefy the ejaculate, enabling fertilization. PSA is present in both benign and malignant cells, although the expression of PSA tends to be reduced in malignant cells and may be absent in poorly differentiated tumours. Large amounts are secreted into the semen and small quantities are found in the urine and blood.

The function of serum PSA is unclear, although it is known to liberate the insulin-like growth factor type 1 from one of its binding proteins. Seventy-five percent of circulating PSA is bound to plasma proteins (complexed PSA) and metabolized in the liver, while 25% is free and excreted in the urine. Complexed PSA is stable, bound to alpha-1 antichymotrypsin and alpha-2 macroglobulin. Free PSA is unstable, recently found to consist of two isoforms:pro-PSA is a peripheral zone precursor, apparently elevated in the presence of prostate cancer, and BPSA is the transition zone precursor and associated with BPH. The half-life of serum PSA is 2.2 days. The normal range for the serum PSA assay in men is <4.0ng/mL, though this varies with age. Table 3.2 shows a published age-specific normal range (95th centile).

In the absence of prostate cancer, serum PSA concentrations also vary physiologically, according to race and prostate volume.

Indications for checking serum PSA

- Patient request, following counselling (see 📖 p. 322).
- LUTS.
- Abnormal DRE.
- Progressive bone pain, especially back pain.
- Unexplained anaemia, anorexia, or weight loss.
- Spontaneous thromboembolism or unilateral leg swelling.
- Monitoring of prostate cancer patients.

Table 3.2 The age-adjusted normal range for PSA

Age range	Normal PSA range (ng/mL)
All ages	<4.0
40–49	<2.5
50–59	<3.5
60–69	<4.5
>70	<6.5

Radiological imaging of the urinary tract

Ultrasound

A non-invasive method of urinary tract imaging. While it provides good images of the kidneys and bladder, anatomical detail of the ureter is poor and the mid-ureter cannot be imaged at all by ultrasound because of overlying bowel gas.

Uses of ultrasound

Renal

- Assessment of haematuria.
- Determination of nature of renal masses—can differentiate simple cysts (smooth, well-demarcated wall, reflecting no echoes; benign) from solid masses (almost always malignant; cystic masses with solid components or multiple septae or calcification may be malignant), from those casting an 'acoustic shadow' (stones; Fig. 3.1).
- Can determine the presence/absence of hydronephrosis (dilatation of the collecting system) in patients with abnormal renal function (Fig. 3.2).
- Allows ultrasound-guided nephrostomy insertion in patients with hydro-nephrosis and renal impairment or with infected, obstructed kidneys.

Bladder

- Measurement of post-void residual urine volume.
- Allows ultrasound-guided placement of a suprapubic catheter.

Prostate: TRUS

- Measurement of prostate size (where gross prostatic enlargement is suspected on the basis of a DRE and surgery in the form of open prostatectomy is contemplated).
- To assist prostate biopsy (allows biopsy of hypo- or hyper-echoic lesions).
- Investigation of azoospermia (can establish the presence of ejaculatory duct obstruction).

Urethra

Can image the urethra and establish the depth and extent of spongiofibrosis in urethral stricture disease.

Testes

- Assessment of the patient complaining of a 'lump in the testicle (or scrotum)'—can differentiate benign lesions (hydrocele, epididymal cyst) from malignant testicular tumours (solid, echo poor, or with abnormal echo pattern).
- When combined with power Doppler, can establish the presence/absence of testicular blood flow in suspected torsion.
- Assessment of testicular trauma (rupture is indicated by abnormal echo pattern due to blood within the body of the testis; surrounding haematoma may be seen—blood within the scrotal soft tissues that has escaped through a tear in the tunica albuginea and the visceral and

parietal layers of the tunica vaginalis; haematocele—blood contained by an intact parietal layer of the tunica vaginalis).
- Investigation of infertility—varicoceles and testicular atrophy may be identified.

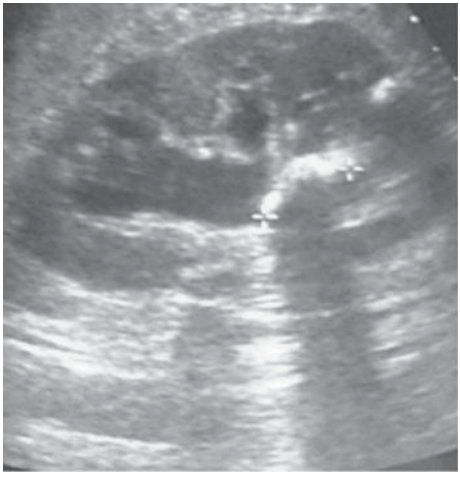

Fig. 3.1 An acoustic shadow cast by a stone within the kidney.

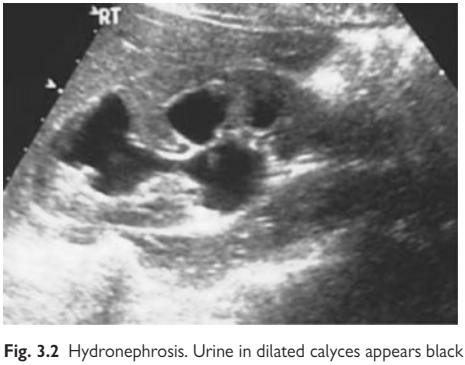

Fig. 3.2 Hydronephrosis. Urine in dilated calyces appears black (hypoechoic).

Uses of plain abdominal radiography (the 'KUB' X-ray—kidneys, ureters, bladder)

- For detection of stones and determination of their size and (to an extent) their location within the kidneys, ureters, and bladder (Fig. 3.3).
- **Renal calculi:** a calcification overlying the kidneys is intrarenal if it maintains its relationship to the kidney on inspiratory and expiratory films (i.e. if it moves with the kidney). If in doubt as to whether an opacity overlying the outline of the kidney is intrarenal or not, get an ultrasound (look for the characteristic 'acoustic shadow' within the kidney), IVU, or CT urogram (CTU).
- **Ureteric calculi:** sensitivity for *detection* of renal calculi is in the order of 50–70% (i.e. the false negative rate is between 30 and 50%; it misses ureteric stones when these are present in 30–50% of cases). CTU or IVU, which relate the position of the opacity to the anatomical location of the ureters, are required to make a definitive diagnosis of a ureteric stone. However, once the presence of a ureteric stone has been confirmed by another imaging study (CTU or IVU) and as long as it is radio-opaque enough and large enough to be seen, plain radiography is a good way of following the patient to establish whether the stone is progressing distally, down the ureter. It is not useful for 'following' ureteric stones that are radiolucent (e.g. uric acid), small (generally a stone must be 3–4mm to be visible on plain X-ray), or when the stones pass through the ureter as it lies over the sacrum. Ability of KUB X-ray to 'see' stones is also dependent on amount of overlying bowel gas.
- Plain tomography (a plain X-ray taken of a fixed coronal plane through the kidneys) can be useful, but is rarely done nowadays with the availability of ultrasound and CT.
- Opacities that may be confused with stones (renal, ureteric) on plain radiography: calcified lymph nodes, pelvic phleboliths (round, lucent centre, usually below the ischial spines).
- Look for the psoas shadow—obscured where there is retroperitoneal fluid (pus or blood; Fig. 3.4).

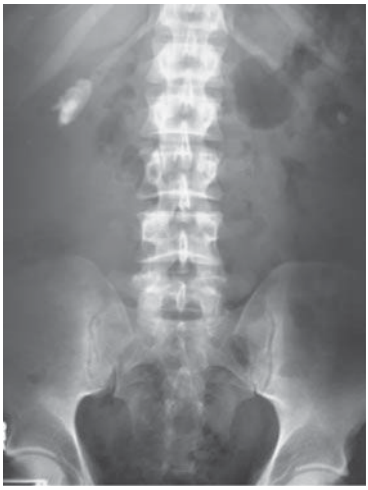

Fig. 3.3 Small staghorn calculus on KUB X-ray.

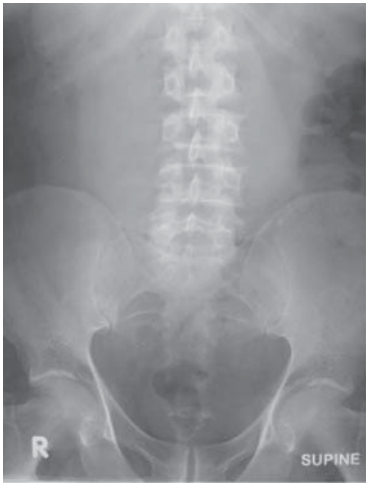

Fig. 3.4 Leaking AAA on plain X-ray; the right psoas shadow cannot be seen due to retroperitoneal haemorrhage.

Intravenous urography (IVU)

Also known as intravenous pyelography (IVP). Now virtually obsolete in the era of CT-KUB scanning (non-contrast CTU) used for the investigation of acute loin pain and CTU (a contrast CT of the kidneys, ureters, and bladder). The author has not requested an IVU for the best part of 10 years. The reconstructed digital images obtained on CTU are superior to those of IVU. However, for the benefit of those urologists in other parts of the world where IVU may still be the standard method of upper tract imaging, the author has retained this section.

A control film is obtained before contrast is given. Intravascular contrast is administered followed by a series of X-rays of the kidneys, ureters, and bladder over the following 30min or so to image their anatomy and pathology and to give some indication of renal function.

- Radio-opacity of contrast agents depends on the presence of a tri-iodinated benzene ring in the molecule.
- Ionic monomers (sodium and meglumine salts) ionize, thereby producing high osmolality solutions (e.g. iothalamate—Conray®, diatrizoate—Hypaque®, Urografin®).
- Non-ionic monomers—low osmolality (e.g. iopamidol—Niopam®, iohexol—Omnipaque®).
- At a concentration of 300mg of iodine per mL, ionic monomers have an osmolality five times higher than plasma, compared with non-ionic monomers which have an osmolality twice that of plasma.
- Excreted from plasma by glomerular filtration.

Films and 'phases' of the IVU

Plain film: looking for calcification overlying the region of the kidneys, ureters, and bladder.

Nephrogram phase: first phase of IVU; film taken immediately following intravenous administration of contrast (peak nephrogram density). The nephrogram is produced by filtered contrast within the lumen of the proximal convoluted tubule (it is a proximal tubular, rather than distal tubular phenomenon).

Pyelogram phase: as the contrast passes along the renal tubule (into the distal tubule), it is concentrated (as water is absorbed, but the contrast agent is not). As a consequence, the contrast medium is concentrated in the pelvicalyceal system and thus this 'pyelogram' phase (Fig. 3.5) is much denser than the nephrogram phase. The pyelogram phase can be made more dense by dehydrating the patient prior to contrast administration. Pelvic compression can be used to distend the pelvicalyceal system and demonstrate their anatomy more precisely. Compression is released and a film taken (20–30min; Fig. 3.6).

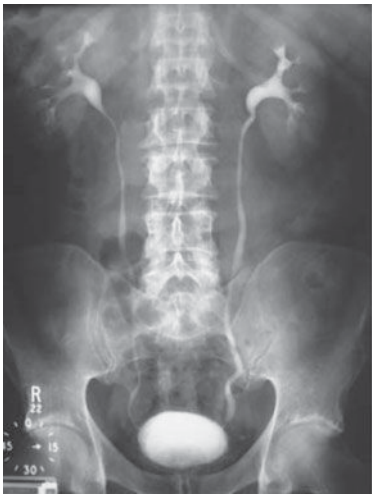

Fig. 3.5 Normal IVU at 15min.

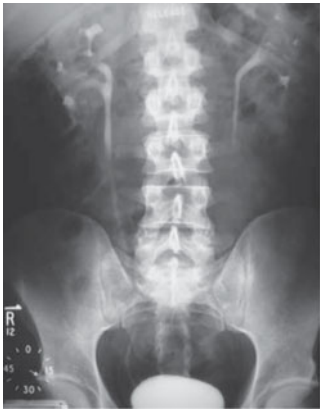

Fig. 3.6 Normal IVU at 20min. Lower abdominal compression has been released.

Side effects of administration of intravenous contrast media

- Occur in 1% of patients given non-ionic and 5% given ionic contrast media.
- The most serious reactions represent an anaphylactic reaction—hypotension with flushing of the skin (marked peripheral vasodilatation), oedema (face, neck, body, and limbs), bronchospasm, urticaria. Rarely, cardiac arrest can occur. The death rate, as a consequence of these reactions, is 1 in 40 000 to 1 in 70 000 with the ionic media and 1 in 200 000 with non-ionic contrast agents.
- A contrast reaction is more likely to occur in patients with an iodine allergy, previous contrast reaction, asthma, multiple other allergies, and heart disease and is less likely with non-ionic contrast media. Steroid premedication (at least 12h before) can reduce the risk of a contrast reaction.
- Contrast media are also nephrotoxic. Ten percent of patients with a raised creatinine will develop an increase in creatinine after an IVU (more likely in diabetics, with dehydration, and with large contrast doses). The increase in creatinine usually resolves spontaneously.

Uses of the IVU

- Investigation of haematuria—detection of renal masses, filling defects within the collecting system of the kidney and within the ureters (stones, TCCs).
- Localization of calcification overlying the urinary tract (i.e. is it a stone or not?).
- Investigation of patients with loin pain (e.g. suspected ureteric colic). Increasingly being replaced with CTU which has superior sensitivity and specificity.
- Very good for identification of congenital urinary tract abnormalities (e.g. ureteric anatomy in duplex systems; Fig. 3.7), malrotation, horseshoe kidneys.
- Used for follow-up of post-ureteric surgery to identify strictures.
- There is a trend towards IVU being replaced by MDCTU (a rapid acquisition CT done following intravenous contrast administration with high spatial resolution) at least in the investigation of haematuria and of loin pain. To a large extent, whether one uses an IVU or MDCTU depends on the availability of the latter in your radiology department.

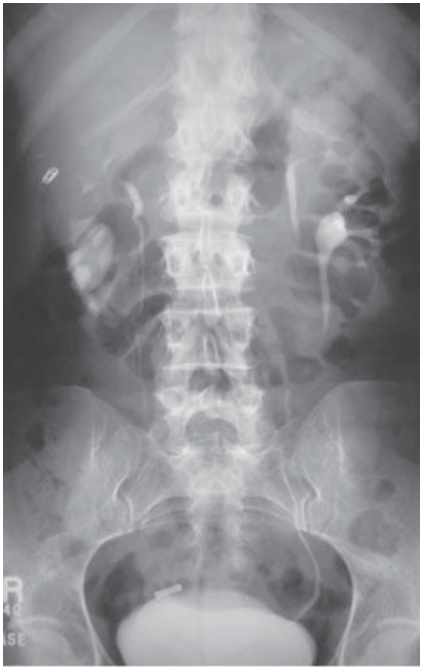

Fig. 3.7 Bilateral duplex as seen on a tomogram from an IVU.

Other urological contrast studies

Videocystourethrography (VCUG) (Fig. 3.8)
To identify the presence of vesicoureteric reflux during filling and emptying of the bladder and the presence and site of obstruction in the outlet of the bladder and within the urethra, particularly in patients with neuropathic bladder problems (e.g. spinal cord injury).

Cystography
Retrograde filling of the bladder via a catheter with contrast. Identifies vesicocolic and vesicovaginal fistulae and bladder rupture (extraperitoneal and intraperitoneal).

Urethrography (Fig. 3.9)
Retrograde filling of the urethra with contrast, to identify the site and length of urethral strictures (Fig. 3.10) or presence, extent, and site of urethral injury (in pelvic fracture, for example).

Ileal loopogram
Retrograde filling of an ileal conduit with contrast, to establish the presence of free reflux into the ureters (a normal finding; absence of free reflux suggests obstruction at the uretero-ileal junction due to ischaemic stenosis or recurrent TCC in the ureters at the uretero-ileal junction) and the presence of TCCs in the ureters or renal pelvis (an occasional finding in patients who have had a cystectomy for bladder TCC with ileal conduit urinary diversion).

Retrograde ureterography
Retrograde instillation of contrast into the ureters by a ureteric catheter inserted into the ureter via a cystoscope (rigid or flexible). Provides excellent definition of the ureter and renal pelvis for detection of ureteric and renal pelvic TCCs or radiolucent stones in patients with persistent haematuria where other tests have shown no abnormality. Also used to diagnose presence and site of ureteric injury (obstruction, ureteric leak) in cases of ureteric injury (e.g. post-hysterectomy or Caesarean section).

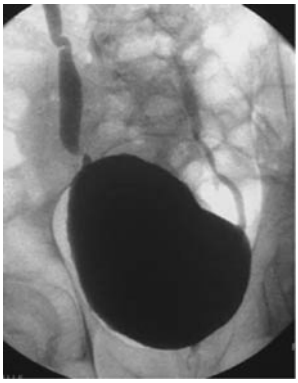

Fig. 3.8 VCUG showing bilateral ureteric reflux.

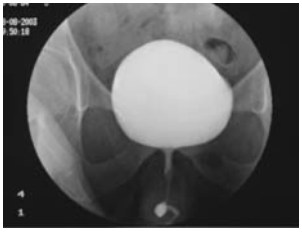

Fig. 3.9 Normal urethrogram.

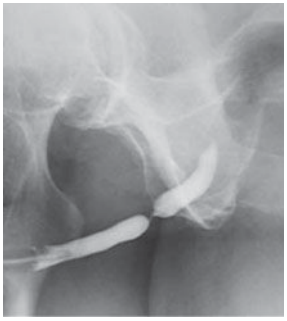

Fig. 3.10 A urethrogram showing a bulbar urethral stricture.

Computed tomography (CT) and magnetic resonance imaging (MRI)

CT

Widely used for investigation of urological symptoms and disease. It can detect very small differences in X-ray absorption values of tissues, providing a very wide range of densities (and, therefore, differentiation between tissues) when compared with plain radiography. The computer calculates the absorption value (attenuation) of each pixel and reconstructs this into an image. The attenuation values are expressed on a scale from –1000 to +1000 Hounsfield units (water = 0, air = –1000, bone = +1000). More recently, advances in computing power have enabled the data to be reformatted so that images can be produced in sagittal and coronal planes as well as in the more familiar horizontal plane (Figs. 3.11 and 3.12).

'Plain' CT scans (without contrast) can detect calcification and calculi within the urinary tract.

Administration of intravenous contrast is used to investigate haematuria, to evaluate the nature of solid renal lesions, and to determine the nature of soft tissue masses (e.g. to differentiate bowel from lymph nodes in cancer staging CTs). 'Spiral' or 'helical' CT (also known as multidetector CT urography—MDCTU—when done following intravenous contrast administration) is very rapid scanning while the table on which the patient is lying is moved though the scanner. Multiple images ('slices') of the patient are taken. A large volume of the body can be imaged in a single breath hold, thus eliminating movement artefact and increasing spatial resolution—particularly useful for identifying suspected ureteric stones in patients with acute loin pain and (with contrast) for determining the nature of renal masses.

Overlapping thin sections can be 'reconstructed' into images in multiple planes (multiplanar reformatting—MPR) so lesions can be imaged in multiple planes (sagittal, coronal) as opposed to the traditional transverse sections.

Uses of CT

Haematuria

Investigation of site and cause of urinary tract bleeding. Has the advantage of a single investigation which potentially could obviate the need for the traditional '4-test' approach to haematuria (IVU, renal ultrasound, flexible cystoscopy, urine cytology), although at the cost of a higher radiation dose. There is evidence suggesting that MDCTU has reasonable sensitivity and high specificity for diagnosing bladder tumours[1] (in patients with macroscopic haematuria—93% sensitivity, 99% specificity) and that it has equivalent diagnostic accuracy to retrograde uretero-pyelography (the retrograde administration of contrast via a catheter inserted in the lower ureter to outline the ureter and renal collecting system).[2] Overall, for patients with haematuria and no prior history of urological malignancy, for the detection of all urological tumours, it has approximately 65% sensitivity and 98% specificity[3]—so it only rarely calls a lesion a tumour when, in fact,

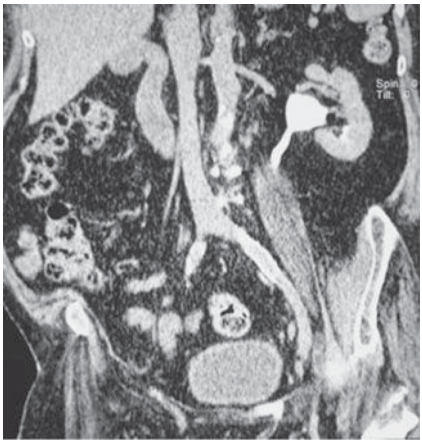

Fig. 3.11 Coronal CT image of abdomen showing the left kidney, aorta, and IVC.

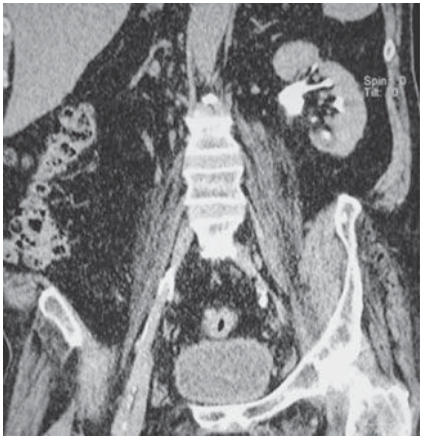

Fig. 3.12 Coronal CT image of abdomen showing the left kidney and paravertebral muscles.

the lesion is benign, but it still fails to diagnose a significant proportion of urinary neoplasms (sensitivity for upper tract neoplasms 80%, for bladder tumours 60%). The role of MDCTU (described by some as the 'ultimate' imaging modality) in the investigation of haematuria remains controversial. MDCTU in all patients with haematuria (microscopic, macroscopic), when most will have no identifiable cause for the haematuria, has a cost (high radiation dose, financial). A targeted approach, aimed at those with risk factors for urothelial malignancy (age >40y, macroscopic as opposed to microscopic haematuria, smoking history, occupational exposure to benzenes and aromatic amines) might be a better use of this resource, rather than using MDCTU as the first imaging test for both high- *and* low-risk patients. Thus, the 'best' imaging probably depends on the context of the patient.

Renal

- Investigation of renal masses—characterizes solid from cystic lesions; differentiates benign (e.g. angiomyolipoma) from malignant solid masses (e.g. renal cell carcinoma).
- Staging of renal cancer (establishes local, nodal, and distant spread).
- Assessment of stone size and location (within the collecting system or within the parenchyma of the kidney).
- Detection and localization of site of intrarenal and perirenal collections of pus (pyonephrosis, perinephric abscess).
- 'Staging' (grading) of renal trauma.
- Determination of cause of hydronephrosis.

Loin pain: imaging the ureters

The IVU, previously the mainstay of imaging in patients with flank pain, has been superseded by CT-KUB, a non-contrast CT of the kidneys, ureters, and bladder. Compared with IVU, CT-KUB:

- Has greater specificity (97%) and sensitivity (94–100%) for diagnosing ureteric stones.[4] Can identify non-stone causes of flank pain.
- Requires no contrast administration so avoiding the chance of a contrast reaction (risk of fatal anaphylaxis following the administration of low osmolality contrast media for IVU is in the order of 1 in 100 000).
- Is faster, taking just a few minutes to image the kidneys and ureters. An IVU, particularly where delayed films are required to identify a stone causing high-grade obstruction, may take hours to identify the precise location of the obstructing stone.
- Is equivalent in cost to IVU in high CT volume hospitals.

CTU is able to locate and measure the size and number of ureteric stones. A non-contrast CT-KUB radiation dose: approximately 4.7mSv compared to 1.5mSv for IVU (fatal cancer risk is estimated at 1 in 2000 for a 10mSv radiation exposure). Ultra-low dose CT (ULDCT) lowers radiation exposure (0.6–2mSv), but at the expense of lower sensitivity (68–86%) for small (<3mm) ureteric stones.[4] Contrast-enhanced ultra-low dose CT (CEULDCT) uses contrast which increases sensitivity (97%) and specificity (100%) for detecting small ureteric stone disease while limiting radiation dose to levels comparable with IVU (1.7mSv vs 1.4mSv).

Bladder

Bladder cancer staging (establishes local, nodal, and distant spread).

Uses of MRI in the urological patient

- Staging of pelvic cancer—bladder and prostate cancer staging (establishes local, nodal, and distant spread). Good for identifying seminal vesicle invasion. As with CT, oedema and fibrosis cannot be reliably distinguished from tumour within the bladder wall, leading to 'overstaging' of cancer. Again, as with CT, microscopic disease cannot be identified, leading to 'understaging' of cancer.
- Especially useful for diagnosing phaeochromocytomas (very bright image on T2-weighted images).
- Investigation of LUTS where the history suggests a possible neurological basis (LUTS in the presence of lumbar or thoracic back pain or associated with loss of perineal sensation or disturbances of bladder sensation or where there is sensory disturbance in the legs or feet).
- Localization of undescended testes.
- Identification of ureteric stones, where ionizing radiation is best avoided (e.g. pregnant women with loin pain). In the authors' experience, few radiologists seem to be able to confidently diagnose or exclude the presence of stones on MR urography, at least in part because this test is still so seldom used.

PET (positron emission tomography) imaging and PET/CT in urological patient

A nuclear medicine imaging technique. Produces three-dimensional images of functional processes in the body. Detects gamma rays emitted by positron-emitting radionuclide tracers which are introduced into the body on biologically active molecules. The molecules to which the radionuclides are bound allow 'visualization' of metabolic processes. Three-dimensional images of tracer concentration within various organs and tissues are then constructed by CT scanning (or MRI) performed within the same machine. It thus involves exposure to ionizing radiation (typically 5–7mSv, but if combined with CT, substantially more).

Radionuclides with short half-lives are attached to biologically active molecules such as glucose ('metabolic' tracers) or molecules that bind to receptors or sites of drug action ('receptor-specific' tracers). As a consequence of the short half-lives, the radionuclides must be made in a cyclotron in a radiochemistry lab in close proximity to the PET imaging unit.

In urological practice, one example is fluoro-2-Deoxy-d-Glucose labelled with an isotope of fluorine, ^{18}F (^{18}F-FDG). This is taken up by cellular glucose transporters and phsophorylated to FDG-6-phosphate by glucose-6-phosphokinase. FDG is trapped in cells and so cells are intensely radiolabelled with ^{18}F-FDG.

The radioisotopes undergo positron emission decay, emitting positrons (the so-called antiparticles of the electron). The emitted positrons travel in tissue for a short distance (<1mm depending on the isotope) and in so doing, lose kinetic energy. They decelerate to a point where they can interact with electron, this interaction leading to the destruction of both

the electrons and positrons and in the process, producing a pair of gamma photons moving in opposite directions. These photons are detected when they reach a scintillator within the scanning device.

Uses

^{18}F-FDG is excreted in urine and this limits the role of ^{18}F-FDG PET scanning in the detection of primary urological cancers, but it has shown promise in the detection of metastatic disease.

Prostate cancer

^{18}F-FDG PET has limited sensitivity for primary staging since prostate cancer cells often do not have increased glucose metabolism (Rioja 2010). It cannot identify lymph node involvement with sufficient sensitivity. Similarly, it lacks sufficient sensitivity to detect recurrence after primary treatment with radical prostatectomy. ^{11}C-methionine PET has shown promise in the restaging of patients with advanced prostate cancer.

Kidney cancer

^{18}F-FDG PET is showing promise as a technique to detect metastases in renal cancer.

Bladder cancer

Again ^{18}F-FDG PET is able to detect metastases in bladder cancer, but is not useful in primary staging.

Germ cell tumours

^{18}F-FDG PET cannot distinguish between inflammatory and neoplastic masses nor can it distinguish mature teratoma from normal or necrotic tissue.

Further reading

Rioja J, Rodríguez-Fraile M, Lima-Favaretto R, *et al.* (2010) Role of positron emission tomography in urological oncology. *Br J Urol Int* **106**:1578–94.

1 Fowler JC *et al.* (2011) Clinical evaluation of ultra-low dose contrast-enhanced CT in patients presenting with acute ureteric colic. *Br J Med Surg Urol* **4**:56–63.

2 Turney BW, Willatt JM, Nixon D, *et al.* (2006) Computed tomography urography for diagnosing bladder cancer. *Br J Urol Int* **98**:345–8.

3 Cowan NC, Turney BW, Taylor NJ, *et al.* (2007) Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumours. *Br J Urol Int 2007*; **99**:1363–70.

4 Sudakoff GS, Dunn DP, Guralnick ML, *et al.* (2008) Multidetector computed tomography urography as the primary imaging modality for detecting urinary tract neoplasms in patients with asymptomatic hematuria. *J Urol* **179**:862–7.

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Radioisotope imaging

A variety of organic compounds can be 'labelled' with a radioactive isotope that emits gamma rays, allowing the radiation to penetrate through tissues and reach a 'gamma' camera placed adjacent to the patient. The most commonly used radioisotope is technetium—^{99m}Tc (half-life 6h, gamma ray emission energy 0.14MeV). The excretion characteristics of the organic compound to which the ^{99m}Tc is bound determine the clinical use.

MAG3 renogram

^{99m}Tc is bound to mercapto acetyl triglycine. Over 90% of mercaptoacetyltriglycyl (MAG3) becomes bound to plasma proteins following intravenous injection. It is excreted from the kidneys, principally by tubular secretion (glomerular filtration is minimal). Following intravenous injection, MAG3 is very rapidly excreted (appearing in the kidney within 15s of injection and starting to appear in the bladder within about 3min). Approximately two-thirds of the injected dose of MAG3 is taken up by the kidneys with each passage of blood through the kidney. The radioactivity over each kidney thus increases rapidly. The peak of radioactivity represents the point at which delivery of MAG3 to the kidney from the renal artery is equivalent to excretion of MAG3. The radioactivity starts to decline as excretion outstrips supply. Thus, a time–activity curve can be recorded for each kidney. This time–activity curve is known as a renogram.

Images are collected onto a film at 30s intervals for the first 3min and then at 5min intervals for the remainder of the study (usually a total of 30min).

A normal renogram has three phases

- **First phase:** a steeply rising curve lasting 20–30s.
- **Second phase:** a more slowly rising curve, rising to a peak. If the curve does not reach a peak, the second phase is said to rise continually. A normal second phase ends with a sharp peak.
- **Third phase:** a curve that descends after the peak. There can be no third phase if there is no peak.

Description of the renogram

No comment is made about the first phase. The second phase is described as being absent, impaired, or normal. The third phase is described as being absent, impaired, or normal.

The time to the peak depends on urine flow and level of hydration and is a crude measure of the time it takes the tracer to travel through the parenchyma of the kidney and through the renal pelvis. The time to the peak of the renogram normally varies between 2 and 4.5min.

If the renogram continues beyond the time at which the peak should normally occur, then there may be a distal obstruction (e.g. at the PUJ or lower down the ureter). In this situation, an injection of 40mg of frusemide is given (at about 18min) and if the curves start to fall rapidly, this is taken as proof that there is no obstruction. If it continues to rise, there is obstruction. If it remains flat (neither rising or falling), this is described as an 'equivocal' result.

Parenchymal transit time can also be measured (PTTI—parenchymal transit time index). The normal range for PTTI is 40–140s and averages 70s. PTTI is prolonged (to >156s) in obstruction and in renal ischaemia. A normal PTTI excludes obstruction.

Uses

- 'Split' renal function (i.e. the % function contributed by each kidney).
- Determination of presence of renal obstruction—based on shape of renogram curve and PTTI.

DMSA scanning

Dimercaptosuccinic acid (DMSA) is labelled with ^{99m}Tc. It is taken up by the proximal tubules and retained there, with very little being excreted in the urine. A 'static' image of the kidneys is thus obtained (at about 3–4h post-intravenous injection of radioisotope). It demonstrates whether a 'lesion' contains functioning nephrons or not.

Uses

- 'Split' renal function (i.e. the % function contributed by each kidney).
- Detection of scars in the kidney (these appear as defects in the cortical outline, representing areas in which the radioisotope is not taken up).

Radioisotope bone imaging

^{99m}Tc-labelled methylene disphosphonate (MDP) is taken up by areas of bone where there is increased blood supply and increased osteoblastic activity. There are many causes of a focal increase in isotope uptake—bone metastases, site of fractures, osteomyelitis, TB, benign bone lesions (e.g. osteoma). Metastases from urological cancers are characterized by their predilection for the spine and the fact that they are multiple (single foci of metastasis are rare). Prostate cancer classically metastasizes in this way.

Uroflowmetry

Measurement of flow rate (Fig. 3.13). Provides a visual image of the 'strength' of a patient's urinary stream. Urine flow rate is measured in mL/s and is determined using commercially available electronic flowmeters (Fig. 3.14). These flowmeters are able to provide a printout, recording the voided volume, maximum flow rate, and time taken to complete the void, together with a record of the flow pattern. Maximum flow rate, Qmax, is influenced by the volume of urine voided, by the contractility of the patient's bladder, and by the conductivity (resistance) of their urethra.

A number of nomograms are available which relate voided volume to flow rate.

Interpretation and misinterpretation of urine flow rate

The 'wag' artefact (Fig. 3.13b) is seen as a sudden, rapid increase in flow rate on the uroflow tracing and is due to the urine flow suddenly being directed at the centre of the flowmeter, producing a sudden artefactual surge in flow rate.

In men with 'prostatic' symptoms, for the same voided volume, flow rate varies substantially on a given day (by as much as 5mL/s if four flows are done).[1] Most guidelines recommend measuring at least two flow rates and using the highest as representing the patient's best effort.

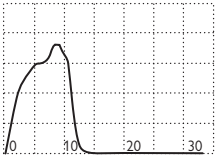
What does a low flow mean?

Uroflowmetry alone cannot tell you why the flow is abnormal. It cannot distinguish between low flow due to BOO and that due to a poorly contractile bladder.

The principal use of urine flow rate measurement is in the assessment of elderly men with suspected prostatic obstruction ('LUTS/BPH'), but there is debate about its usefulness as a test for predicting outcome of various treatments. Some studies suggest that men with poor outcomes are more likely to have had higher flows preoperatively compared with those with good outcomes, whereas other studies report equivalent improvements in symptoms whether or not preoperative flow rate is high or low. A recent Veterans Administration trial comparing transurethral resection of the prostate (TURP) with watchful waiting in men with LUTS/BPH found that flow rate could not predict the likelihood of a good symptomatic outcome after TURP.[2]

As a consequence, different guidelines give different guidance with regard to performing uroflowmetry in men with LUTS/BPH. It is regarded as an optional test by the AUA (American Urological Association),[3] recommended by the 4th International Consultation on BPH,[4] and the EAU (European Association of Urology) BPH Guidelines state that it 'is obligatory prior to undertaking surgical treatment'.[5]

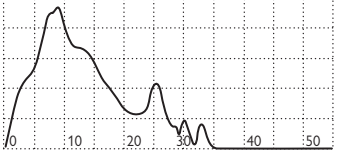
(a) 25ml/s flow rate



Results of uroflowmetry

Voiding time	T100	13s
Flow time	TQ	13s
Time to max flow	TQmax	8s
Max flow rate	Qmax	18.1ml/s
Average flow rate	Qave	11.7ml/s
Voided volume	Vcomp	151ml

(b) 25ml/s flow rate



Results of uroflowmetry

Voiding time	T100	34s
Flow time	TQ	34s
Time to max flow	TQmax	9s
Max flow rate	Qmax	23.5ml/s
Average flow rate	Qave	10.2ml/s
Voided volume	Vcomp	354ml

Fig. 3.13 (a) A uroflow trace; (b) A uroflow trace with a 'wag' artefact occurring between 5–10s. The true Qmax is not 23.5mL/s as the readout suggests, but is nearer 18mL/s.

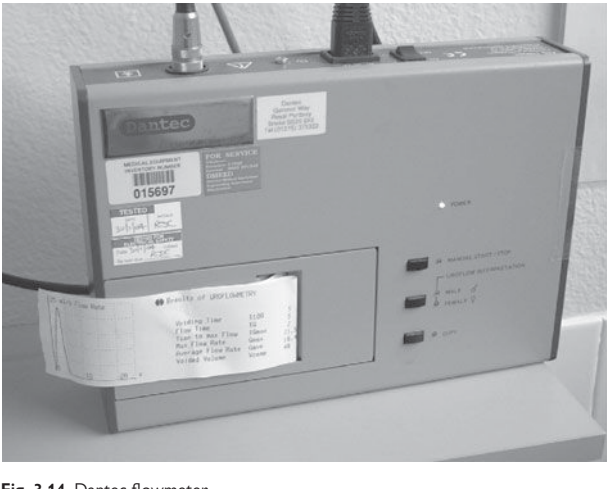


Fig. 3.14 Dantec flowmeter.

Generally speaking, urine flow rate measurement is regarded as having insufficient diagnostic accuracy for it to be useful in the assessment of female lower urinary tract dysfunction. Although urine flow measurement can be used to assess voiding function in men with urethral strictures, it has limited value in younger men because in this age group, the bladder can compensate for a marked degree of obstruction by contracting more forcefully. Thus, a young man may have a normal flow rate despite have a marked urethral stricture.

1 Reynard JM, Peters TJ, Lim C, Abrams P (1996) The value of multiple free-flow studies in men with lower urinary tract symptoms. *Br J Urol* **77**:813–8.

2 Bruskewitz RC, Reda DJ, Wasson JH, *et al.* (1997) Testing to predict outcome after transurethral resection of the prostate. *J Urol* **157**:1304–8.

3 McConnell JD, Barry MJ, Bruskewitz RC, *et al.* (1994) *Benign prostatic hyperplasia: diagnosis and treatment. Clinical practice guideline.* Rockville: Agency for Health Care Policy and Research.

4 Denis L, Griffiths K, Khoury S, *et al.* (eds) (1998) Fourth International Consultation on Benign Prostatic Hyperplasia (BPH), Paris, July 1997. Plymouth: Health Publications.

5 de la Rosette JJ, Alivizatos G, Madersbacher S, *et al.* (2001) EAU guidelines on benign prostatic hyperplasia (BPH) (2001) *Eur Urol* **40**:256–63.

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Post-void residual urine volume measurement

Post-void residual (PVR) urine volume is the volume of urine remaining in the bladder at the end of micturition. In normal individuals, there should be no urine remaining in the bladder at the end of micturition. A PVR may be caused by detrusor underactivity (due to ageing—as the older bladder is less able to sustain a contraction than the younger bladder or neurological disease affecting bladder innervation), BOO, or a combination of both. In clinical practice, PVR volume is measured by ultrasound after the patient has attempted to empty their bladder. A commonly used formula for calculating bladder volume is:[1–5]

$$\text{Bladder volume (mL)} = \text{bladder height (cm)} \times \text{width (cm)} \times \text{depth (cm)} \times 0.7$$

Interpretation and misinterpretation of PVR volume

PVR volume shows considerable day-to-day variability, with volumes recorded on different days over a 3-month period varying between 150 and 670mL.[1]

Clinical usefulness of PVR volume measurement

Analysis of the placebo-treated men (n=737) in the MTOPS trial suggests that PVR volume did not seem to be a strong predictor of the likelihood of developing acute urinary retention. There was no difference in retention rates in men with a residual urine volume of <39mL compared with those with a residual urine volume 39mL or more (although the higher PVR was associated with a greater chance of symptomatic progression and of need for invasive therapy).[6] Similarly, there was no difference in retention rates in 389 men treated with alpha blockers or 553 treated with placebo with a residual urine volume of <300mL compared with those with a residual urine volume of >300mL.[7] In 170 men with urodynamically confirmed BOO who initially opted for conservative (non-surgical) treatment, 141 (83%) remained untreated at 10y and 29 (17%) had undergone surgery (22 for LUTS, 7 for retention). PVR at baseline did not predict the chance of developing urinary retention or of the need for TURP for worsening LUTS.[8]

PVR volume measurement cannot predict symptomatic outcome from TURP. For these reasons, residual urine volume measurement is regarded as an optional test in the AUA guidelines, but is recommended by the 4th International Consultation on BPH.[2]

Residual urine volume measurement is useful (along with measurement of serum creatinine) as a safety measure. It indicates the likelihood of back pressure on the kidneys and thus it tells the urologist whether it is safe to offer watchful waiting rather than TURP. In men with moderate LUTS, it is safe not to operate where the PVR volume is less than 350mL and this probably holds true for those with higher PVR volumes (<700mL).[3]

Does an elevated residual urine volume predispose to urinary infection?

Though intuition would suggest yes, what evidence there is relating residual volume to urine infection suggests that an elevated residual urine may not, at least in the neurologically normal adult, predispose to urine infection.[4,5] There has been no longitudinal study to determine of an elevated PVR increases the risk of developing urinary tract infection.

1 Dunsmuir WD, Feneley M, Corry DA, *et al.* (1996) The day-to-day variation (test–retest reliability) of residual urine measurement. *Br J Urol* **77**:192–3.

2 Denis L, Griffiths K, Khoury S, *et al.* (eds) (1998) Fourth International Consultation on Benign Prostatic Hyperplasia (BPH), Paris, July 1997. Plymouth: Health Publications.

3 Bates TS, Sugiono M, James ED, *et al.* (2003) Is the conservative management of chronic retention in men ever justified? *Br J Urol Int* **92**:581–3.

4 Riehmann M, Goetzmann B, Langer E, *et al.* (1994) Risk factor for bacteriuria in men. *Urology* **43**:617–20.

5 Hampson SJ, Noble JG, Rickards D, Milroy EG (1992) Does residual urine predispose to urinary tract infection. *Br J Urol* **70**:506–8.

6 Crawford ED, Wilson SS, McConnell JD, *et al.* (2006) Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. *J Urol* **175**:1422.

7 Mochtar CA, Kiemeney LA, van Riemsdijk MM, *et al.* (2006) Post-void residual urine volume is not a good predictor of the need for invasive therapy among patients with benign prostatic hyperplasia. *J Urol* **175**:213–6.

8 Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P (2005) The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic follow-up of untreated bladder outlet obstruction. *BJU Int* **96**:1301–6.

Cystometry, pressure flow studies, and videocystometry

- **Cystometry:** the recording of bladder pressure during bladder filling.
- **Pressure–flow studies (PFS):** the simultaneous recording of bladder pressure during voiding.
- **Videocystometry:** fluoroscopy (X-ray screening) combined with PFS during voiding (see 📖 p. 57; Fig. 3.8).

These techniques provide the most precise measurements of bladder and urethral sphincter behaviour during bladder filling and during voiding. Cystometry precedes the pressure–flow study. Bladder pressure (Pves, measured by a urethral or suprapubic catheter) and abdominal pressure (Pabd, measured by a pressure line inserted into the rectum) are recorded as the bladder fills (cystometric phase) and empties (voiding phase) and flow rate is simultaneously measured during the voiding phase. The pressure developed by the detrusor (the bladder muscle), Pdet, cannot be directly measured, but it can be derived by subtracting abdominal pressure from the pressure measured within the bladder (the intravesical pressure). This allows the effect of rises in intra-abdominal pressure caused by coughing or straining to be subtracted from the total (intravesical) pressure so that a 'pure' detrusor pressure is obtained.

All pressures are recorded in cmH_2O and flow rate is measured in mL/s. The pressure lines are small-bore, fluid-filled catheters attached to an external pressure transducer or catheter-tip pressure transducers can be used.

A computerized printout of Pves, Pabd and Pdet, and flow rate (Qmax) is obtained (Fig. 3.15). During bladder filling, the presence of overactive bladder contractions can be detected. During voiding, the key parameters are Qmax and the detrusor pressure at the point at which Qmax is reached, Pdet Qmax. This pressure, relative to Qmax, can be used to define the presence of BOO by using a variety of nomograms, of which the ICS nomogram is most widely used.

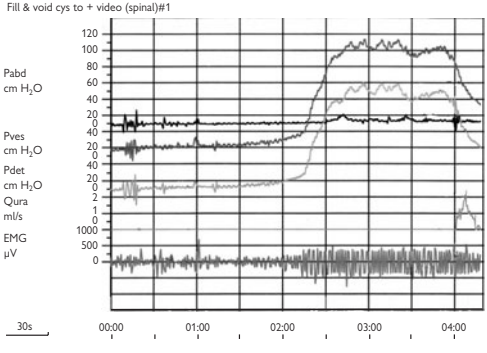

Fig. 3.15 A computerized printout of intravesical pressure (Pves), intra-abdominal pressure (Pabd), subtracted detrusor pressure (Pdet), and flow rate (Qmax).

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Chapter 4

Bladder outlet obstruction

Regulation of prostate growth and development of benign prostatic hyperplasia (BPH)

BPH is characterized by an increase in epithelial and stromal cell numbers (hyperplasia) in the peri-urethral area of the prostate. New epithelial gland formation is normally only seen during foetal development. The development of new glands in the adult prostate has given rise to the concept of 'reawakening' of the inductive effect of the prostatic stroma on the prostatic epithelium.

The increase in prostate cell number could reflect proliferation of epithelial and stromal cells, impairment of programmed cell death, or a combination of both. During the early phases of development of BPH, cell proliferation occurs rapidly. In established BPH, cell proliferation slows down and there is impairment of programmed cell death (androgens and oestrogens actively inhibit cell death).

The role of androgens in BPH

Testosterone can bind directly to the androgen receptor or may be converted to a more potent form, dihydrotestosterone (DHT), by the enzyme 5α-reductase (5AR). There are two isoforms of 5AR, type I or 'extraprostatic' 5AR (which is absent in prostatic tissue and present in, for example, skin and liver) and type II or 'prostatic' 5AR (which is found exclusively on the nuclear membrane of stromal cells, but not within prostatic epithelial cells). Type I 5AR is not inhibited by finasteride whereas type II 5AR is. Dutasteride inhibits both types I and II 5AR. Finasteride reduces serum DHT by about 70% and dutasteride by about 95%. Finasteride reduces prostatic DHT (type II) by about 80% and dutasteride by about 94%. We do not know whether these differences translate into differences in clinical efficacy since neither drugs has been compared against the other.

Testosterone diffuses into prostate and stromal epithelial cells. Within *epithelial* cells, it binds directly to the androgen receptor. In prostate *stromal* cells, a small proportion binds directly to the androgen receptor, but the majority binds to 5AR (type II) on the nuclear membrane, is converted to DHT, and *then* binds (with greater affinity and, therefore, greater potency than testosterone) to the androgen receptor in the stromal cell. Some of the DHT formed in the stromal cells diffuses out of these cells and into nearby epithelial cells (a paracrine action). The androgen receptor/testosterone or androgen receptor/DHT complex then binds to specific binding sites in the nucleus, thereby inducing transcription of androgen-dependent genes and subsequent protein synthesis.

It is thought that stromal/epithelial interactions may be mediated by soluble growth factors—small peptides that stimulate or inhibit cell division and differentiation. Growth stimulating factors include basic fibroblastic growth factor (bFGF), epidermal growth factor (EGF), keratinocyte growth factor (KGF), and insulin-like growth factor (IGF). Transforming growth factors (e.g. TGFβ) normally inhibit epithelial cell proliferation and it is possible that in BPH, TGFβ is downregulated.

Pathophysiology and causes of bladder outlet obstruction (BOO) and BPH

The principal cause of BOO in men is BPH. Less common causes are urethral stricture and malignant enlargement of the prostate. BOO in women is altogether less common, the causes including pelvic prolapse (cystocele, rectocele, uterine), the prolapsing organ directly compressing the urethra; urethral stricture; urethral diverticulum; post-surgery for 'stress' incontinence; Fowler's syndrome (impaired relaxation of external sphincter occurring in premenopausal women, often in association with polycystic ovaries); and pelvic masses (e.g. ovarian masses). In either sex, neurological disease (spinal cord injury, spina bifida, multiple sclerosis (MS)) can cause failure of relaxation of the external sphincter during voiding (detrusor sphincter dysynergia, DSD).

The pathophysiological basis of BOO due to benign prostatic enlargement (BPE) secondary to BPH (benign prostatic obstruction, BPO) has been studied more than any other type of obstruction. BPO has dynamic and static components:

- **Dynamic component of BPO:** 1-adrenoceptor-mediated prostatic smooth muscle contraction. Smooth muscle accounts for approximately 40% of the area density of the hyperplastic prostate and human prostate contracts following administration of alpha adrenergic agonists. This effect is the rationale for α-adrenoceptor blocker treatment for symptomatic BPO.
- **Static component of BPO:** mediated by the volume effect of BPE.

Pathophysiological consequences of BOO

John Hunter (1786), who founded the Royal College of Surgeons of England, noted that 'The disease of the bladder arising from obstruction alone is increased irritability and its consequences, by which it admits of little distension, becomes quick in its action, and thick and strong in its coats'. BOO causes thickening of the wall of the bladder. Microscopically, smooth muscle cells enlarge and there is an increase in connective tissue (collagen and elastin) between the smooth muscle bundles. In some cases, this may lead to poor compliance, with development of high bladder and intrarenal pressures. Progressive hydronephrosis can develop, with impairment of renal function and even renal failure (high-pressure chronic urinary retention).

Experimentally created BOO causes development of bladder overactivity (unstable bladder contractions during bladder filling). This may be due to prolonged increased intravesical pressure during voiding, causing ischaemia and leading to ischaemic damage to neurons within the bladder (i.e. denervation). Symptomatically, many patients with BOO develop frequency, urgency, and urge incontinence.

Benign prostatic obstruction (BPO): symptoms and signs

Clinical practice guidelines

Developed to standardize the approach to diagnosis (and treatment) of men presenting with symptoms suggestive of BPH.[1] Every guideline agrees that a history should be taken, an examination performed, and that the severity of urinary symptoms should be formally assessed using the IPSS. This includes a measure of the 'bother' caused by the patient's symptoms (i.e. the degree to which the symptoms are troubling).

Urinary symptoms—what do they mean?

During the 1990s, the classic 'prostatic' symptoms of frequency, urgency, nocturia, hesitancy, poor flow, intermittent flow, and terminal dribbling—traditionally said to indicate the presence of BOO due to BPE—were shown to bear little relationship to prostate size, flow rate, residual urine volume, or indeed, urodynamic evidence of BOO. Age-matched elderly men and women have similar symptom scores (IPSS), despite the fact that women have no prostate and rarely have BOO.

Prostatism vs LUTS vs LUTS/BPH

'Prostatism' has, therefore, been replaced by the expression 'LUTS', which avoids any implication about the cause of these symptoms. More recently, the expression 'LUTS/BPH' has been used to describe the symptoms of BPH. It doesn't really matter whether you use 'prostatism', 'LUTS', or 'LUTS/BPH', as long as you remember that urinary symptoms may have non-prostatic causes. Try to avoid treating the prostate when the problem may lie elsewhere.

Ask specifically about the presence of:

- **Bedwetting:** suggests the presence of high-pressure chronic retention (look for distension of the abdomen due to a grossly enlarged bladder that is tense on palpation and dull to percussion).
- **Marked frequency and urgency, particularly when also combined with bladder pain:** look for carcinoma *in situ* of the bladder (urine cytology, flexible cystoscopy, and bladder biopsy).
- **Macroscopic haematuria:** sometimes due to a large vascular prostate, but exclude other causes (bladder and kidney cancer and stones) by flexible cystoscopy and upper tract imaging.
- **Back pain and neurological symptoms** (sciatica, lower limb weakness, or tingling)**:** rarely, LUTS can be due to neurological disease.

1 Irani J, Brown CT, van der Meulen J, Emberton M (2003) A review of guidelines on benign prostatic hyperplasia and lower urinary tract symptoms: are all guidelines the same? *BJU Int* **92**:937–42.

Websites for BPH clinical practice guidelines

- AUA guidelines. http://hstat.nlm.NIH.gov/ftrs/arahcpr.
- EAU guidelines. http://www.uroweb.org/files/uploaded_files/*BPH*.pdf.
- WHO (International Consensus Committee) guidelines. http://www.who.int/ina-ngo/ngo/ngo048.htm.
- Australian guidelines. http://www.health.gov.au/nhmrc/publications/pdf/cp42.pdf.
- German guidelines. http://dgu.springer.de/Leit/pdf/3_99.pdf.
- Singapore guidelines. http://www.urology-singapore.org.html/guidelines_*BPH*.htm.
- Malaysian guidelines. http://www.mohtrg.gov.my/guidelines/BPH98.pdf.
- UK guidelines. http://www.rcseng.ac.uk/publications/.

Diagnostic tests in men with LUTS thought to be due to BPH

Clinical practice guidelines

Developed as an attempt to standardize the approach to diagnosis and treatment of men presenting with symptoms suggestive of BPH.[1] All agree that a history should be taken, an examination performed, and all recommend assessment of symptom severity using the IPSS. This includes a measure of the 'bother' caused by the patient's symptoms. There is considerable variation between guidelines in terms of recommended diagnostic tests. High-quality guidelines (e.g. based on results of randomized trials) recommend few diagnostic tests[2]—urine analysis, completion of a voiding diary (frequency–volume chart) to detect the presence of polyuria and nocturnal polyuria (which may be the cause of a patient's increased frequency or nocturia), and measurement of serum creatinine. They regard flow rate measurement and assessment of residual urine volume as optional tests.

DRE and PSA

Done to detect nodules that may indicate an underlying prostate cancer and to provide a rough indication of prostate size. Size alone is not an indication for treatment, but if surgical treatment is contemplated, marked prostatic enlargement can be confirmed by transrectal ultrasound scan (prostate volume in the order of 100mL or more increases the likelihood of an open prostatectomy). Discuss the pros and cons of PSA testing with the patient.

Serum creatinine

Baseline measure of renal function and to detect renal failure secondary to high-pressure urinary retention.

Post-void residual urine volume (PVR)

Varies considerably (by as much as 600mL between repeat measurements) on the same or different days.[3] It cannot predict symptomatic outcome from TURP. Along with serum creatinine, it indicates whether watchful waiting is safe. It is safe *not* to operate where the PVR volume is <350mL,[4,5] since the majority of men show no worsening of creatinine, no increase in PVR, no worsening of symptoms, and do not require TURP.

Flow rate measurement

This is variously regarded as *optional*, *recommended*, and *obligatory* prior to undertaking surgical treatment for BPH. Like PVR, measurement of flow rate varies substantially on a given day,[6] cannot distinguish between BOO and a poorly contractile bladder, and is not good at predicting the likelihood of a good symptomatic outcome after TURP.

Pressure flow studies

Reasonably good at predicting symptomatic outcome after TURP. However, most patients without obstruction have a good outcome and the time, cost, and invasiveness of pressure flow studies is perceived by most urologists as not justifying their routine use. The AUA Guidelines on the management of BPH (🖱 http://www.auanet.org) regards pressure flow studies as optional since they are unable to reliably predict treatment failure in the individual patient (treatment failure is somewhat higher in the absence of obstruction, but unobstructed individuals still have a reasonable chance of improvement with TURP). The AUA Guidelines specifically state that 'If interventional therapy is planned without clear evidence of the presence of obstruction, the patient needs to be informed of possible higher failure rates of the procedure'.

Renal ultrasonography

To detect hydronephrosis if serum creatinine is elevated. The percentage of patients having upper tract dilatation on ultrasound according to serum creatinine is: creatinine <115mmol/L: 0.8%; creatinine 115–130mmol/L: 9%; and creatinine >130mmol/L: 33%.[7]

1 Roehrborn CG, Bartsch G, Kirby R, *et al.* (2001) Guidelines for the diagnosis and treatment of benign prostatic hyperplasia: a comparative international overview. *Urology* **58**:642–50.

2 Irani J, Brown CT, van der Meulen J, Emberton M (2003) A review of guidelines on benign prostatic hyperplasia and lower urinary tract symptoms: are all guidelines the same? *Br J Urol Int* **92**:937–42.

3 Dunsmuir WD, Feneley M, Corry DA, *et al.* (1996) The day-to-day variation (test–retest reliability) of residual urine measurement. *Br J Urol* **77**:192–3.

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6 Reynard JM, Peters TJ, Lim C, Abrams P (1996) The value of multiple free-flow studies in men with lower urinary tract symptoms. *Br J Urol* **77**:813–18.

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The management of LUTS in men: NICE 2010 Guidelines

(🔗 www.nice.org.uk/CG97)
For those practising in the UK, the NICE 2010 LUTS Guidelines provide a helpful summary of diagnostic and treatment options for men with LUTS. Like guidelines in general, they are not written in stone—there is no absolute requirement to follow them to the letter; you may 'step outside' the guidelines as long as your rationale for doing so has a logical (reasonable) basis. Differences exist between those aspects of the NICE Guidelines that cover BPH-related LUTS and the AUA 2010 Guidelines on the management of BPH (🔗 http://www.auanet.org) and these differences are highlighted where relevant.

LUTS are classified according to IPSS as mild 0–7, moderate 8–19, and severe 20–35.

Initial assessment (i.e. primary care)

Assess general medical history to identify possible causes of LUTS and comorbidities; examine abdomen, genitals, DRE; dipstick urine for blood, glucose, protein, leucocytes, nitrites; complete FVC; serum creatinine and eGFR only if suspected renal impairment.

Offer information, advice, and time to decide if they wish to have PSA testing if LUTS are suggestive of BOO secondary to BPE or abnormal feeling of prostate on DRE or patient concerned about prostate cancer.

Do not routinely offer cystoscopy, flow rate, or residual urine volume measurement.

Offer lifestyle advice (e.g. advice on fluid intake); mild or moderate *bothersome* LUTS—discuss active surveillance* (reassurance, lifestyle advice, no immediate treatment, regular follow-up) or active intervention (conservative management, drugs, surgery).

Conservative management

- **Storage symptoms:** If overactive bladder (OAB) suspected, offer supervised bladder training, advice on fluid intake, lifestyle advice and, if needed, containment products, i.e. pads or sheaths; offer supervised pelvic floor exercises for stress incontinence caused by—continue for at least 3 months before considering other options.
- **Voiding symptoms:** offer intermittent self-catheterization (ISC) before indwelling or suprapubic catheterization if less invasive means fail to correct LUTS; tell men with proven BOO that bladder training is less effective than surgery; for post-micturition dribbling, explain how to do urethral milking.

* AUA 2010 Guidelines use the terms 'watchful waiting' and 'active surveillance' interchangeably; it defines 'watchful waiting' as 'a management strategy in which the patient is monitored by his physician, but currently receives no active intervention'. Watchful waiting is recommended for patients with mild symptoms (AUA-SI <8) and patients with AUA-SI of 8 or more who are not bothered by their LUTS.

Drug treatment

- Offer drug treatment where conservative options are unsuccessful or inappropriate; take account of comorbidities and current treatments; do not offer homeopathy, phytotherapy, or acupuncture (Table 4.1).

Table 4.1 Drug treatment

Indication	Treatment	Review
Moderate to severe LUTS	Offer an alpha blocker (alfuzosin, doxazosin, tamsulosin, terazosin)	At 4–6wk (AUA Guidelines 2–4wk), then every 6–12mo
OAB	Offer an anticholinergic	At 4–6wk until stable, then every 6–12mo
LUTS, prostate estimated >30g or PSA >1.4ng/mL and high risk of progression	Offer 5A-reductase inhibitor	At 3–6mo, then every 6–12mo
Bothersome moderate to severe LUTS and prostate estimated >30g or PSA >1.4ng/mL	Consider an alpha blocker plus 5A-reductase inhibitor	At 4–6wk, then every 6–12mo for the alpha blocker; at 3–6mo, then every 6–12mo for the 5A-reductase inhibitor
Storage LUTS despite alpha blocker treatment alone	Consider adding an anticholinergic	At 4–6wk until stable, then every 6–12mo

- **Nocturnal polyuria:** exclude other medical causes—diabetes mellitus and insipidus, adrenal insufficiency; hypercalcaemia; liver failure; polyuric renal failure; chronic heart failure; obstructive sleep apnoea, dependent oedema; chronic venous stasis; calcium channel blockers; diuretics; selective serotonin reuptake inhibitor antidepressants.
- Consider a late afternoon loop diuretic. Consider offering oral desmopressin—measure serum sodium 3 days after first dose; stop if sodium falls below normal reference range.

Refer for specialist assessment

If bothersome LUTS that fails to respond to conservative management or drugs; LUTS complicated by recurrent or persistent urinary tract infection (UTI); retention; renal impairment suspected to be caused by LUT dysfunction; suspected urological cancer; stress incontinence.

Specialist assessment

(i.e. secondary care—'health care professional with specific training in managing LUTS in men') . A summary of surgical treatment options, based on prostatic size, for voiding symptoms is shown in Table 4.2 and for storage symptoms in Table 4.3.

Table 4.2 Voiding symptoms

Prostate size	Type of surgery
All	TURP (monopolar or bipolar); TUVP (monopolar); HoLEP*
Estimated <30g	TUIP (BNI) as an alternative to the above
Estimated >30g	TURP, TUVP, HoLEP*, open prostatectomy

* At a centre specializing in the technique or with mentorship arrangement in place, holmium laser enucleation of the prostate.

- Offer the following only as part of a randomized controlled trial (RCT): prostatic botox injection; laser vaporization techniques; bipolar TUVP; TUVRP (monopolar or bipolar transurethral vaporization resection of the prostate).
- Do not offer any of the following as an alternative to TURP, TUVP, or HoLEP:
  - Transurethral needle ablation of the prostate (TUNA); transurethral microwave thermotherapy of the prostate (TUMT); high intensity focused ultrasound (HIFU); laser coagulation; transurethral ethanol ablation of the prostate (TEAP) (AUA 2010 Guidelines include TUNA and TUMT as treatment options for the patient with moderate to severe LUTS, i.e. IPSS 8 or more).

Table 4.3 Storage symptoms

Indication	Type of surgery
Detrusor overactivity	Consider offering bladder wall botox injection (must be willing and able to do ISC); SNS*; cystoplasty (must be willing and able to do ISC)
Stress incontinence	Consider AUS (intramural injectables, implanted adjustable compression devices, male slings—only as part of an RCT)
Intractable LUTS if cystoplasty or SNS not clinically appropriate or unacceptable to patient	Consider offering urinary diversion

* SNS = sacral nerve stimulation (the Interstim).

Why do men seek treatment for their symptoms?

Men seek treatment for their LUTS for several reasons:

- The symptoms may be bothersome.
- They may fear that the symptoms are a warning that acute urinary retention will develop.
- They may be concerned that their symptoms indicate that they have prostate cancer.

Establish what the patient wants from his consultation with you. Once reassured that the likelihood of urinary retention and prostate cancer is low, he may not want treatment for symptoms that, on the surface, may appear quite bad and he may be happy to adopt a policy of watchful waiting.

Goals of treatment

- To improve bothersome symptoms.
- To prevent symptom progression.
- To reduce long-term complications (urinary retention, renal insufficiency).
- Management options include watchful waiting, lifestyle modification, drug treatments (α-adrenergic blockers, 5α-reductase inhibitors, anticholinergics, plant extracts), minimally invasive surgery, TURP, open prostatectomy. The choice of treatment is determined by the patient based on his perception of how bad (bothersome) his symptoms are, balanced against the perceived benefit and risks of the various options. Drug treatments have the least impact on symptoms, but are generally safe. Minimally invasive surgery has a somewhat greater impact, with a higher risk of side effects. TURP and open prostatectomy have the greatest impact on symptoms, but at the risk of potentially serious complications.

Bothersome symptoms

Bothersomeness does not necessarily equate with symptom severity as assessed by symptom scores. Thus, a man with a low symptom score may find his symptoms very bothersome and may want treatment, whereas another man with a high symptom score may not be bothered and may want no treatment. If one symptom is particularly bad, but the other six symptoms in the 7-symptom score are minimal, overall symptom score will obviously be relatively low, but the patient may find that one symptom very bothersome (e.g. urgency and nocturia tend to be more bothersome than hesitancy or poor flow).

'Are my symptoms due to prostate cancer?'

No particular LUTS are specific for prostate cancer. Even if it later turns out that he does have prostate cancer, a patient's symptoms might be due to coexistent BPH or some other LUT pathology. If he is concerned about the possibility of prostate cancer, counsel him with regard to PSA testing and prostate biopsy.

'Am I likely to develop retention of urine?'

Many patients are understandably concerned that their urinary symptoms may be a harbinger for the development of acute urinary retention.

This may influence their decision to seek help for symptoms, which they may perceive as indicating a risk of subsequent retention and it may affect the type of treatment they choose. Table 4.4 can help give the patient some idea of his risk of developing urinary retention.

Table 4.4 Yearly risk of retention according to age and symptom score (i.e. number of men experiencing an episode of retention every year)*

Age (y)	Mild symptoms (AUA symptom score 7 or less)	Moderate or severe symptoms (AUA symptom score >7)
440–49	3 3 men in every 1000	33 men in every 1000
770–79	9 9 men in every 1000	334 men in every 1000

Adjusting for age and flow rate, those with an AUA symptom score of 8 or more had a 2.3-fold increased risk of going into urinary retention when compared with those with an AUA score of 7 or less. Those men with a peak flow rate of <12mL/s had a 4-fold increased risk of urinary retention when compared with those with a flow rate of >12mL/s. Prostate volume >30mL was associated with a 3-fold increased risk of urinary retention compared with those with prostate volumes <30mL.

* This table is taken from Jacobsen's report, a 4-year prospective study of a cohort of >2000 men.[1] The presence of LUTS, a low flow rate, an enlarged prostate, and old age were associated with an increased risk of urinary retention.

1 Jacobsen SJ, Jacobson DJ, Girman CJ, *et al.* (1997) Natural history of prostatism: risk factors for acute urinary retention. *J Urol* **158**:481–7.

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Watchful waiting for uncomplicated BPH

A number of studies have shown that in a substantial proportion of men, symptoms do not progress, even for those with severe symptoms.

- **Ball:**[1] a total of 107 men followed with watchful waiting over 5y. In none was there an absolute indication for surgery. Half of the patients were obstructed on urodynamic testing. A third of the patients got better, just under a half stayed the same, a quarter got worse (of whom eight underwent TURP); 2% went into retention.
- **PLESS study (Proscar long-term efficacy and safety study):**[2] a total of 1500 men with moderate to severe symptoms were randomized to placebo (and a similar number to active drug). Those on placebo had an average fall in symptom score of 1 point at 4y.
- **Wasson study of watchful waiting versus TURP:**[3] for men with moderate symptoms, the risk of progression to retention, worsening symptoms, or need for TURP was relatively low in those who chose watchful waiting; 40% noticed an improvement in their symptoms, 30% got worse, and TURP was required in about a quarter.
- **Five centres' study:**[4] a total of 500 men referred by their family doctors for consideration for TURP were managed non-operatively after viewing an educational programme. Over the following 4y period, a proportion of the men chose drug treatment or surgery. For men with mild, moderate, or severe symptoms, 10%, 24%, and 39%, respectively, had undergone surgery at the end of 4y. For the same symptom categories, 63%, 45%, and 33% were still not receiving any treatment at the end of 4y. Almost a quarter of men who initially presented with severe symptoms noted an improvement in their symptoms to mild or moderate.

On the basis of these studies, we can say that symptoms, even if severe, do not necessarily get worse, even over fairly long periods of time. This forms the foundation of watchful waiting as an option for many patients, even if the symptoms at baseline are severe. The IPSS measures both symptom 'severity', but more importantly, the *bother* that the symptoms cause the patient. Thus, if a patient has a high symptom score (severe symptoms), but is not bothered by these symptoms, there is no indication for treatment. Some patients, on the other hand, have a low symptom score, but may find even this degree of symptoms very bothersome. Treatment is indicated in such cases (usually starting with medical therapy such as an alpha blocker or 5α-reductase inhibitor).

1 Ball AJ, Feneley RC, Abrams PH (1981) Natural history of untreated 'prostatism'. *Br J Urol* **53**:613–16.

2 McConnell JD, Bruskewitz R, Walsh PC, *et al.* (1998) The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia (PLESS). *N Engl J Med* **338**:557–63.

3 Wasson JH, Reda DJ, Bruskewitz RC, *et al.* (1995) A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. *N Engl J Med* **332**:75–9.

4 Barry MJ, Fowler FJJ, Bin L, *et al.* (1997) The natural history of patients with benign prostatic hyperplasia as diagnosed by North American urologists. *J Urol* **157**:10–4.

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Medical management of BPH: alpha blockers

The rationale for blocker therapy in BPH

As described earlier, BPO is caused partly by α1-adrenoceptor-mediated prostatic smooth muscle contraction and this is the rationale for α-adrenoceptor blocker treatment for symptomatic BPO.

There are two broad subtypes of α-adrenoceptor (AR)—α1 and α2. Molecular cloning studies have identified three α1-AR subtypes—α1a (predominant in human stroma and, therefore, mediates prostate smooth muscle contraction), α1b (predominant in human prostate epithelium), and α1L (believed to be a conformational state of the α1a-AR). The AR subtypes mediating efficacy and side effects of α-adrenoceptor blocking drugs are unknown.

Alpha blocker classification

Alpha blockers are categorized by their selectivity for the AR and by their elimination half-life.

- Non-selective: phenoxybenzamine—effective symptom control, but high side effect profile.
- α1: prazosin, alfuzosin, indoramin.
- Long-acting α1: terazosin, doxazosin, alfuzosin SR.
- Subtype selective: tamsulosin—relatively selective for α1a-AR subtype compared to the α1b subtype.

No study has directly compared one alpha blocker with another in terms of efficacy *or* side effects. Terazosin and doxazosin require dose titration to minimize dizziness and syncope at the start of treatment.

Indications for treatment

Bothersome LUTS where watchful waiting has failed *or* the patient wishes to have treatment.

Efficacy

Percentage of patients who respond to alpha blockers

Patients are able to perceive a 4-point improvement in IPSS. If 'response' is defined as >25% improvement in symptoms relative to placebo, most studies describe response rates of 30–40%.[1] The mean probability for improvement in symptom score after TURP is in the order of 80% (i.e. 8 out of 10 men will notice an improvement in their symptoms after TURP). For those men who respond, the alpha blockers have a much more rapid onset than do the 5α-reductase inhibitors. Their effect will be maximal within a month of starting treatment.

Improvements in symptom score in men who 'respond' to alpha blockers

The average improvement in symptom score after TURP is about 85%.[2] While some of this may represent a placebo response, this improvement is considerably better than that seen with the alpha blockers, which result in a 10–30% improvement in symptom score relative to placebo.[3] This equates to a 4–5 points' improvement in symptom score over placebo.

Side effects

A substantial proportion of men stop taking their medication either because of side effects (15–30% report some constellation of side effects) or because of a perceived lack of effectiveness (approximately 50% of men stop taking an alpha blocker within 3y because of a perception that it has not worked).[4] Side effects include asthenia (weakness in 5%), dizziness (2–14%), headache (2%) and postural hypotension (1%), and retrograde ejaculation (8%). There is little data on the safety of concomitant use of the alpha blockers with drugs for erectile dysfunction.[1]

Intraoperative floppy iris syndrome (IFIS) and alpha blocker use

A triad of progressive intraoperative miosis (constriction of the pupil) despite preoperative dilation, billowing of a flaccid iris, and iris prolapse toward the incision site during cataract surgery lead to complications such as posterior capsule rupture with vitreous loss and post-operative intraocular pressure spikes (visual acuity outcomes appeared preserved). The original report linked this condition with the preoperative use of tamsulosin; iris dilator smooth muscle inhibition has been suggested as a potential mechanism.[5,6]

Risk of IFIS among men taking tamsulosin is substantial (43–90% in ten retrospective and prospective studies).[7] The risk of IFIS appears to be lower with older, generic alpha blockers such as terazosin and doxazosin (0–25%).[7]

Whether stopping alpha blocker treatment at any time before surgery mitigates the risk of IFIS is unclear. The AUA 2010 BPH Guidelines[7] recommend that men with LUTS secondary to BPH where alpha blocker therapy is planned should be asked about planned cataract surgery. Those with planned cataract surgery should avoid the initiation of alpha blockers until their cataract surgery is completed.

1 Lowe F (1999) Alpha-1-adrenoceptor blockade in the treatment of benign prostatic hyperplasia. *Prostate Cancer and Prostatic Diseases* **2**:110–9.

2 McConnell JD, Barry MD, Bruskewitz RC, *et al.* (1994) *The BPH Guideline Panel. Benign Prostatic Hyperplasia: diagnosis and treatment. Clinical Practice Guideline.* Agency for Health Care Policy and Research, publication No.94–0582, 1994, Rockville, Maryland. Public Health Service, US Department of Health and Human Sciences.

3 Boyle P, Robertson C, Manski R, *et al.* (2001) Meta-analysis of randomized trials of terazosin in the treatment of benign prostatic hyperplasia. *Urology* **58**:717–22.

4 de la Rosette, Kortmann B, Rossi C, *et al.* (2002) Long term risk of retreatment of patients using alpha blockers for lower urinary tract symptoms. *J Urol* **167**:1734–9.

5 Chang D, Campbell J (2005) Intraoperative floppy iris syndrome associated with tamsulosin. *J Cataract Refract Surg* **31**:664.

6 Bell C, Hatch WV, Fischer HD, *et al.* (2009) Association between tamsulosin and serious ophthalmic adverse events in older men following cataract surgery. *JAMA* **301**:1991–6.

7 American Urological Association (2010) The AUA 2010 BPH Guidelines [online]. Available from: http://www.auanet.org.

Medical management of BPH: 5α-reductase inhibitors

5α-reductase inhibitors inhibit the conversion of testosterone to DHT, the more potent androgen in the prostate. This causes shrinkage of the prostatic epithelium and, therefore, a reduction in prostate volume, thereby reducing the 'static' component of BPE. This takes some months to occur so urinary symptoms will not improve initially. Finasteride is a competitive inhibitor of the enzyme 5α-reductase (type II isoenzyme), which converts testosterone to DHT. Finasteride, therefore, lowers serum and intraprostatic DHT levels. Epristeride is a dual inhibitor of 5α-reductase. Whether it has any clinically significant advantages over finasteride remains to be established.

Efficacy

- **Finasteride:** a number of large studies have shown symptom improvement over placebo in the order of 2–3 points on the IPSS and improvements in flow rate in the order of 1–2mL/s (SCARP[1] (Scandinavian BPH Study Group), PROSPECT[2] (Proscar safety plus efficacy Canadian two-year study), PROWESS Study Group,[3] and more recently, PLESS[4] (Proscar long-term efficacy and safety study)). The PLESS data also show a small reduction in the risk of urinary retention.
- **Dutasteride:** evidence for its efficacy is derived from a 2y RCT with an open-label extension;[6] SMART 1, which evaluated the effect of a placebo-controlled withdrawal of an alpha blocker from a combination therapy arm;[7] and from the CombAT study (comparison of dutasteride vs tamsulosin vs dutasteride + tamsulosin).[8]

Side effects

Generally speaking, fairly mild. Principally centre around sexual problems (e.g. loss of libido, 5%; impotence, 5%; reduced volume of ejaculate in a few percent).

5α-reductase inhibitors and the risk of urinary retention

The PLESS data[5] have been widely publicized as showing a substantial reduction in the risk of urinary retention. In this 4y follow-up study, 42 of 1471 men on finasteride went into urinary retention (3%) while 99 of 1404 on placebo experienced an episode of retention (7%). This represents an impressive 43% *relative* reduction in risk in those taking finasteride. However, the *absolute* risk reduction over a 4y period is a less impressive 4%. So finasteride does reduce the risk of retention, *but it is reducing the risk of an event which is actually quite rare*, as suggested by the fact that 93% of men on placebo in this study did not experience retention over a 4y period. Put another way, to prevent one episode of retention, 25 men would have to continue treatment with finasteride for 4y.

5α-reductase inhibitors for haematuria due to BPH

Finasteride suppresses vascular endothelial growth factor (VEGF). Shrinking large vascular prostates probably helps reduce the frequency of haematuria in men with BPH.[5]

1 Andersen JT, Ekman P, Wolf H, *et al.* (1995) Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo-controlled study. The Scandinavian BPH Study Group. *Urology* **46**:631–7.

2 Nickel J, Fradet Y, Boake RC, *et al.* (1996) Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomised controlled trial (the PROSPECT study). PROscar Safety Plus Efficacy Canadian Two Year Study. *Can Med Assoc J* **155**:1251–9.

3 Marberger MJ (1998) Long-term effects of finasteride in patients with benign prostatic hyperplasia: a double-blind, placebo-controlled, multicenter study. PROWESS Study Group. *Urology* **51**:677–86.

4 McConnell JD, Bruskewitz R, Walsh PC, *et al.* (1998) The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia (PLESS). *N Engl J Med* **338**:557–63.

5 Foley SJ, Soloman LZ, Wedderburn AW, *et al.* (2000) Finasteride for haematuria due to BPH. A prospective study of the natural history of hematuria associated with BPH and the effect of finasteride. *J Urol* **163**:496–8.

6 Roehrborn C, Lukkarinen O, Mark S, *et al.* (2005) Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5alpha-reductase inhibitor dutasteride: results of 4-year studies. *BJU Int* **96**:572–7.

7 Barkin J, Guimaraes M, Jacobi G, *et al.* (2003) Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride. *Eur Urol* **44**:461–6.

8 Roehrborn C, Siami P, Barkin J, *et al.* (2008) The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J Urol* **179**:616.

Medical management of BPH: combination therapy

A combination of an alpha blocker and a 5α-reductase inhibitor. The studies:

- **MTOPS study** (Medical Therapy of Prostatic Symptoms):[1] 3047 men; mean prostate volume 36mL. This combination prevented progression of BPH when compared with either drug alone (progression being defined as a worsening of symptom score by 4 or more or the development of complications such as UTI or acute urinary retention).
- **Veterans Affairs Combination Therapy Study:**[2] 1200 men randomized to placebo, finasteride, terazosin, or both terazosin and finasteride. At 1y follow-up, relative to placebo, finasteride had reduced the symptom score by an average of 3 points whereas terazosin alone or in combination with finasteride had reduced the symptom score by an average of 6 points.
- **PREDICT study** (Prospective European Doxazosin and Combination Therapy):[3] randomized >1000 men to placebo, finasteride, doxazosin, or both finasteride and doxazosin. Difference in symptom score at baseline and 1y were: placebo –5.7, finasteride –6.6, doxazosin –8.3, combination therapy –8.5.
- **ALFIN study** (alfuzosin, finasteride, and combination in the treatment of BPH):[4] 1000 men randomized to alfuzosin, finasteride, or both. At 6 months, the improvement in the IPSS was not significantly different in the alfuzosin vs the combination group.
- **CombAT trial**.[8] 4844 men; mean prostate volume 55mL. Compared tamsulosin, dutasteride, and a combination of both. Prostate volume was >30mL (TRUS). Only 2y data are available as of 2011. Combination therapy resulted in significantly greater improvements in symptoms compared to dutasteride from month 3 and tamsulosin from month 9 and significantly greater improvement in peak urinary flow from month 6. There was a significant increase in drug-related adverse events with combination therapy. Analysis of the primary endpoints (4y progression of LUTS, urinary retention, and need for prostate surgery) are awaited.

Thus, most studies, except for MTOPS, suggest that combination therapy is no more useful than an alpha blocker alone. Disadvantages of combination therapy—greater risk of side effects, no additional benefit over alpha blockers alone in most men, need for treatment for >1y before an improvement in symptoms is seen, sexual side effects.

In the Prostate Cancer Prevention Trial,[5] 18 000 men were randomized to finasteride or placebo over a 7y period. Those in the finasteride group had a lower prevalence of prostate cancer detected on prostate biopsy (26.5% of men receiving finasteride had a positive biopsy v 29.5% in the placebo group). However, higher-grade tumours (i.e. biologically more aggressive than low-grade cancers) were more common in the finasteride group (there was a 1.3% increase in high-grade cancers in the finasteride group). The jury is out on whether finasteride causes higher-grade cancers

or whether these findings are a histological or sampling artefact. Finasteride increases the ability (increased sensitivity) of both PSA, DRE, and prostate biopsy to diagnose high-grade prostate cancer[6,7]—so-called cytoreduction of the prostate, leading to a greater likelihood of finding high-grade cancer (the argument is that finasteride has less of an effect on PSA reduction in men with high-grade than low-grade cancers, so men with high-grade cancer are more likely to have an elevated PSA and therefore, to undergo prostate biopsy and thus cancer detection).

1 McConnell JD, Roehrborn CG, Bautista OM, *et al.* (2003) The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *New Engl J Med* **349**:2387–98.

2 Lepor H, Williford WO, Barry MJ, *et al.* (1996) The efficacy of terazosin, finasteride, or both in benign prostatic hypertrophy. *N Engl J Med* **335**:533–39.

3 Kirby RS, Roerborn C, Boyle P, *et al.* (2003) Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* **61**:119–26.

4 Debruyne FM, Jardin A, Colloi D, *et al.* (1998) Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia. *Eur Urol* **34**:169–75.

5 Thompson IM, Goodman PJ, Tangen CM, *et al.* (2003) The influence of finasteride on the development of prostate cancer. *N Engl J Med* **349**:215–24.

6 Thompson IM, Chi C, Ankerst DP, *et al.* (2006) Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* **98:**1128.

7 Thompson IM, Tangen CM, Goodman PJ, *et al.* (2007) Finasteride improves the sensitivity of digital rectal examination for prostate cancer detection. *J Urol* **177:**1749.

8 Roehrborn C, Siami P, Barkin J, *et al.* (2008) The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J Urol* **179:** 616.

Medical management of BPH: alternative drug therapy

Anticholinergics

For a man with frequency, urgency, and urge incontinence—symptoms suggestive of an overactive bladder—consider prescribing an anticholinergic (e.g. oxybutynin, tolterodine, trospium chloride, or flavoxate). There is the concern that these drugs could precipitate urinary retention in men with BOO (because they block parasympathetic/cholinergic-mediated contraction of the detrusor), but the risk of this occurring is probably very low, even in men with urodynamically proven BOO.[1]

Phytotherapy

An alternative drug treatment for BPH symptoms and one which is widely used in Europe and increasingly in North America is phytotherapy. Fifty percent of all medications consumed for BPH symptoms are phytotherapeutic ones.[2]

Examples include the Saw palmetto plant (*Serenoa repens*) and extracts from the stinging nettle (*Urtica dioica*), among several others. While previous editions of this book quoted studies, including a meta-analysis, that suggested similar efficacy to 5ARs in terms of improvements in symptoms and flow rates,[2,3] more recent studies have generally failed to confirm a clinically important role for Saw palmetto in the management of BPH.[4,5]

NICE in the UK does not recommend phytotherapy for LUTS in men (🔗 www.nice.org.uk/CG97) and similarly, in the United States, phytotherapy is no longer recommended by the AUA 2010 BPH Guidelines (🔗 http://www.auanet.org).

1 Reynard J (2004) Does anticholinergic medication have a role for men with lower urinary tract symptoms/benign prostatic hyperplasia either alone or in combination with other agents? *Curr Opin Urol* **14**:13–6.

2 Wilt T, Ishani A, Stark G, *et al.* (1998) Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. *JAMA* **280**:1604–8.

3 Wilt T, Ishani A, Rutks I, *et al.* (2000) Phytotherapy for benign prostatic hyperplasia. *Public Health Nutr* **3**:459.

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Minimally invasive management of BPH: surgical alternatives to TURP

In 1989, Roos reported a seemingly higher mortality and reoperation rate after TURP when compared with open prostatectomy.[1] This, combined with other studies suggesting that symptomatic outcome after TURP was poor in a substantial proportion of patients and that TURP was associated with substantial morbidity, prompted the search for less invasive treatments.

The two broad categories of alternative surgical techniques are minimally invasive and invasive. All are essentially heat treatments, delivered at variable temperature and power and producing variable degrees of coagulative necrosis (minimally invasive) of the prostate or vaporization of prostatic tissue (invasive).

For those practising in the UK, note that the 2010 NICE Guidelines (www.nice.org.uk/CG97) recommend that TUNA, TUMT, and HIFU should not be offered as alternatives to TURP, TUVP, or HoLEP. These techniques are used in other countries, hence a discussion of the various techniques here.

Transurethral radiofrequency needle ablation (TUNA) of the prostate

Low-level radiofrequency is transmitted to the prostate via a transurethral needle delivery system; the needles which transmit the energy are deployed in the prostatic urethra once the instrument has been advanced into the prostatic urethra. It is done under local anaesthetic, with or without intravenous sedation. The resultant heat causes localized necrosis of the prostate.

Improvements in symptom score and flow rate are modest. Side effects include bleeding (one third of patients), UTI (10%), and urethral stricture (2%). No adverse effects on sexual function have been reported.[2] Concerns remain with regard to long-term effectiveness.

Transurethral microwave thermotherapy (TUMT)

Microwave energy can be delivered to the prostate via an intraurethral catheter (with a cooling system to prevent damage to the adjacent urethra), producing prostatic heating and coagulative necrosis. Subsequent shrinkage of the prostate and thermal damage to adrenergic neurons (i.e. heat-induced adrenergic nerve block) relieves obstruction and symptoms.

Many reports of TUMT treatment are open studies, all patients receiving treatment (no 'sham' treatment group where the microwave catheter is inserted, but no microwave energy is given—this results in 10-point symptom improvements in approximately 75% of men). Compared with TURP, TUMT results in symptom improvement in 55% of men and TURP in 75%. Sexual side effects after TUMT (e.g. impotence, retrograde ejaculation) are less frequent than after TURP, but catheterization period is longer and UTI and irritative urinary symptoms are more common.[3] EAU Guidelines state that TUMT 'should be reserved for patients who prefer to avoid surgery orwho no longer respond favourably to medication'. TUMT is still a popular treatment in the United States.

High intensity focused ultrasound (HIFU)

A focused ultrasound beam can be used to induce a rise in temperature in the prostate or indeed in any other tissue to which it is applied. For HIFU treatment of the prostate, a transrectal probe is used. A general anaesthetic or heavy intravenous sedation is required during the treatment. It is regarded as an investigational therapy.

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Invasive surgical alternatives to TURP

Transurethral electrovaporization of the prostate (TUVP)

Vaporizes and dessicates the prostate. TUVP seems to be as effective as TURP for symptom control and relief of BOO, with durable (5y) results. Operating time and inpatient hospital stay are equivalent. Requirement for blood transfusion may be slightly less after TUVP.[1,2] TUVP does not provide tissue for histological examination so prostate cancers cannot be detected. NICE in the UK has endorsed TUVP as a surgical treatment option for prostatic symptoms.[3]

Laser prostatectomy

Several different techniques of 'laser prostatectomy' evolved during the 1990s. Essentially, in the year 2012, we are left with just holmium laser prostatectomy (endorsed by NICE 2010 Guidelines) and the green light laser (NICE 2010 Guidelines recommending its use only in the context of RCTs).[3]

Transurethral ultrasound-guided laser-induced prostatectomy (TULIP)
Performed using a probe consisting of a Nd:YAG laser adjacent to an ultrasound transducer.

Visual laser ablation of the prostate (VLAP)
This side-firing system used a mirror to reflect or a prism to refract the laser energy at various angles (usually 90°) from a laser fibre located in the prostatic urethra onto the surface of the prostate. The principal tissue effect was one of coagulation with subsequent necrosis.

Contact laser prostatectomy
Produces a greater degree of vaporization than VLAP, allowing the immediate removal of tissue.

Interstitial laser prostatectomy (ILP)
Performed by transurethral placement of a laser fibre directly into the prostate that produces a zone of coagulative necrosis some distance from the prostatic urethra.

TULIP, VLAP, contact laser prostatectomy, and ILP have been succeeded by holmium laser prostatectomy.

KTP laser vaporization of the prostate

Also known as 'greenlight' photoselective vaporization of the prostate (PVP). A ytrium-aluminium-garnet (YAG) laser light is shone through a potassium titanyl phosphate (KTP) crystal, doubling the frequency and halving the emitted light wavelength to 532nm. This is in the green part of the visible spectrum and is strongly absorbed by haemoglobin, producing efficient prostate tissue vaporization (Fig. 4.1). KTP energy is poorly absorbed by water/saline (the irrigant) and therefore, a non-contact vaporization is possible. The benefits include less heating of the delivery fibre, which can last for a longer period of time. Laser systems of 80 and 120W are available. In the 80W system, approximately 100kJ will be delivered to the average prostate in 30min by rapid pulses of 'quasi-continuous'

energy. Laser heat is concentrated over a small area, which allows rapid vaporization of tissue with minimal coagulation of underlying structures (2mm rim of coagulated tissue is left), but creating effective haemostasis. It can be used for larger prostates (>100mL)[4] and higher risk patients on anticoagulants.[5]

Indications

The 2010 NICE Guidelines on Management of LUTS in men state that laser vaporization techniques, of which greenlight laser is one, should be offered only as part of an RCT.[6]

Technique

Using a KTP/532 80W laser (Laserscope®), a 6F side-firing fibre is placed through a 24F continuous irrigation cystoscope, with normal saline irrigation. Generally, the median lobe is treated first, then the lateral lobes, using a sweeping movement of the laser fibre across the prostate, starting at the bladder neck and working distally to the level of the verumontanum. No tissue is available for histology.

Advantages over TURP

KTP laser prostatectomy can be performed safely as a day surgery operation, and in selected cases, a catheter may not be needed post-operatively or can be removed within 24h. It provides a virtually bloodless operation with no reported need for blood transfusion, even in anticoagulated patients. Irrigation with saline or water avoids the risk of transurethral resection (TUR syndrome. The incidence of retrograde ejaculation is lower than TURP (8.3–52%),[7,8] with no reported cases of new erectile dysfunction. When directly compared to TURP, equivalent short-term efficacies are seen, but with significantly shorter catheterization times and inpatient stays in the laser group.[9,10]

Outcomes

Short- and medium-term outcomes (up to 5y follow-up) demonstrate sustained and statistically significant improvements in symptom scores (IPSS/AUA), flow rate, and post-void residual volumes.[7–12]

Post-operative complications

Haematuria (1–11%); dysuria (2–21%); acute urinary retention (1–11%); reoperation rate (0–5% at 1y).

Holmium (Ho): YAG laser

The holmium laser is a pulsed solid state laser with a wavelength of 2140nm which is strongly absorbed by water. It is absorbed into prostate tissue to a depth of 0.4mm and the heat created (>100°C) causes good tissue vaporization, whilst causing coagulation of small to medium-sized blood vessels. The coagulative depth is about 2–3mm beyond the tissue that has been vaporized. The irrigant is normal saline so the risk of TUR syndrome is avoided.

Holmium laser enucleation of the prostate (HoLEP) *(endorsed by 2010 NICE Guidelines on management of LUTS in men* *www.nice.org.uk/CG97)*

HoLEP is particularly useful for treating larger prostates. An end-firing laser fibre is used to cut grooves into the prostate down to the level of the capsule. The prostate lobes are then dissected off and pushed into the

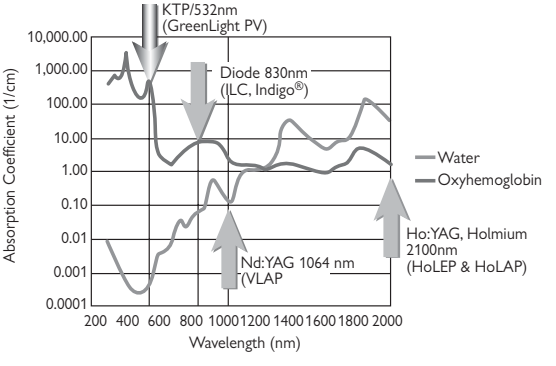

Fig. 4.1 Absorption curve of water and oxyhaemoglobin. From Laserscope® Physician training manual 2006. (Reproduced with permission from the American Medical Systems Inc, Minnesota.)

bladder where a mechanical morcellator is used to fragment and aspirate the tissue. HoLEP is technically more difficult to master than laser vaporization and has a longer learning curve, but the overall results are at least equivalent to TURP with fewer associated risks.

In a randomized trial comparing holmium laser enucleation with TURP for prostates >40g, HoLEP was equivalent to TURP, but with those in the HoLEP group having a shorter catheterization time and hospital stay. A larger volume of prostatic tissue was removed.[13] Long-term follow-up (7y) demonstrates sustained significant improvements in symptom scores and flow rates.[14] In a direct comparison with open prostatectomy, HoLEP has also demonstrated equivalent improvement in symptom scores and flow rates at 3y follow-up.[15]

Other techniques of holmium laser prostatectomy

Holmium laser ablation of the prostate (HoLAP)

A side-firing dual wavelength fibre is used in a near-contact mode to vaporize prostatic tissue circumferentially to produce a satisfactory channel. Original techniques used 60W lasers, however, lasers up to 100W are now available. Symptom improvements are sustained in the long term,[16] and when directly compared with TURP, similar efficacy was seen in the short term, but with shorter hospital stay and catheter times in the HoLAP group and less bleeding than for TURP.[17] Studies suggest overall, it is most effective for smaller prostate glands.

Holmium laser resection of the prostate (HoLRP)

This technique copies that of TURP, whereby the precise cutting ability of the holmium laser is used to remove pieces of prostate down to the capsule to create a large and relatively bloodless channel. It can be used

on prostate glands of all sizes. Again, it has short catheterization times and hospital stays and is associated with minimal post-operative dysuria.[18]

1 Hammadeh MY, Madaan S, Hines J, Philp T (2000) Transurethral electrovaporization of the prostate after 5 years; is it effective and durable? *BJU Int* **86**:648–51.

2 Mc Allister WJ, Karim O, Plail RO, *et al.* (2003) Transurethral electrovaporization of the prostate: is it any better than conventional transurethral resection of the prostate? *BJU Int* **91**:211–4.

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9 Bachmann A, Schürch L, Ruszat R, *et al.* (2005) Photoselective vaporisation (PVP) versus transurethral resection of the prostate (TURP): a prospective bi-centre study of perioperative morbidity and early functional outcome. *Eur Urol* **48**:965–72.

10 Bouchier-Hayes DM, Anderson P, Van Appledorn S, *et al.* (2006) KTP laser versus transurethral resection: early results of a randomised trial. *J Endourol* **20**:580–5.

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14 Elzayat EA, Habib EI, Elhilali MM (2005) Holmium laser enucleation of the prostate: a size-independent new 'gold standard'. *Urology* **66**:108–13.

15 Kuntz RM, Ahyai S, Lehrich K (2006) Transurethral holmium laser enucleation of the prostate compared with transvesical open prostatectomy: 3 years follow-up of a randomised trial. *Proc SPIE* **6078**:11.

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17 Mottet N, Anidjar M, Bourdon O, *et al.* (1999) Randomised comparison of transurethral electroresection and holmium:YAG laser vaporization for symptomatic benign prostatic hyperplasia. *J Endourol* **13:**127–30.

18 Gilling PJ, Cass CB, Cresswell MD, *et al.* (1996) The use of holmium laser in the treatment of benign prostatic hyperplasia. *J Endourol* **5**:459-61.

TURP and open prostatectomy

TURP

Removal of the obstructing tissue of BPH or obstructing prostate cancer from within the prostatic urethra, leaving the compressed outer zone intact (the 'surgical capsule'). An electrically heated wire loop is used, through a resectoscope, to cut the tissue and diathermy bleeding vessels. The cut 'chips' of prostate are pushed back into the bladder by the flow of irrigating fluid and at the end of resection, are evacuated using specially designed 'evacuators'—a plastic or glass chamber attached to a rubber bulb which allows fluid to be flushed in and out of the bladder.

Indications for TURP

- Bothersome LUTS that fail to respond to changes in lifestyle or medical therapy.
- Recurrent acute urinary retention.
- Renal impairment due to BOO (high-pressure *chronic* urinary retention).
- Recurrent haematuria due to BPE.
- Bladder stones due to prostatic obstruction.

Open prostatectomy

Indications

- Large prostate (>100g).
- TURP not technically possible (e.g. limited hip abduction).
- Failed TURP (e.g. because of bleeding).
- Urethra too long for the resectoscope to gain access to the prostate.
- Presence of bladder stones which are too large for endoscopic cystolitholapaxy, combined with marked enlargement of the prostate.

Contraindications

- Small fibrous prostate.
- Prior prostatectomy in which most of the gland has been resected or removed; this obliterates the tissue planes.
- Carcinoma of the prostate.

Techniques

Suprapubic (transvesical)

The preferred operation if enlargement of the prostate involves mainly the middle lobe. The bladder is opened, the mucosa around the protruding adenoma is incised, and the plane between the adenoma and capsule is developed to enucleate the adenoma. A 22 Ch urethral and a suprapubic catheter are left, together with a retropubic drain. Remove the urethral catheter in 3 days and clamp the suprapubic at 6 days, removing it 24h later. The drain can be removed 24h after this (day 8).

Simple retropubic

Popularized by Terence Millin (Ireland, 1947). Compared with the suprapubic (transvesical) approach, it allows more precise anatomic exposure of the prostate, thus giving better visualization of the prostatic cavity, which allows more accurate removal of the adenoma, better control of bleeding

points, and more accurate division of the urethra so reducing the risk of incontinence.

As well as the contraindications noted, the retropubic approach should not be employed when the middle lobe is very large because it is difficult to get behind the middle lobe and so to incise the mucosa (safely) distal to the ureters.

The prostate is exposed by a Pfannenstiel or lower midline incision. Haemostasis is achieved before enucleating the prostate by ligating the dorsal vein complex with sutures placed deeply through the prostate. The prostatic capsule and adenoma are incised transversely with the diathermy just distal to the bladder neck. The plane between the capsule and adenoma is found with scissors and developed with a finger. Sutures are used for haemostasis. A wedge of bladder neck is resected. A catheter is inserted and left for 5 days and the transverse capsular incision is closed. A large tube drain (30Ch Robinson's) is left for 1–2 days.

Complications

- Haemorrhage.
- Urinary infection.
- Rectal perforation (close and cover with a colostomy).

Acute urinary retention: definition, pathophysiology, and causes

Definition

Painful inability to void, with relief of pain following drainage of the bladder by catheterization.

The combination of reduced or absent urine output with lower abdominal pain is not, in itself, enough to make a diagnosis of acute retention. Many acute surgical conditions cause abdominal pain and fluid depletion, the latter leading to reduced urine output and this reduced urine output can give the erroneous impression that the patient is in retention when in fact they are not. Thus central to the diagnosis is the presence of a *large* volume of urine which, when drained by catheterization, leads to resolution of the pain. What represents 'large' has not been strictly defined, but volumes of 500–800mL are typical. Volumes <500mL should lead one to question the diagnosis. Volumes >800mL may be defined as acute-on-chronic retention.

Pathophysiology

Normal micturition requires:

- Afferent input to the brainstem and cerebral cortex.
- Coordinated relaxation of the external sphincter.
- Sustained detrusor contraction.
- The absence of an anatomic obstruction in the outlet of the bladder.

Four broad mechanisms can lead to urinary retention:

- Increased urethral *resistance* (i.e. BOO).
- Low bladder *pressure* (i.e. impaired bladder contractility).
- Interruption of sensory or motor innervation of bladder.
- Central failure of coordination of bladder contraction with external sphincter relaxation.

Causes in men

- Benign prostatic enlargement.
- Malignant enlargement of prostate.
- Urethral stricture; prostatic abscess.

Urinary retention in men is either *spontaneous* or *precipitated* by an event. Precipitated retention is less likely to recur once the event, which caused it, has been removed. Spontaneous retention is more likely to recur after trial of catheter removal and therefore, to require definitive treatment (e.g. TURP). Precipitating events include anaesthetic and other drugs (anticholinergics, sympathomimetic agents such as ephedrine in nasal decongestants); non-prostatic abdominal or perineal surgery; immobility following surgical procedures.

Risk factors for retention in men

Advancing age is a strong predictor of the risk of urinary retention in men. Other factors that predict risk of urinary retention are the presence of LUTS (higher symptom scores), previous episodes of spontaneous

retention, low Qmax (though there is some debate), and larger prostate volume. Elevated PVR does not seem to predict risk of retention and nor does treatment with anticholinergic medication.[1]

Causes of acute urinary retention in either sex

- Haematuria, leading to clot retention.
- Drugs (as above).
- Pain (adrenergic stimulation of the bladder neck).
- Post-operative retention (see Risk factors for post-operative retention).
- Sacral cord (S2–4) injury.
- Sacral (S2–4) nerve or compression or damage, resulting in detrusor areflexia—cauda equina compression (due to prolapsed L2–L3 disc or L3–L4 intervertebral disc pressing on sacral nerve roots of the cauda equina, trauma to vertebrae, benign or metastatic tumours).
- Suprasacral spinal cord injury (results in loss of coordination of external sphincter relaxation with detrusor contraction—so-called detrusor sphincter dyssynergia (DSD)—so external sphincter contracts when bladder contracts).
- Radical pelvic surgery damaging pelvic parasympathetic plexus (radical hysterectomy, abdominoperineal resection): unilateral injury to pelvic plexus (preganglionic parasympathetic and post-ganglionic sympathetic neurons) denervates motor innervation of detrusor muscle.
- Pelvic fracture rupturing urethra (more likely in men than women).
- Neurotropic viruses involving sensory dorsal root ganglia of S2–4 (*Herpes simplex* or *zoster*).
- Multiple sclerosis (can affect any part of CNS; Fig. 4.2); retention caused by detrusor areflexia or DSD.
- Transverse myelitis.
- Diabetic cystopathy (causes sensory and motor dysfunction).
- Damage to dorsal columns of spinal cord, causing loss of bladder sensation (tabes dorsalis, pernicious anaemia).

Causes in women

- Pelvic prolapse (cystocoele, rectocoele, uterine); urethral stricture; urethral diverticulum.
- Post-surgery for 'stress' incontinence.
- Pelvic masses (e.g. ovarian masses).
- Fowler's syndrome: increased electromyographic activity can be recorded in the external urethral sphincters of these women (which, on ultrasound, is of increased volume) and is hypothesized to cause impaired relaxation of external sphincter; occurs in premenopausal women, often in association with polycystic ovaries.

Risk factors for post-operative retention

Instrumentation of lower urinary tract; surgery to perineum or anorectum; gynaecological surgery; bladder overdistension; reduced sensation of bladder fullness; pre-existing prostatic obstruction; epidural anaesthesia. Postpartum retention is not uncommon, particularly with epidural anaesthesia and instrumental delivery.

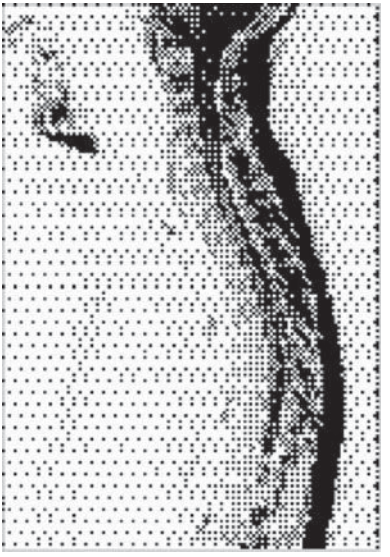

Fig. 4.2 MRI of cervical and sacral cord in a young patient presenting with urinary retention. The patient had undiagnosed multiple sclerosis. Signal changes are seen in the cervical, thoracic, and lumbosacral cord.

1 Kaplan SA, Wein AJ, Staskin DR, Roehrborn CG, Steers WD (2008). Urinary retention and post-void residual urine in men: separating truth from tradition. *J Urol* **180**:47–54.

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Acute urinary retention: initial and definitive management

Initial management

Urethral catheterization to relieve pain (suprapubic catheterization if urethral route not possible). Record the volume drained—this confirms the diagnosis, determines subsequent management, and provides prognostic information with regards to outcome from this treatment.

Definitive management in men

Discuss trial without catheter (TWOC) with the patient. Precipitated retention often does not recur; spontaneous retention often does. Fifty percent with *spontaneous* retention will experience a second episode of retention within the next week or so and 70% within the next year. A maximum flow rate (Qmax) <5mL/s and low voiding detrusor pressure predict subsequent retention. Thus while most will require definitive treatment (e.g. TURP), a substantial minority will get away without needing surgery.

In men, mortality in the first year after acute urinary retention is 2–3 times higher than the general male population. Not surprisingly it increases with age (Table 4.5). A substantial proportion of this increased mortality seems to be linked to comorbidity in these men.[1] Thus when deciding whether to 'subject' a man to TURP for retention, remember that acute retention represents a harbinger of severe systemic disease. A careful assessment for comorbidity (cardiovascular disease, diabetes, chronic pulmonary disease) should be made and referral for appropriate specialist advice on management of this comorbidity should be considered.

Table 4.5 One-year mortality rates in men with acute retention

Age (y)	Spontaneous acute retention (%)	Precipitated acute retention (%)
45–54	4	10
85 or over	33	45
All ages	15	25

Options to avoid TURP

- Prostate shrinking drugs followed by a TWOC several months later (5α-reductase inhibitors in those with benign-feeling prostates, luteinizing hormone-releasing hormone (LHRH) agonists in those with malignant feeling prostates on DRE, confirmed by TURS-guided prostate biopsy).
- Prostatic stents.
- Long-term urethral or suprapubic catheter.
- Clean intermittent self-catheterization (CISC)—not a realistic option for most men, but some will be able and happy to do this.

Definitive management in women

CISC, either until normal voiding function recovers or permanently if it does not. Fowler's syndrome—sacral neuromodulation (e.g. Medtronic Interstim).

Risks and outcomes of TURP for retention

Relative risks of TURP for retention vs TURP for LUTS: post-operative complications, 26:1; blood transfusion, 2.5:1; in-hospital death, 3:1.[1,2]

Failure to void after initial catheter removal: high retention volume, greater age, and low maximum detrusor pressure are predictive for failure to void after TURP. Ten percent in those with acute retention of urine and 40% in those with acute-on-chronic retention fail to void after initial post-TURP TWOC. Overall, 1% of men will fail to void after subsequent TWOCs and will require long-term catheterization.[3]

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2 Pickard R, Emberton M, Neal D (1998) The management of men with acute urinary retention. *Br J Urol* **81**:712–20.

3 Reynard JM (1999) Failure to void after transuretural resection of the prostate and mode of presentation. *Urology* **53**:336–9.

Indications for and technique of urethral catheterization

Indications

- Relief of urinary retention.
- Prevention of urinary retention—a period of post-operative catheterization is commonly employed after many operations where limited mobility makes normal voiding difficult.
- Monitoring of urine output (e.g. post-operatively); prevention of damage to the bladder during Caesarean section.
- Bladder drainage following surgery to the bladder, prostate, or urethra (e.g. TURP, TURBT, open bladder stone removal, radical prostatectomy).
- Bladder drainage following injuries to the bladder.

Technique

Explain the need for and method of catheterization to the patient. Use the smallest catheter—in practical terms, usually a 12Ch, with a 10mL balloon. For longer catheterization periods (weeks), use a silastic catheter to limit tissue 'reaction', thereby reducing risk of a catheter-induced urethral stricture. If clot retention, use a 3-way catheter (20Ch or greater) to allow evacuation of clots and bladder irrigation to prevent subsequent catheter blockage.

Technique is aseptic. One gloved hand is sterile, the other is 'dirty'. Dirty hand holds penis or separates labia to allow cleansing of urethral meatus; this hand should not touch catheter. Use sterile water or sterile cleaning solution to 'prep' skin around meatus.

Apply lubricant jelly to urethra. Traditionally, this contains local anaesthetic (e.g. 2% lignocaine), which takes between 3 and 5min to work. However, a randomized, placebo-controlled trial showed that 2% lignocaine was no more effective for pain relief than anaesthetic-free lubricant,[1] suggesting that it is lubricant action that prevents urethral pain. If using local anaesthetic lubricant, warn patient that it may 'STING'. Local anaesthetic lubricant is contraindicated in patients with allergies to local anaesthetics and in those with urethral trauma where there is a (theoretical) risk of complications arising from systemic absorption of lignocaine. When instilling jelly, do so gently—a sudden, forceful depression of the plunger of the syringe can rupture the urethra! In male, 'milk' gel towards posterior urethra while squeezing meatus to prevent it from coming back out of meatus.

Insert the catheter using sterile hand until flow of urine confirms it is in the bladder. Failure of urine flow may indicate that the catheter balloon is in the urethra. Intraurethral inflation of balloon can rupture urethra. If no urine flows, attempt aspiration of urine using a 50mL bladder syringe (lubricant gel can occlude eye-holes of catheter). Absence of urine flow indicates either catheter is not in the bladder or, if the indication for catheterization is retention, that the diagnosis is wrong

(there will usually be a few mL of urine in the bladder even in cases where the absence of micturition is due to oliguria or anuria so complete absence of urine flow usually indicates the catheter is not in the bladder). If the catheter will not pass into the bladder and you are sure that the patient is in retention, proceed with suprapubic catheterization.

1 Birch BR (1994) Flexible cystoscopy in men: is topical anaesthesia with lignocaine gel worthwhile? *Br J Urol* **73**:155.

Technique of suprapubic catheterization

Indications

- Failed urethral catheterization in urinary retention.
- Preferred site for long-term catheters, e.g. intractable urinary incontinence where other methods have failed; neurological disease (long-term bladder management in spinal cord injury or multiple sclerosis). Long-term *urethral* catheters commonly lead to acquired hypospadias in males (ventral splitting of glans penis) and patulous urethra in females (leading to frequent balloon expulsion and bypassing of urine around the catheter); hence, suprapubic site is preferred for long-term catheters.
- Used in the initial management of urethral trauma where urethral catheterization has failed.

Contraindications

Insertion of suprapubic catheterization is best avoided in:

- Patients with clot retention, the cause of which may be an underlying bladder cancer (the cancer could be 'spread' along the catheter track to involve the skin).
- Patients with known carcinoma of the bladder.
- Patients with lower midline incisions (bowel may be 'stuck' to the deep aspect of the scar, leading to the potential for bowel perforation).
- Pelvic fractures, where the catheter may inadvertently enter the large pelvic haematoma which always accompanies severe pelvic fracture. This can lead to infection of the haematoma and the resulting sepsis can be fatal. Failure to pass a urethral catheter in a patient with a pelvic fracture usually indicates a urethral rupture (confirmed by urethrography) and is an indication for formal open, suprapubic cystotomy.
- Patients on anticoagulation and antiplatelet treatment.
- Abdominal wall sepsis.
- Patients with subcutaneous vascular graft in the suprapubic region, e.g. femoro-femoral cross-over graft.

Assessment prior to insertion

- Ask if previous abdominal surgery in the suprapubic or pelvic region.
- Enquire if there is neurological disease (bladder capacity often small and urethral incompetence in women is common which makes bladder distension difficult; spinal cord injury (SCI) autonomic dysreflexia is common in bladder distension so a spinal or general anaesthetic may be required).
- Abdominal examination: inspect for lower abdominal scars; palpate and percuss the lower abdomen to confirm the bladder is distended.
- Consider stopping anticoagulation (or modifying with heparin 'bridging' therapy) and antiplatelet treatment if safe to do so.

Consent for suprapubic catheter (SPC) insertion

British Association of Urological Surgeons (BAUS) suprapubic catheter practice guidelines. Risks include:

- Haemorrhage, including haematuria and intra-abdominal bleeding.
- Infection, including UTI and infection of track site or wound.
- Pain.
- Injury to abdominal organs.
- General risks of long-term catheterization.

Technique

Local anaesthetic or spinal or general anaesthetic if:

- At risk of autonomic dysreflexia (or at patient's request).
- The bladder cannot be distended sufficiently to allow safe SPC insertion.

Give antibiotic prophylaxis if there is likely to be urine bacterial colonization.

Prior to insertion of trocar, be sure to confirm the diagnosis by:

- Abdominal examination (palpate and percuss lower abdomen to confirm bladder is distended).
- Ultrasound: BAUS suprapubic catheter practice guidelines state that ultrasound can be used to determine if there is interposing bowel in the planned suprapubic track 'if carried out by a competent, trained practitioner'. They do not define 'competent' or 'trained'. They admit that 'the reliability of ultrasonography in excluding the presence of a loop of intestine in the suprapubic region has not been formally evaluated'.
- Aspiration of urine using a 21G (green) needle, usually 2cm above the pubic symphysis.

Use a wide-bore trocar if you anticipate that the catheter will be in place for more than 24h (small-bore catheters will block within a few days). Aim to place the catheter about 2cm above the pubis symphysis. Placement too close to the symphysis will result in difficult trocar insertion (the trocar will hit the symphysis). Instil a few mL of local anaesthetic into the skin of intended puncture site and down to the rectus sheath. Confirm the location of bladder by drawing back on the needle to aspirate urine from the bladder. This helps guide the angle of trocar insertion. Make a 1cm incision with a sharp blade through the skin. Hold the trocar handle in your right hand and steady the needle end with your left hand (this hand helps prevent insertion too deeply). Push the trocar in the same direction in which you previously aspirated urine. As soon as urine issues from the trocar, withdraw the latter, holding the attached sheath in place. Push the catheter in as far as it will go. Inflate the balloon. Peel away the side of the sheath and remove it.

Complications of urethral and suprapubic catheters

At the time of insertion

- Bowel perforation that accounts for the reported mortality of SPC insertion of 1–2%.[1,2] Try to avoid the temptation to describe SPC insertion as a 'minor' procedure. BAUS suprapubic catheter practice

guidelines state the patient and their carers should be given written guidance, including instructions for 'prompt referral to the team who inserted the catheter if the patient is unexpectedly unwell and/or has marked abdominal pain. The instructions should include contact numbers and clear instructions to make contact in the event of bleeding that is either heavy or persistent, symptoms to suggest infection, or the presence of lower abdominal pain that is failing to improve or spreading away from the immediate catheter site'.

- Persistent haematuria (may require bladder washouts and even very occasionally, return to theatres for cystoscopic diathermy of the bleeding point if it can be found). Pass a urethral catheter to assist bladder washouts and irrigation. Pull the SPC balloon back against the anterior bladder wall to tamponade the bleeding.
- Track site or wound infection. Antibiotics and if an abscess, incision and drainage. The author has never seen a case of cellulitis, 'track infection', or abscess in over 500 SPC insertions in patients at high risk of these potential complications, i.e. SCI patients with urine bacterial colonization. He advises patients of the very common occurrence of granulation tissue around the SPC track and that this does not represent track infection and should not be treated with antibiotics. The track often takes many months to 'mature', i.e. for skin to grow down the track. BAUS suprapubic catheter practice guidelines state 'Systemic antibiotics should not be used to treat uncomplicated pericatheter discharge or asymptomatic bacteriuria'.

Long-term problems and complications:

- **Recurrent UTIs.** The definition of what represents a 'UTI' is a source of much confusion and the cause of much inappropriate prescribing of antibiotics, which inevitably leads to the development of resistant bacteria in the urine. Inevitably, any foreign body in the bladder will become colonized with bacteria very rapidly. We do not regard the mere presence of bacteria or pus cells (of whatever number) as indicative of a UTI (the presence of bacteria in the absence of constitutional symptoms of feeling unwell, fever, and cloudy smelly urine is not regarded as 'active' infection, but rather is better termed 'colonization'). Avoid the temptation to prescribe antibiotics for mere colonization. Symptomatic UTIs (fever, feeling generally unwell, smelly cloudy urine) can be a very difficult problem to manage. Not infrequently, patients (particularly those with SCI managed with long-term catheter drainage) report such symptoms in the absence of *any* bacterial growth in the urine. Others report feeling perfectly well, for months on end, in the face of urine that is full of bacteria! Remember, although short courses of antibiotics (7–10 days) may resolve what we think may be the symptoms of UTI, no amount of antibiotics will, over the long term, be able to sterilize the urine of a patient with a foreign body such as a catheter in it. Low-dose antibiotics (a quarter of the normal daily treatment dose) may keep the symptoms at bay or reduce the frequency of 'infective' episodes (but long-term use of nitrofurantoin or trimethoprim—two popular low-dose antibiotics—is associated, albeit rarely, with severe side effects such

as blood dyscrasias or pulmonary fibrosis). In some patients, the only solution is to change bladder management. There is a greater risk of pyelonephritis in the chronically catheterized patient.

- **Catheter blockages** due to encrustation of the lumen of the catheter with bacterial biofilms. *Proteus mirabilis*, *Morganella* and *Providencia* species secrete a polysaccharide matrix. Within this, urease-producing bacteria generate ammonia from nitrogen in urine, raising urine pH and precipitating magnesium and calcium phosphate crystals. The matrix–crystal complex blocks the catheter. Catheter blockage causes bypassing which soils the patient's clothes. Bladder distension can cause autonomic dysreflexia in patients with thoracic or cervical spinal cord injuries, leading to extreme rises in blood pressure that, believe it or not, can cause stroke and death! Regular bladder washouts and increased catheter size sometimes help. There is a suggestion, based on *in vitro* experiments on catheters in the laboratory, that intermittent catheter drainage (by the use of a valve inserted between the catheter and the drainage bag) can reduce the likelihood of catheter blockages. Whether this holds true in patients remains to be documented.
- **Bladder stone formation**, necessitating surgical removal (endoscopic or open cystolithotomy) occurs in 1 in 4 patients followed over a 5y period.[3]
- **'Track' problems at the time of catheter changes:** difficultly removing the catheter (some catheter balloons have a 'memory', retaining an awkward shape such that they resist removal); difficulty reinserting the catheter (may require repositioning of the SPC site).
- In female patients managed by a long-term urethral catheter, the pressure of the catheter can cause urethral and bladder neck erosion, leading to a so-called patulous urethra. In the male, a long-term urethral catheter can lead to pressure atrophy of the meatus of the penis, leading to an acquired hypospadias ('kippering' of the glans penis and even the shaft of the penis). While a mild acquired hypospadias has no great functional effect, cosmetically it does.
- **Catheter bypassing**, either around the suprapubic site or per urethra. Management is empirical. Try as small a balloon size as possible. If the leakage is due to bladder spasms, then a smaller balloon may possibly reduce their intensity and frequency. Anticholinergics may help as may intravesical botox injections. Other options include condom sheath drainage (in men) or bladder neck closure. This is not the minor operation ('just a few stitches') that patients are sometimes led to believe and often—30% of cases—the closure breaks down so the leak persists. Bladder neck closure is irreversible and access to the bladder via the suprapubic track is not always easy, particularly if access to the ureteric orifices is required for upper tract endoscopy.
- **Bladder cancer** (SCC of the bladder): there is conflicting evidence regarding the incidence of bladder cancer in SCI patients, some studies suggesting an increased risk and others suggesting the risk is the same as in the non-spinal injured population.[4] The author feels that the risk of SCC is greater than in the ambulant, non-catheterized population, but that the risk is still low. The pathogenesis is likely to involve chronic bacterial colonization of the bladders of spinal patients,

whether managed with indwelling catheters, ISC, or sheath drainage and so the presence of the catheter *per se* is not enough to induce development of a cancer. Screening cystoscopy studies have either failed to result in a downstaging of bladder cancer when compared with non-screened patients or have simply not detected any cases of bladder cancer. Screening cystoscopy remains a subject of debate.[5]

Catheter care

- When should the first change be done and who should do it? BAUS suprapubic catheter practice guidelines state 'It is not necessary for the first catheter change to be carried out by the team who inserted the catheter; the first change is generally deferred for at least 2 weeks (and typically 6–12 weeks) after catheter insertion to allow the track to 'mature'.
- How often should the catheter be changed? Usually 6 weekly to 3 monthly, but there is no hard and fast rule that a catheter must be changed at a given interval.
- To maintain bladder capacity over the long term, should the catheter be clamped and should long-term anticholinergic medication be given? Nice idea in theory, but no evidence of efficacy of either method.
- Can a flip-flow valve be used to allow intermittent bladder emptying? Yes, as long as the patient does not get autonomic dysreflexia with bladder distension and does not leak urethrally with a full bladder.
- Can the patient or carer change the SPC? Yes, if adequately trained.
- What should I do for bypassing of urine (leakage of urine either per urethra or around the SPC)? Try anticholinergics and if this fails bladder botox injections. If all else fails, a bladder neck or urethral closure may be necessary.
- The catheter keeps blocking. What can I do? BAUS suprapubic catheter practice guidelines state that 'Repeated catheter blockages are frequently related to the development of bladder calculi'. The author agrees that blockages are 'related to' the same process that causes bladder stones, but catheter blockages are not caused by bladder stones for in the authors' experience of managing many, many hundreds of patients with bladder stones, such stones are often far too large to block the catheter eye-holes. Catheter blockages and bladder stones are caused by the same process—chronic bacterial colonization of the bladder and any artificial device left within the bladder such as a catheter, followed by the development of a biofilm around the colonies of bacteria, followed by infiltration of this biofilm with calcium and phosphate. This is the process of catheter encrustation (which blocks catheters) and it is also the process of bladder stone formation. Where blockages become problematic, increase the SPC size, increase fluid intake, and consider bladder washouts (daily or every few days)—the evidence base for the efficacy of all of this is weak. The evidence base for *in vivo* use of a flip-flow valve to stop blockages is non-existent. In the authors' experience, full-dose courses of antibiotics or low-dose prophylactic antibiotics only very occasionally resolve this problem and more often than not, lead to the emergence of multiresistant bacteria in the urine.

1 Ahluwalia RS, Johal N, Kouriefs C, *et al.* (2006) The surgical risk of suprapubic catheter insertion and long-term sequelae. *Ann R Coll Surg Engl* **88**: 171–6.

2 Sheriff MK, Foley S, McFarlene J, *et al.* (1998) Long-term suprapubic catheterization: clinical outcome and satisfaction survey. *Spinal Cord* **36**:171–6.

3 Ord J, Lunn D, Reynard J (2003) Bladder management and risk of bladder stone formation in spinal cord injured patients. *J Urol* **170**:1734–7.

4 Subramonian K, Cartwright RA, Harnden P, Harrison SCW (2004) Bladder cancer in patients with spinal cord injuries. *Br J Urol Int* **93:**739–43.

5 Hamid R, Bycroft J, Arya M, Shah PJ (2003) Screening cystoscopy and biopsy in patients with neuropathic bladder and chronic suprapubic indwelling catheters: is it valid? *J Urol* **170**(2 Pt 1):425–7.

Further reading

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Warren JW, Muncie HL, Hebel JR, Hall-Craggs M (1994) Long-term urethral catheterisation increases risk of chronic pyelonephritis and renal inflammation. *J Am Geriatr Soc* **42:**1286–90.

Management of nocturia and nocturnal polyuria

Nocturia is often particularly resistant to treatment.

First, establish whether the patient is polyuric (>3L of urine/24h) by getting them to complete a frequency volume chart. If they are polyuric, this may account for their daytime and night-time voiding frequency. Establish whether they have a solute or water diuresis and the causes thereof (Box 4.1).

If non-polyuric (<3L urine output/24h), determine the *distribution* of urine output over the 24h period. If >1/3 of urine output is between the hours of midnight and 8 a.m., then the patient has nocturnal polyuria (NP).

If there is nocturnal polyuria, exclude other medical causes—diabetes mellitus and inspidus, adrenal insufficiency; hypercalcaemia; liver failure; polyuric renal failure; chronic heart failure; obstructive sleep apnoea, dependent oedema; chronic venous stasis; calcium channel blockers; diuretics; selective serotonin reuptake inhibitor antidepressants.

Non-polyuric nocturia

BPH medical therapy

The impact of alpha blockers, 5α-reductase inhibitors, and anticholinergics on nocturia is modest.

TURP

Nocturia persists in 20–40% of men after TURP.

Medtronic Interstim therapy for nocturia

Patients preselected on the basis of a favourable symptomatic response to a test stimulation can experience a reduction in nocturia,[1] but not all patients respond to the test stimulation and the treatment is expensive and not yet widely available in all countries.

Treatment for NP

The evidence base for NP treatments is limited (very few randomized, placebo-controlled trials).

Fluid restriction

Many patients have reduced their afternoon and evening fluid intake in an attempt to reduce their night-time diuresis.

Diuretics

Diuretics, taken several hours before bedtime, reduce nocturnal voiding frequency in some patients.[2,3]

DDAVP

A synthetic analogue of arginine vasopressin (endogenous ADH) which, if taken at night, can reduce urine flow by its antidiuretic action. It has been suggested that NP may be caused by a lack of endogenous production of ADH in elderly people. However, adults both with and without NP have *no* rise in ADH at night (i.e. ADH secretion remains remarkably *constant* throughout the day in adults with and without NP). Furthermore,

the diuresis in adults with NP is a *solute* diuresis due to a nocturnal natriuresis.[4] Thus, lack of ADH secretion at night is *not* the cause of the diuresis in nocturnal polyuric adults and, therefore, from a theoretical perspective, there is no logical basis for using desmopressin in NP.[5] There is limited evidence that it reduces night-time voiding frequency (at least in responder enrichment studies) and increases sleep duration in a proportion of patients with NP.[6]

Side effects Hyponatraemia (Na <130mmol/L) in 5% of patients. Measure serum Na 3 days after starting DDAVP and stop if hyponatraemia develops.[3]

Box 4.1 Investigation of the polyuric patient (urine output >3L per 24h)

- **Urine osmolality?**
  - >250mOsm/kg = solute diuresis.
  - <250mOsm/kg = water diuresis.
- **Solute diuresis**: poorly controlled diabetes mellitus, saline loading (e.g. post-operative diuresis), diuresis following relief of HPCR.
- **Water diuresis**: primary polydipsia, diabetes insipidus (nephrogenic—e.g. lithium therapy, central—ADH deficiency).

Nocturia and sleep apnoea

Obstructive sleep apnoea (OSA) is highly prevalent in those over 65y of age. It is often manifested by snoring. There is a strong association between OSA symptoms and nocturia.[7] Large negative intrathoracic pressure swings may trigger a cardiac-mediated natriuresis and hence, cause NP.

1 Spinelli M (2003) New sacral neuromodulation lead for percutaneous implantation using local anesthesia: description and first experience. *J Urol* **170**:1905–7.

2 Reynard JM, Cannon A, Yang Q, Abrams P (1998) A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. *Br J Urol* **81**:215–8.

3 National Institute for Health and Clinical Excellence (2010) The management of lower urinary tract symptoms in men [online]. Available from: www.nice.org.uk/CG97.

4 Matthiesen TB, Rittig S, Norgaard JP, Pedersen EB, Djurhuus JC (1996) Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. *J Urol* **156**:1292–9.

5 McKeigue P, Reynard J (2000) Relation of nocturnal polyuria of the elderly to essential hypertension. *Lancet* **355**:486–8.

6 Mattiasson A (2002) Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. *Br J Urol* **89**:855–62.

7 Umlauf M (1999) Nocturia and sleep apnea symptoms in older patients: clinical interview. *Sleep* **22**:S127.

Chronic retention

Anyone who retains a certain volume of urine in their bladder after voiding or attempted voiding can be said to be in chronic retention. For those who retain the ability to pass urine, such a situation can be termed 'chronic retention' and this may be low pressure (normal creatinine and absence of hydronephrosis on ultrasound) or high pressure (raised creatinine which falls post-catheterization, usually with hydronephrosis on ultrasound). Those with chronic retention who suddenly become unable to pass urine (and this is usually painful) can be said to have developed acute-on-chronic retention. Again, this can be low pressure or high pressure. A workable definition (one that is related to the outcome of TURP) for the acute setting of painful inability to void is that acute retention (non-chronic) is painful inability to void with a catheterization volume of <800mL and acute-on-chronic retention is painful inability to void with a catheterization volume of >800mL.[1]

In the context of chronic retention, precisely what 'a certain volume' means is variably defined. Some say a patient has chronic retention when they consistently leave 300mL behind post-void, others 800mL[2,3], and NICE[4] describes it as a residual volume >1000mL or the presence of a palpable/percussable bladder (though the bladder can certainly be palpated or percussed when containing <1000mL so this definition is not strictly consistent).

The 2010 NICE guidelines on management of LUTS in men provide a useful algorithm for management of chronic retention (Fig. 4.3). A creatinine and renal ultrasound are done.

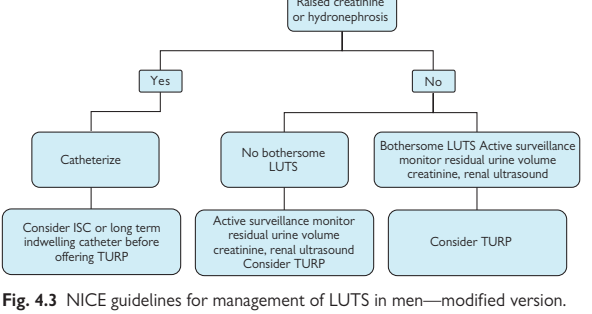

Fig. 4.3 NICE guidelines for management of LUTS in men—modified version.

1 Reynard JM (1999) Failure to void after transuretural resection of the prostate and mode of presentation. *Urology* **53**:336–9.

2 Mitchell JP (1984) Management of chronic urinary retention. *BMJ* **289**:515–6.

3 Abrams P, Dunn M, George N (1978) Urodynamic findings in chronic retention of urine and their relevance to results of surgery. *BMJ* **2**:1258–60.

4 National Institute for Health and Clinical Excellence (2010) The management of lower urinary tract symptoms in men [online]. Available from: www.nice.org.uk/CG97.

High-pressure chronic retention (HPCR)

In the 2nd edition of this book, this was defined as maintenance of voiding, with a bladder volume of >800mL and an intravesical pressure above 30cmH_2O, accompanied by hydronephrosis[1,2] and since this definition has been shown to be helpful in predicting the outcome of the commonest surgical treatment for urinary retention,[1] it is one that I have decided to keep for this 3rd edition. Over time, this leads to renal failure. When the patient is suddenly unable to pass urine, acute-on-chronic high-pressure retention of urine has occurred.

A man with high-pressure retention who continues to void spontaneously may be unaware that there is anything wrong. He will often have *no* sensation of incomplete emptying and his bladder seems to be insensitive to the gross distension. Often, the first presenting symptom is that of bedwetting. This is such an unpleasant and disruptive symptom that it will cause most people to visit their doctor. Visual inspection of the patient's abdomen may show marked distension due to a grossly enlarged bladder. The diagnosis of chronic retention can be confirmed by palpation of the enlarged, tense bladder which is dull to percussion.

Acute treatment

Catheterization relieves the pressure on the kidneys and allows normalization of renal function. A large volume of urine is drained from the bladder (often in the order of 1–2L and sometimes much greater). The serum creatinine is elevated and an ultrasound will show hydronephrosis with a grossly distended bladder if the scan is done before relief of retention.

Anticipate a profound diuresis following drainage of the bladder due to:

- Excretion of salt and water that has accumulated during the period of renal failure.
- Loss of the corticomedullary concentration gradient, due to continued perfusion of the kidneys with diminished flow of urine through the nephron (this washes out the concentration gradient between the cortex and medulla).
- An osmotic diuresis caused by elevated serum urea concentration.

A small percentage of patients have a postural drop in blood pressure. It is wise to admit patients with HPCR for a short period of observation until the diuresis has settled. A few will require intravenous fluid replacement if they experience a symptomatic fall in blood pressure when standing.

Definitive treatment

TURP or a long-term catheter. In those unable to void who have been catheterized, a TWOC is clearly not appropriate in cases where there is back pressure on the kidneys. Rarely, a patient who wants to avoid a TURP and does not want an indwelling catheter will be able to empty their bladder by ISC.

1 Reynard JM (1999) Failure to void after transuretural resection of the prostate and mode of presentation. *Urology* **53**:336–9.

2 Mitchell JP (1984) Management of chronic urinary retention. *BMJ* **289**:515–6.

Bladder outlet obstruction and retention in women

Relatively rare (~5% of women undergoing pressure flow studies have BOO, compared with 60% of unselected men with LUTS).[1,2]

It may be symptom-free, and present with LUTS or as acute urinary retention. In broad terms, the causes are related to obstruction of the urethra (e.g. urethral stricture, compression by a prolapsing pelvic organ such as the uterus, post-surgery for stress incontinence) or have a neurological basis (e.g. injury to sacral cord or parasympathetic plexus, degenerative neurological disease, e.g. MS, diabetic cystopathy).

Voiding studies in women

Women have a higher Qmax, for a given voided volume than do men. Women with BOO have lower Qmax than those without BOO. There are no universally accepted urodynamic criteria for diagnosing BOO in women.

Treatment of BOO in women

Treat the cause (e.g. dilatation of a urethral stricture; repair of a pelvic prolapse). Where this it is not possible (because of a neurological cause such as MS or SCI), the options are:

- ISC or intermittent catheterization by a carer.
- Indwelling catheter (preferably suprapubic rather than urethral).
- Mitrofanoff catheterizable stoma.

Where urethral intermittent self-catheterization is technically difficult, a catheterizable stoma can be constructed between the anterior abdominal wall and the bladder, using the appendix, Fallopian tube, or a narrowed section of small intestine. This is the Mitrofanoff procedure. It is simply a new urethra which has an abdominal location rather than a perineal one and is, therefore, easier to access for ISC.

For women with a suprasacral SCI with preserved detrusor contraction and urinary retention due to DSD, sacral deafferentation combined with a Brindley stimulator can be used to manage the resulting urinary retention.

Fowler's syndrome

A primary disorder of sphincter relaxation (as opposed to secondary to, for example, SCI). Increased electromyographic activity (repetitive discharges on external sphincter EMG) can be recorded in the external urethral sphincters of these women (which, on ultrasound, are of increased volume) and is hypothesized to cause impaired relaxation of external sphincter. Occurs in premenopausal women, typically aged 15–30, often in association with polycystic ovaries (50% of patients), acne, hirsutism, and menstrual irregularities. May also be precipitated by childbirth or gynaecological or other surgical procedures. They report no urgency with bladder volumes >1000mL, but when attempts are made to manage their retention by ISC, they experience pain, especially on withdrawing the catheter.

Pathophysiology: may be due to a channelopathy of the striated urethral sphincter muscle, leading to involuntary external sphincter contraction.

Treatment: ISC, sacral neuromodulation with Medtronic Interstim (90% void post-implantation and 75% are still voiding at 3y follow-up). The mechanism of action of sacral neuromodulation in urinary retention is unknown.

1 Madersbascher S, Pycha A, Klingler CH, *et al.* (1998) The aging lower urinary tract: a comparative urodynamic study of men and women. *Urology* **51**:206–12.

2 Swinn MJ, Wiseman OJ, Lowe E, Fowler CJ (2002) The cause and treatment of urinary retention in young women. *J Urol* **167**:151–6.

Urethral strictures and stenoses

A urethral stricture is a scar in the subepithelial tissues of the corpus spongiosum which constricts the lumen of the urethra. Since it is only the *anterior* urethra that is surrounded by the corpus spongiosum, by consensus, urethral strictures are said only to affect the *anterior* urethra (Mundy).[1] A narrowing of the caliber of the posterior urethra is termed a stenosis.

Anterior urethral strictures

The process of scar formation occurs in the spongy erectile tissue (corpus spongiosum) of the penis that surrounds the urethra—spongiofibrosis.

- Inflammation (e.g. balanitis xerotica obliterans—BXO), gonococcal infection leading to gonococcal urethritis (less common nowadays because of prompt treatment of gonorrhoea).
- Trauma.
  - Straddle injuries—blow to bulbar urethra (e.g. cross-bar injury).
  - Iatrogenic—instrumentation (e.g. traumatic catheterization, traumatic cystoscopy, TURP, bladder neck incision).

The role of non-specific urethritis (e.g. *Chlamydia*) in the development of anterior urethral strictures has not been established.

Posterior urethral stenoses

Fibrosis of the tissues around the urethra results from trauma—pelvic fracture or surgical (radical prostatectomy, TURP, urethral instrumentation). By consensus, they are now described as stenosis and are no longer described as strictures. These are essentially *distraction* injuries (leading to a stenosis of the urethra), where the posterior urethra has been pulled apart and the subsequent healing process results in the formation of a scar which contracts and thereby narrows the urethral lumen.

Symptoms and signs of urethral stricture

- Voiding symptoms—hesitancy, poor flow, post-micturition dribbling.
- Urinary retention—acute, or high pressure acute-on-chronic.
- Urinary tract infection—prostatitis, epididymitis.

Management of urethral strictures

Where the patient presents with urinary retention, the diagnosis is usually made following a failed attempt at urethral catheterization. In such cases, avoid the temptation to 'blindly' dilate the urethra. Dilatation may be the wrong treatment option for this type of stricture—it may convert a short stricture, which could have been cured by urethrotomy or urethroplasty, into a longer and more dense stricture, thus committing the patient to more complex surgery and a higher risk of recurrent stricturing. Place a suprapubic catheter instead and image the urethra with retrograde and antegrade urethrography to establish the precise position and the length of the stricture.

Similarly, avoid the temptation to inappropriately dilate a urethral stricture diagnosed at flexible cystocopy (urethroscopy). Arrange retrograde urethrography so appropriate treatment can be planned.

Treatment options

Urethral dilatation: designed to stretch the stricture without causing more scarring; bleeding post-dilatation indicates tearing of the stricture (i.e. further injury has been caused) and re-stricturing is likely.

Internal (optical) urethrotomy: stricture incision with an endoscopic knife or laser. Divides the stricture, followed by epithelialization of the incision. If deep spongiofibrosis is present, the stricture will recur. Best suited for short (<1.5cm) bulbar urethral strictures with minimal spongiofibrosis.[2] Leave a catheter for 3–5 days (what evidence there is suggests keeping a catheter for 3 days reduces the risk of extravasation of urine and infective complications that may result;[1] longer catheterization does not reduce long-term re-stricturing). Consider ISC for 3–6 months, starting several times daily, reducing to once or twice a week towards the end of this period. For strictures in other parts of the anterior urethra or where there has been a previous optical urethrotomy or dilatation, an optical urethrotomy will almost certainly fail to cure the stricture. Avoid optical urethrotomy for sphincter strictures (e.g. post-TURP) because the sphincter may be rendered incompetent—dilatation is a safer option.

Excision and reanastomosis or tissue transfer: best chance of cure; excises the area of spongiofibrosis with primary re-anastomosis or closure of defect with buccal mucosa or pedicled skin flap. Stricturotomy and buccal mucosal grafting, rather than transecting the entire urethra and then re-anastomosing it, is becoming increasingly popular (but not for strictures that obliterate the entire urethral lumen).

A stepwise progression up this 'reconstructive ladder' (the process of starting with a simple procedure and moving onto the next level of complexity when this fails) is not appropriate for every patient. For the patient who wants the best chance of long-term cure, offer excision and re-anastomosis or tissue transfer up front. For the patient who is happy with lifelong 'management' of his stricture (with repeat dilatation or optical urethrotomy), offer dilatation or optical urethrotomy.

Balanitis xerotica obliterans (BXO)

Genital lichen sclerosis and atrophicus in the male. Hyperkeratosis is seen histologically. Appears as a white plaque on the foreskin, glans of the penis, or within the urethral meatus. Most common cause of stenosis of the meatus. Foreskin becomes thickened and adheres to the glans, leading to phimosis (a thickened, non-retractile foreskin). Patients with longstanding BXO and meatal stenosis often have more proximal urethral strictures.

1 Mundy AR, Andrich DE (2010) Urethral strictures. *BJU Int* **107**:6-26.

2 Pansadoro V, Emiliozzi P (1996) Internal urethrotomy in the management of anterior urethral strictures: long term follow-up. *J Urol* **156**:73–5.

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Chapter 5

Incontinence and female urology

Incontinence: classification

Definition

Urinary incontinence (UI) is the complaint of any involuntary leakage of urine.[1] It results from a failure to store urine during the filling phase of the bladder due to dysfunction of the bladder smooth muscle (detrusor), urethral sphincter, or anatomical abnormalities (congenital or acquired). Urine loss is either urethral or extraurethral (i.e. due to ectopic ureter or vesicovaginal fistula).

Prevalence

There is wide variation in the reported prevalence of UI worldwide. It affects about 3.5 million people in the UK. The prevalence is approximately twice as common in females compared to males and increases with age (Table 5.1).[2] International studies show a gradual increase in the prevalence of female UI during adulthood to 30%, stabilizing between the ages of 50 and 70y old, before rising again.[3] Approximately 50% of women suffer stress UI, 11% urgency UI, and 36% mixed UI.[3]

Classification

Stress urinary incontinence (SUI): involuntary urinary leakage on effort, exertion, sneezing, or coughing.[1] It is due to hypermobility of the bladder base, pelvic floor and/or intrinsic urethral sphincter deficiency. When confirmed on urodynamic testing, it is termed urodynamic stress incontinence. It was further categorized by Blaivas[4] (using videourodynamics) into:

- **Type 0:** report of UI, but without clinical signs.
- **Type I:** leakage that occurs during stress with <2cm descent of the bladder base below the upper border of the symphysis pubis.
- **Type II:** leakage on stress accompanied by marked bladder base descent (>2cm) that occurs only during stress (II_a) or is permanently present (II_b).
- **Type III:** bladder neck and proximal urethra are already open at rest (with or without descent), which is also known as intrinsic sphincter deficiency (ISD).

Urgency urinary incontinence (UUI): involuntary urine leakage accompanied by or immediately preceded by urgency (a sudden, strong desire to void).[1] Previously called 'urge' urinary incontinence, it is due to an overactive detrusor muscle. The urodynamic diagnosis is termed 'detrusor overactivity incontinence'. It is a component of the overactive bladder syndrome (see OAB 📖 p. 148).

Mixed urinary incontinence (MUI): involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing.[1] It contains symptoms of both SUI and UUI.

Overflow incontinence: is leakage of urine when the bladder is abnormally distended with large residual volumes. Typically, men present with chronic urinary retention (with a degree of detrusor failure) and dribbling incontinence. This can lead to back pressure on the kidneys and renal failure in 30% of patients. BOO must be corrected; detrusor failure can be managed with clean intermittent self-catheterization (CISC) or indwelling catheter.

Nocturnal enuresis: the complaint of loss of urine occurring during sleep.[1] The prevalence in adults is about 0.5%[5] and 7–10% in children aged 7y old.[6] Nocturnal enuresis can be further classified into primary types (never been dry for longer than a 6-month period) or secondary (the re-emergence of bedwetting after a period of being dry for at least 6–12 months; see 🕮 p. 694). In an adult male, nocturnal incontinence may be an indicator of high-pressure chronic retention (see 🕮 p. 120).

Post-micturition dribble: involuntary loss of urine immediately after the individual has finished passing urine, usually after leaving the toilet in men or after rising from the toilet in women.[1] In men, it is due to pooling of urine in the bulbous urethra after voiding.

A recent standardization report by the International Urogynaecology Association and the International Continence Society on female pelvic floor dysfunction[7] recommend new definitions, including:

- **Continuous incontinence:** the complaint of continuous involuntary loss of urine.
- **Insensible incontinence:** the complaint of UI where the women has been unaware of how it occurred.
- **Coital incontinence:** the complaint of involuntary loss of urine with coitus.

Table 5.1 Prevalence of urinary incontinence in the UK

Age (y)	Females	Males
15–44	5–7%	3%
45–64	8–15%	3%
65+	10–20%	7–10%

1 Abrams P, Cardozo L, Fall M, *et al.* (2002) The standardization of terminology of lower urinary tract function: report from the standardization sub-committee of the International Continence Society. *Neurourol Urodyn* **21**:167–78.

2 Royal College of Physicians. *Incontinence: causes, management and provision of services.* Report of a working party. London: RCP 1995. Available from: www.rcplondon.ac.uk.

3 Hannestad YS, Rortveit G, Sandvik H, *et al.* (2000) A community-based epidemiological survey of female urinary incontinence: The Norwegian EPINCONT Study. *J Clin Epidemiol* **53**:1150–7.

4 Blaivas JG, Olsson CA (1988) Stress incontinence: classification and surgical approach. *J Urol* **139**:727–31

5 Hirasing RA, van Leerdam FJM, Bolk-Bennink L, *et al.* (1997) Enuresis nocturna in adults. *Scan J Urol Nephrol* **31**:533–6.

6 Abrams P, Cardozo L, Khoury S, Wein A (2009) *Epidemiology of Urinary and Faecal Incontinence and Pelvic Organ Prolapse.* 4th International Consultation on Incontinence, pp 39–41. London: Health Publications Ltd.

7 BT Haylen, D de Ridder, RM Freeman, *et al.* (2010) An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J* **21**:5–26.

Incontinence: causes and pathophysiology

General risk factors for UI

Predisposing factors

- Gender (female > males).
- Race (Caucasian > Afro-Caribbean).
- Genetic predisposition.
- Neurological disorders (spinal cord injury (SCI), stroke, multiple sclerosis, Parkinson's disease).
- Anatomical disorders (vesicovaginal fistula, ectopic ureter in girls, urethral diverticulum, urethral fistula, bladder exstrophy, epispadias)
- Childbirth (vaginal delivery, increasing parity) and pregnancy.
- Anomalies in collagen subtype.
- Pelvic, perineal, and prostate surgery (radical hysterectomy, prostatectomy, TURP), leading to pelvic muscle and nerve injury.
- Radical pelvic radiotherapy.
- Diabetes.

Promoting factors

- Smoking (causing chronic cough and raised intra-abdominal pressure).
- Obesity.
- Infection (UTI).
- Increased fluid intake.
- Medications (i.e. alpha blockers in women).
- Poor nutrition.
- Ageing.
- Cognitive deficits.
- Poor mobility.
- Oestrogen deficiency.

Pathophysiology

Urodynamic studies can help determine the underlying aetiology for UI.

Bladder abnormalities

Detrusor overactivity: a urodynamic observation characterized by involuntary bladder muscle (detrusor) contractions during the filling phase of the bladder, which may be spontaneous or provoked and can consequently cause UI. The underlying cause may be neuropathic where there is a relevant neurological condition or idiopathic where there is no defined cause. It leads to the symptoms of urgency incontinence and overactive bladder (OAB).

The pathogenesis of detrusor overactivity is most likely to be multifactorial. Theories include:

- **Myogenic hypothesis:** partial detrusor denervation, leading to increased excitability and activity between muscle cells.[1]
- **Neurogenic hypothesis:** disruption of primary neural control in muscle cells.[2]

- **Integrative hypothesis:** detrusor muscle is arranged in modules which are thought to be controlled by a peripheral myovesical plexus composed of intramural ganglia and interstitial cells. Detrusor overactivity results from abnormal or exaggerated peripheral autonomic activity (within this plexus).[3]

Low bladder compliance: characterized by a decreased volume-to-pressure relationship where there is a high increase in bladder pressure during filling due to alterations in elastic properties of the bladder wall or changes in muscle tone (secondary to myelodysplasia, SCI, radical hysterectomy, interstitial or radiation cystitis).

Urethral and sphincter abnormalities

In females, there may be functional abnormalities of urethral hypermobility and/or ISD. These are the main causes of SUI.

Urethral hypermobility: due to a weakness of pelvic floor support, causing a rotational descent of the bladder neck and proximal urethra during increases in intra-abdominal pressure. If the urethra opens concomitantly, there will be urinary leaking.

Intrinsic sphincter deficiency: describes an intrinsic malfunction of the sphincter, regardless of its anatomical position, which is responsible for type III SUI (described by McGuire). Causes include inadequate urethral compression (previous urethral surgery, ageing, menopause, radical pelvic surgery, anterior spinal artery syndrome) or deficient urethral support (pelvic floor weakness, childbirth, pelvic surgery, menopause). In males, the urethral sphincter may be damaged after prostatic or pelvic surgery (TURP, radical prostatectomy) or radiotherapy.

Theories for the pathogenesis of SUI include:

- **Integral theory:** laxity of anterior vaginal wall and pubourethral ligaments, causing bladder neck hypermobility.[4]
- **Hammock hypothesis:** failure of support of urethra by the endopelvic fascia and vaginal wall.[5]

1 Brading AF (1997) A myogenic basis for the overactive bladder. *Urology* **50**:57–67

2 De Groat WC (1997) A neurological basis for the overactive bladder. *Urology* **50**:36–52.

3 Drake MJ, Mills IW, Gillespie JI (2001) Model of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function. *Lancet* **358**:401–3.

4 Petros PE, Ulmsten UI (1990) An integral theory of female urinary incontinence. Experimental and clinical considerations. *Acta Obstet Gynecol Scand Suppl.* **153:**7–31.

5 DeLancey JO (1994) Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. *Am J Obstet Gynecol* **170**:1713–20.

Incontinence: evaluation

History

Aim: to establish the type of incontinence (stress, urgency or mixed). Enquire about LUTS (storage or voiding symptoms); triggers for incontinence (cough, sneezing, exercise, position, urgency); frequency, severity, and degree of bother of symptoms. Establish risk factors (abdominal/pelvic surgery or radiotherapy, neurological disorders, obstetric and gynaecology history, medications). Enquire about bowel function and symptoms of sexual dysfunction and pelvic organ prolapse in women (see 🕮 p. 170) A validated patient-completed questionnaire is helpful to assess initial symptoms and patient-reported outcome following intervention (ICIQ-UI short form,[1,5] ICIQ-FLUTS,[2] ICIQ-MLUTS,[3] SF36 QoL[4]) (Fig. 5.1).

'Red flag' symptoms which require further specific investigation are incontinence associated with pain, haematuria, recurrent UTI, significant voiding or obstructive symptoms, and a previous history of pelvic surgery/radiotherapy.

Physical examination

Women

Perform a chaperoned pelvic examination in the supine, standing, and left lateral position with a Sim's speculum. Ask the patient to cough or strain and inspect for anterior and posterior vaginal wall prolapse, uterine or vaginal vault descent, and urinary leakage (stress test). Internal pelvic examination can be performed to assess the strength of voluntary pelvic floor muscle strength and for bladder neck mobility. Inspect the vulva for oestrogen deficiency (causing vaginal atrophy), which may require topical oestrogen treatment. Calculate of body mass index (BMI) as a tool to counsel patients as higher BMIs are associated with incontinence.

Both sexes

Examine the abdomen for a palpable bladder (indicating urinary retention if the patient has recently passed urine). A neurological examination should include assessment of gait, anal reflex, perineal sensation, and lower limb function. DRE should be performed to exclude constipation, a rectal mass, and to test anal tone.

'Red flag' signs requiring further investigation include (new) neurological deficit, haematuria, urethral, bladder or pelvic masses, and suspected fistula.

Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1 Please write in your date of birth: ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

2 Are you *(tick one)*: Female ☐ Male ☐

3 How often do you leak urine? *(Tick one box)*

never	☐	0
about once a week or less often	☐	1
two or three times a week	☐	2
week once a day	☐	3
several times a day	☐	4
all the time	☐	5

4 We would like to know how much urine you think leaks.
How much urine do you usually leak (whether you wear protection or not)? *(Tick one box)*

none	☐	0
a small amount	☐	2
a moderate amount	☐	4
a large amount	☐	6

5 Overall, how much does leaking urine interfere with your everyday life?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

ICIQ score: sum scores 3+4+5 ☐☐

6 When does urine leak? *(Please tick all that apply to you)*

never – urine does not leak	☐
leaks before you can get to the toilet	☐
leaks when you cough or sneeze	☐
leaks when you are asleep	☐
leaks when you are physically active/exercising	☐
leaks when you have finished urinating and are dressed	☐
leaks for no obvious reason	☐
leaks all the time	☐

Thak you very much for answering these questions.

Fig. 5.1 International Consultation on Incontinence Modular Questionnaire, ICIQ UI SF (short form). Reproduced with permission from: Abrams P, Cardozo L, Khoury S, Wein A. (eds) (2009) 4th International Consultation on Incontinence. International Consultation on Incontinence Modular Questionnaire (ICIQ) UI SF (short form). London: Health Publications Ltd.

Basic investigation

Bladder diaries: record fluid intake, the frequency and volume of urine voided, incontinent episodes, pad usage, and degree of urgency over a 3-day period.

Urinalysis ± culture: treat any infection and reassess symptoms.

Flow rate and post-void residual (PVR) volume: patients need to void 150mL of urine for an accurate result. A reduced flow rate suggests BOO or reduced bladder contractility. The volume of urine remaining in the bladder after voiding (PVR) is also informative (<50mL is normal; >200mL is abnormal; 50–200mL requires clinical correlation). PVR is measured with transabdominal USS.

Pad testing: weighing of perineal pads to estimate urine loss after a specific time or provocation test. It is performed with a full bladder. A pad weight gain >1g is positive for a 1h test and a pad weight gain >4g is positive for a 24h test. This is not standardized and not always reliable.

Further investigation

Blood tests, imaging (USS) and cystoscopy: indicated for complicated cases with persistent or severe symptoms, haematuria, bladder pain, voiding difficulties, recurrent UTI, abnormal neurology, previous pelvic surgery or radiation therapy, or suspected extraurethral incontinence.

Urodynamics (see 🕮 p. 68)

- Multichannel cystometry measures bladder and bladder outlet behaviour during filling and voiding, including incontinence episodes. In SUI, it measures the minimal pressure at which leakage occurs on straining (abdominal leak point pressure). Pressures >90–100cmH_2O suggest hypermobility, <60cmH_2O suggest ISD. Detrusor overactivity is manifest as detrusor contractions during filling or an abnormal detrusor pressure rise with position change (lying to standing). Poor bladder compliance is seen as a persistent gradual rise in detrusor pressure during bladder filling.
- Ambulatory urodynamics are thought to be a more physiological and accurate diagnostic test.
- Videourodynamics can visualize movement of the proximal urethra and bladder neck with filling or provocation and identify risk factors for the development of upper tract deterioration (i.e. DSD, vesicoureteric reflux).

Sphincter electromyography (EMG): measures electrical activity from striated muscles of the urethra or perineal floor and provides information on synchronization between the bladder muscle (detrusor) and external urethral sphincter.

1 ICIQ-UI short form: International Consultation on Incontinence Questionnaire (short form) for men and women, to assess symptom score and quality of life (see Fig. 5.1).

2 ICIQ-FLUTS: ICIQ on Female Lower Urinary Tract Symptoms. Assesses occurrence and bother of symptoms relating to incontinence and other urinary symptoms in females.

3 ICIQ-MLUTS: ICIQ Male Lower Urinary Tract Symptoms.

4 SF36 QOL: Short Form 36 health survey questionnaire. Assesses health status in persons with incontinence.

5 Avery K, Donovan J, Peters TJ, *et al.* (2004) ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn* **23**:322–30.

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Stress and mixed urinary incontinence

Stress urinary incontinence (SUI)

This accounts for up to 50% of reported UI in women and causes the symptoms of involuntary urinary leakage on effort (e.g. lifting), exertion (e.g. running), sneezing, and coughing. It is associated with an intrinsic loss of urethral strength and/or urethral hypermobility.

Specific risk factors for female SUI

- Childbirth (increased risk with vaginal delivery, forceps delivery).
- Ageing.
- Oestrogen withdrawal.
- Previous pelvic surgery.
- Obesity.

Specific risk factors for male SUI

External urethral sphincter damage (from pelvic fracture, prostatectomy, pelvic surgery, or radiotherapy).

Other risk factors

Neurological disorders causing sphincter weakness (SCI, multiple sclerosis, spina bifida).

Investigation of SUI (also see 🕮 p. 132)

Women

- **Stress test:** a leakage of urine from the urethra on cough denotes a positive test.
- **Pad test:** number and weight of pads used to estimate urine loss.
- **Pelvic exam:** check for pelvic organ prolapse (POP). Elevation of an existing anterior wall prolapse will unmask any occult sphincter incompetence in those who are continent as a result of obstruction caused by the prolapse. Assess oestrogen status and requirement for topical oestrogen treatments.
- **Q-tip test:** although not performed routinely, the Q-tip angle is a measure of urethral mobility in women. With the patient in lithotomy position and the bladder comfortably full, a well lubricated sterile cotton-tipped applicator is gently inserted through the urethra into the bladder. Once in the bladder, the applicator is withdrawn to the point of resistance which is at the level of the bladder neck. The resting angle from the horizontal is recorded. The patient is then asked to strain and the degree of rotation is assessed. Hypermobility is defined as a resting or straining angle of greater than 30° from the horizontal.
- **Urethral pressure profile** (selected cases only): microtransducers are mounted in a catheter that is placed into the bladder, then slowly withdrawn, measuring intraluminal urethral pressures. A measure of urethral closure pressure can be obtained.
- **Urodynamics:** recommended for women before SUI surgery if:[1]
  - There is suspicion of concomitant detrusor overactivity.
  - History of previous surgery for SUI or anterior compartment prolapse.
  - Symptoms of voiding dysfunction.

Men

- Abdominal exam to detect a palpable bladder.
- External genitalia exam to assess for penile abnormalities.
- DRE.
- Flow rate and PVR.
- Consider imaging of upper tracts if evidence of BOO.

Conservative treatment

- **Pelvic floor muscle training (PFMT):** for a minimum of 3 months is the first-line treatment, performing at least eight contractions, three times per day. PMFT improve symptoms in 30% of women with mild SUI.
- **Lifestyle modification:** weight loss, stop smoking, avoid constipation, modify fluid intake.
- **Biofeedback:** the technique by which information on ability and strength of pelvic floor muscle contraction is presented back to the patient as a visual, auditory, or tactile signal. Patients may also be helped by the perineometer which measures pelvic floor contraction.
- **Medication:** duloxetine inhibits the reuptake of both serotonin and noradrenaline. It is given orally 20–40mg twice daily and acts to increase sphincteric muscle activity during bladder filling. Recommended as an alternative to surgery rather than first-line treatment due to adverse effects.[1]
- **Extracorporal magnetic innervation:** involves sitting the patient in a chair and using a pulsed magnetic field to stimulate the nerves of the sphincter and pelvic floor. Possible benefit in mixed incontinence.
- **High frequency electrical stimulation:** produces contraction of the pelvic floor (35–50Hz). No proven therapeutic benefit in SUI.

Surgical treatment

- Urethral bulking agents (see 🕮 p. 138).
- Retropubic suspension (see 🕮 p. 140).
- Suburethral slings (see 🕮 p. 142).
- Artificial urinary sphincters (see 🕮 p. 146).

Mixed urinary incontinence

Approximately 30% of women will report symptoms of MUI, with involuntary urinary leakage associated with urgency and also with exertion, effort, sneezing, or coughing. The underlying aetiologies and evaluation remain the same as for SUI and UUI, but also consider further investigation to rule out pathologies such as bladder cancer, stones, and interstitial cystitis. The aim of management is to treat the predominant symptoms first.

1 National Institute for Health and Clinical Excellence (2006) Urinary Incontinence: the management of urinary incontinence in women [online]. Available from: 🖱 http://www.nice.org.uk/CG40.

Surgery for stress incontinence: injection therapy

Indications

The injection of bulking materials into bladder neck and periurethral muscles is a minimally invasive surgical technique used to increase outlet resistance (Table 5.2). The main indication is for female stress incontinence secondary to demonstrable ISD in the presence of normal bladder muscle function. There is also evidence of benefit in urethral hypermobility.

Table 5.2 Periurethral bulking agents

Product	Material
Macroplastique®	Silicone (polydimethyl siloxane elastomer)
Bulkamid®	Polyacrylamide hydrogel
Durasphere®	Carbon-coated zirconium beads
Teflon®	Polytetrafluoroethylene paste (PTFE)
Coaptite®	Calcium hydroxylapatite
Permacol®	Porcine dermal implant
Autologous fat	Adipose tissue

Of note, several products are either no longer available for clinical use or have been withdrawn. These includes Contigen®—cross-linked GAX bovine collagen; Zuidex®—hyaluronic acid and dextranomer microspheres; Tegress®—ethylene vinyl alcohol copolymer in DMSO.

Contraindications

- Active infection (UTI).
- Untreated bladder overactivity.
- Bladder neck stenosis.

Injection techniques

- Under local anaesthetic (LA) block or general anaesthesia, agents are injected submucosally under endoscopic guidance.
- In women, a periurethral (percutaneous) technique can be used with endoscopic or ultrasound guidance.
- A 'blind' mid-urethral technique using LA and an instillation device is available to administer Macroplastique® and Bulkamid®.

The aim is to achieve urethral muscosal apposition and closure of the lumen. In women, 2–4 injections are recommended (depending on agent) while in men, 3–4 circumferential injections are administered. Overall success rates are variable, depending on both the agent and patient selection (reported in ranges of 50–80%).[1–4] Results tend to deteriorate with time and repeat treatments are often needed.

Complications

- Temporary urinary retention (2–15%).
- *De novo* urgency incontinence (6–12%).
- Uncomplicated UTI (5%).
- Haematuria (5%).
- Distant migration of the injected particles (PTFE, Macroplastique®) and risk of granuloma formation (PTFE), although no adverse consequences are reported.

Outcomes

Overall success rates are variable, depending on both the agent and patient selection, with reported ranges of 10–80%.[1-5] Results tend to deteriorate with time (i.e. the success of Durasphere® decreases from 80% at 1y to 12% at 3y).[5] Patients should be counselled on outcomes and the need for repeat treatments. As the results are not durable, periurethral bulking agents are not commonly used as a first-line intervention.

1 Koelbl H, Saz V, Doerfler D, *et al.* (1998) Transurethral injection of silicone microimplants for intrinsic urethral sphincter deficiency. *Obstet Gynaecol* **92**:332–6.

2 Appell RA (1994) Collagen injection therapy for urinary incontinence. *Urol Clin N Am* **21**: 177–82.

3 Dmochowski R, Apell RA, Klimberg I, *et al.* Initial clinical results from coaptite injections for stress urinary incontinence, comparative clinical study. Program of the International Continence Society, 2002. Heidelberg, Germany, August 2002.

4 Lighter D, Calvosa C, Andersen R, *et al.* (2001) A new injectable bulking agent for treatment of stress urinary incontinence: results of a multicentre, randomized, controlled, double-blind study of Durasphere™. *Urology* **58**:12–5.

5 PE Keegan, K Atiemo, J Cody, S McClinton, R Pickard (2007) Urethral injection therapy for urinary incontinence in women, *Cochrane Database Syst Rev* **3**:CD003881.

Surgery for stress incontinence: retropubic suspension

Retropubic suspension procedures are used to treat female stress incontinence predominantly caused by urethral hypermobility. The aim of surgery is to elevate and fix the bladder neck and proximal urethra in a retropubic position in order to support the bladder neck and regain continence. There is a lower chance of clinical benefit in the presence of significant ISD.

Types of surgery

Surgery is considered after conservative methods have failed. There are three main operations, all of which can be performed open via a Pfannenstiel or lower midline abdominal incision to approach the bladder neck and develop the retropubic space. Burch colposuspension can also be performed laparoscopically. Better results are seen in patients with pure stress incontinence and primary repair (as opposed to 're-do' surgery).

Burch colposuspension

This is the most widely used technique with the best durability. Patients that are selected require good vaginal mobility as the vaginal wall is elevated and attached to the lateral pelvic wall where the formation of adhesions over time will secure its position. It is also considered an option for patients with concurrent SUI and anterior vaginal wall prolapse. This operation involves exposing the paravaginal fascia and approximating it to the iliopectineal (Cooper's) ligament of the superior pubic rami. Initial success rates for open repair are about 85–90% at 1y and 70% at 5y.[1] Success rates when used for recurrent incontinence are 83% at 1y.[2] Overall success rates are slightly higher for open repair over the laparoscopic approach.[3,4] Open repair has a shorter operating time and the laparoscopic approach is more costly, but has a shorter hospital stay.

Complications of Burch colposuspension

- Posterior compartment prolapse (10–25%).
- *De novo* urgency incontinence (15%).
- Voiding dysfunction (10%).

Vagino-obturator shelf/paravaginal repair

A variant of the Burch procedure. Sutures are placed by the vaginal wall and paravaginal fascia and then passed through the obturator fascia to attach to part of the parietal pelvic fascia below the tendinous arch (arcus tendoneus fascia). It aims to disperse tension on the paravesical tissues laterally to reduce the risk of prolapse. Cure rates are up to 85%, although it is considered less effective than the Burch colposuspension.

Marshall–Marchetti–Krantz (MMK) procedure

Sutures are placed on ither side of the urethra around the level of the bladder neck and then tied to the hyaline cartilage of the pubic symphysis. Short-term success is about 90%,[1] however, this declines over time and is now considered less effective than the Burch procedure. Complications include a 3% risk of osteitis pubis which typically presents up to 8 weeks post-operatively with pubic pain radiating to the thigh. Treatment is with simple analgesia, bed rest, and steroids.

1 Lapitan MCM, Cody JD, Grant A (2009) Open retropubic colposuspension for urinary incontinence in women. *Cochrane Database Syst Rev* **2**:CD002912.

2 Jarvis CG (1994) Surgery for genuine stress incontinence. *Br J Obstet Gynaecol* **101**:371–4.

3 Moehrer B, Carey M, Wilson D (2003) Laparoscopic colposuspenion: a systematic review. *BJOG* **110**:230–5.

4 Ankardal M, Ekerydh A, Crafoord K, *et al.* (2004) A randomized trial comparing open Burch colposuspension using sutures with laparoscopic colposuspension using mesh and staples in women with stress urinary incontinence. *BJOG* **111**:974–81.

Surgery for stress incontinence: suburethral tapes and slings

Types of sling* (Figs. 5.2, 5.3)

- **Synthetic tapes:** type I (>75μm pores), soft, monofilamentous polypropylene mesh. Examples include:
  - **Retropubic tape**, i.e. tension-free vaginal tape (TVT); Lynx®.
  - **Transobturator tape (TOT)**, i.e Monarc Subfascial Hammock; TVT obturator system (TVTO); Obtryx®.
- **Autologous:** rectus fascia, fascia lata (from the thigh), vaginal wall slings.
- **Non-autologous:** allograft fascia lata from donated cadaveric tissue.

Synthetic tapes

Widely practised first-line surgical treatment for female SUI. Tapes can be inserted under general or local anaesthetic as day cases. They are less invasive than colposuspension with fewer complications. They are placed via a retropubic route (TVT) or a transobturator route (TOT, TVTO). The bladder should be empty and catheterized. All techniques use cystoscopy to detect bladder perforation during sling placement. Post-operatively, patients may temporarily require CISC until post-void residuals are less than 100–150mL.

Retropubic tapes

A small midline anterior vaginal incision is made over the mid-urethra. The TVT tape has long trocars on each end. These are inserted either side of the urethra and perforate through the endopelvic fascia. They are then pushed up behind the symphysis pubis and out onto the lower abdominal wall in the midline, just above the pubic bone (i.e. trocar passes from ***bottom upwards***). Once the tape is positioned loosely (tension-free) over the mid-urethra, its covering is removed and the ends cut flush to the abdomen. Vaginal epithelium is closed over the top.

Outcomes

- **TVT:** success rates at 1y are up to 90% and at 5y are up to 80%.[1]
- **TVT vs colposuspension:** although there is a trend in favour of TVT, Ward and Hilton studies have not detected a statistically significant difference between TVT and colposuspension for the cure of SUI at 6 months, 2 or 5y follow-up.[2,3] At 2y, 63% of patients were dry with TVT vs 51% with colposuspension.[2] At 5y, they still have equivalent cure rates, but the TVT group have lower OAB symptoms and prolapse (1.8% vs 7.5% with colposuspension).[3]

Transobturator tapes

A midline anterior vaginal incision is made for dissection around the urethra. Two small incisions are made lateral to the labia majora at the level of the clitoris. In the Monarc Subfascial Hammock (AMS), the curved handle device is placed through the skin incision and turned downwards, passing through the anterior part of the obturator foramen and exiting alongside the urethra on each side (i.e. trocar passes from ***outside to inside***). The tape is attached to the end of each handle and brought back out to

the skin surface. It is positioned loosely around the mid-urethra and the ends cut flush with the skin. In TVTO, the tape is passed in a reverse route (i.e. trocar passes from ***inside to outside***).

Outcomes

- **TOT vs TVT:** TOT has equivalent subjective cure rates to TVT at 1y, but objective cure rates are slightly lower (84% vs 88%).[4] TOT has less voiding dysfunction, blood loss, bladder perforation, and a shorter operating time as compared to TVT.[4] Bladder perforation and voiding difficulties are lower in TOT compared to TVT.[4,5] Vaginal injuries/erosion and pain in the groin/thigh is higher with TOT.[5] *De novo* urgency and frequency symptoms were the same in both groups.[5]
- **TVTO vs TVT:** TVTO has reported statistically similar objective cure rate to TVT in randomized control trials (81% vs 86%, respectively), but significantly increased risk of leg pain.[6]

Mini tapes (Fig. 5.4)

Examples of self-retaining mini tapes inserted via a single vaginal incision are the MiniArc® (AMS) and GYNECARE TVT SECUR™. The short-term success rates are around 80–90%,[7,8] although results may not be sustained over time.[8]

General complications of tapes

- Voiding dysfunction (urinary retention, *de novo* bladder overactivity).
- Vaginal, urethra, and bladder perforation or erosions.
- Pain (groin/thigh with transobturator route).
- Damage to bowel or blood vessels (rare).

Pubovaginal (autologous) slings

Most commonly, a segment of rectus fascia measuring 10–20cm in length is harvested via a Pfannenstiel approach and non-absorbable long sutures placed on both ends. The sling is placed under the mid-urethral and the sutures placed through the endopelvic fascia up to the remaining rectus fascia where the suture ends are tied using the minimal amount of tension needed to prevent urethral movement. Autologous slings have been shown to have a better outcome as compared to colposuspension, but at the expense of higher complications (UTI, voiding dysfunction, and urge incontinence).[9] Autologous retropubic slings are not commonly used as first-line surgical procedures for SUI.

Male tapes

There are many new male continence slings and devices available, but follow-up data are limited. Examples include:

- **AdVance**™ Male Sling System (AMS): indications include mild to moderate SUI (<3–4 pads per day) with some residual sphincter function. A small incision is made in the perineum and two further incisions in each groin. The sling is passed through the obturator foramina and positioned over the bulbar urethra to support and slightly elevate the urethra. Success rates at 1y are 60–80%.
- **InVance**™ Male Sling System (AMS): mesh is attached to the pubic bone by three titanium screws on both sides to compress the bulbar urethra. Success rates at 3–4y are 70–80%.

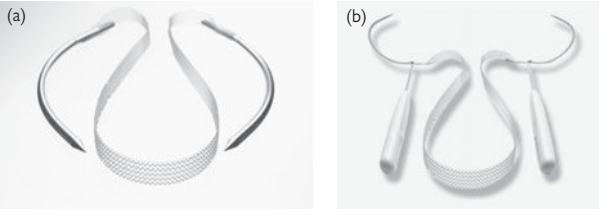

Fig. 5.2 (a) GYNECARE TVT™ retropubic system tension-free support for incontinence. (b) GYNECARE TVT™ obturator system. Reproduced with permission, courtesy of ETHICON, Inc.

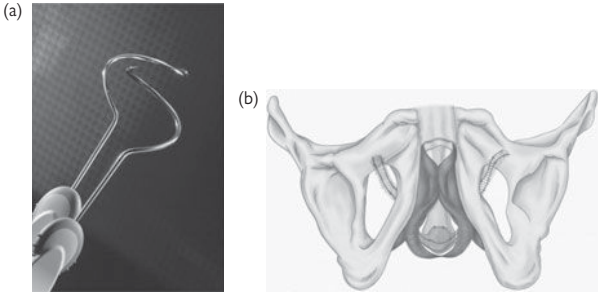

Fig. 5.3 (a)Trocar handles for the Monarc® Subfascial Hammock (TOT). (b) AdVance™ Male Sling System. (Reproduced with permission, courtesy of American Medical Systems.)

Fig. 5.4 GYNECARE TVT SECUR™ system. Reproduced with permission, courtesy of ETHICON, Inc.

* Of note, many other products are available. Full product names:
Retropubic tapes: Lynx® Suprapubic Mid-urethral Sling System (Boston Scientific); GYNECARE TVT™ Retropubic System Tension-free Support for Incontinence (Ethicon)
Transobturator tapes: Monarc® Subfascial Hammock (AMS); Obtryx™ Transobturator Mid-Urethral Sling (Boston Scientific); GYNECARE TVT™ Obturator System (Ethicon)
Mini-tapes: **GYNECARE TVT SECUR™ System (Ethicon); MiniArc® Single Incision Sling System (AMS)

1 Chene G, Amblard J, Tardieu AS, *et al.* (2007) Long-term results of tension-free vaginal tape (TVT) for the treatment of female urinary stress incontinence. *Eur J Obstet Gynaecol Reprod Biol* **134**:87–94.

2 Ward K, Hilton P (2006) Multicentre randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: five year follow up. *Neurourol Urodyn* **25**:568–9.

3 Ward KL, Hilton P (2008) Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. *BJOG* **115**:226–33.

4 Latthe PM, Foon R, Toozs-Hobson P (2007) Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications. *BJOG* **114**:522–31.

5 Ogah J, Cody JD, Rogerson L (2009) Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev* **4**:CD006375.

6 Teo R, Moran P, Mayne C, Tincello D (2011) Randomised trial of tension-free vaginal tape and tension-free vaginal tape-obturator for urodynamic stress urinary incontinence in women. *J Urol* **185**:135–5.

7 Oliveira R, Botelho F, Silva P, *et al.* (2001) Single-incision sling system as primary treatment of stress urinary incontinence: prospective 12 months data from a single institution. *BJU Int* **108**:1616–21.

8 Cornu JN, Sèbe P, Peyrat L, *et al.* (2010) Midterm prospective evaluation of TVT-Secur reveals high failure rate. *Eur Urol* **58:**157–61.

9 Albo ME, Richter HE, Brubaker L, *et al.* (2007) Burch colposuspension versus fascial sling to reduce stress urinary incontinence. *N Engl J Med* **356**:2143–55.

** Of note, as of June 2012, GYNECARE TVT SECUR™ System has been withdrawn.

Surgery for stress incontinence: artificial urinary sphincter

The artificial urinary sphincter (AUS) (AMS800™; Fig. 5.5) is a closed pressurized system with three components. The inflatable cuff is commonly placed around the bulbar urethra or alternatively, the bladder neck (in both women and men). A pressure-regulating balloon is placed extraperitoneally in the abdomen. An activating pump is placed in the scrotum or labia majora. The cuff provides a constant circumferential pressure to compress the urethra. To void, the pump is squeezed, which transfers fluid to the reservoir balloon, thereby deflating the cuff. The cuff then automatically refills within 3min. Voiding takes place in the interval taken for the cuff to refill. The reservoir balloon pressure can be 61–70mmHg for bulbar urethral placement or 71–80mmHg for bladder neck placement.

Indications and patient selection

Used for moderate to severe SUI, secondary to urethral sphincter deficiency in patients with normal bladder capacity and compliance. In men, it is used for sphincter damage due to radical prostatectomy, TURP, pelvic radiotherapy, pelvic fracture, and following complicated urethral reconstruction. In women, it is used after other treatments for incontinence have failed. It can be used for neuropathic sphincter weakness (e.g. SCI, spina bifida). If there is combined bladder overactivity and sphincter weakness, treat the bladder first (i.e. lower bladder pressures with anticholinergics, intravesical botulinum injections, augmentation), which, in some cases, will be enough to achieve continence. If incontinence persists, proceed with AUS at a later date.

Contraindications to AUS: bladder neck stenosis, poor patient manual dexterity or cognition, active infection.

Patient evaluation

Patients should undergo urodynamics, cystoscopy, and upper tract imaging to evaluate voiding function and identify anatomical abnormalities that might affect the efficacy of the AUS. Good manual dexterity is required to manipulate the pump and sufficient cognitive function to operate the AUS themselves several times daily.

Results

AUS can function well for many years (≥10y). Overall long-term success (continued continence, no device malfunction) is 70–90%; revision rates are 20–30%.[1]

Complications

Recurrent incontinence due to:

- 'Urethral atrophy' underneath the cuff (10% in the first 5y). Thought not to be true atrophy, but due to the formation of a constricting sheath of tissue over the urethra.
- Mechanical failure (of the pump or slow leak of fluid from the system).
- Urethral erosion (essentially a pressure sore in the urethra due to chronic pressure from the cuff).

- Bladder overactivity or reduced compliance. Investigate recurrent incontinence by cystoscopy (to exclude erosion), X-ray to determine leaks from the system (the balloon loses its round shape), and urodynamics (to detect high bladder pressures).

Erosion: occurs in 5%, most commonly at 3–4 months, with 75% occurring in the first year. Presents with pain and swelling of scrotum, labia or perineum, incontinence, and bloody discharge. Increased risk after pelvic radiotherapy.

Infection: primary implant infection rates are 1–5%. With infection or erosion, remove the entire device and wait 3–6 months before reinsertion.

Other: haematoma (scrotum or labia); late urinary retention which may signify obstruction from urethral stricture or bladder neck contracture (higher risk with previous pelvic irradiation). Always ensure that the AUS is deactivated (i.e. the cuff is deflated) prior to urethral instrumentation or catheterization.

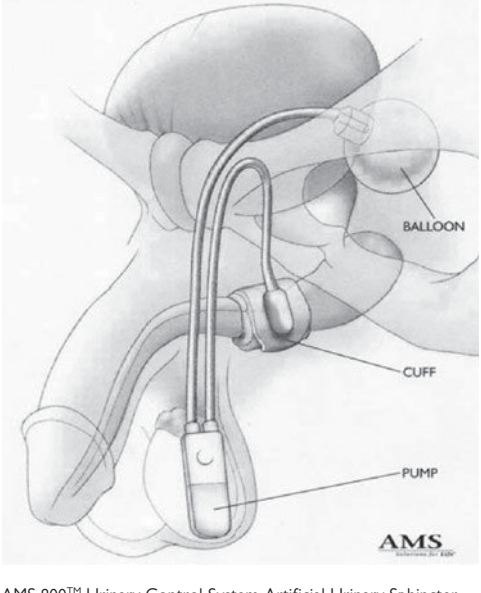

Fig. 5.5 AMS 800™ Urinary Control System Artificial Urinary Sphincter. (Reproduced with permission. Courtesy of American Medical Systems Inc., Minnesota.)

1 Lai HH, Hsu EI, Teh BS, *et al.* (2007) 13y of experience with artificial urinary sphincter implantation at Baylor College of Medicine. *J Urol* **177**:1021–5.

Overactive bladder: conservative and medical treatment

Definition

Overactive bladder (OAB) is a symptom syndrome that includes urgency, with or without urge incontinence, usually with frequency and nocturia. The symptoms are usually caused by bladder (detrusor) overactivity, but can be due to other forms of voiding dysfunction (Fig. 5.6). Seventeen percent of the population aged >40y in Europe have symptoms of OAB.[1] The prevalence increases with age.

Conventional treatment

Conservative

Patient management involves a multidisciplinary team approach (urologists, urogynaecologists, continence nurse specialists, physiotherapists, and community-based health care workers). Pelvic floor muscle training (PFMT), biofeedback, acupuncture, and electrical stimulation therapy (which strengthens the pelvic floor and sphincter by increasing tone through sacral neural feedback systems) may provide some benefit.

Behavioural modification

This involves modifying fluid intake, avoiding stimulants (caffeine, alcohol), and bladder training (delayed micturition for increasing periods of time by inhibiting the desire to void). If this fails, consider medication.

Anticholinergic medication

Acetylcholine acts on muscarinic receptors (M3 ± M2 subtypes) on the bladder smooth muscle (detrusor) to cause involuntary contractions and provoke the symptoms of bladder overactivity. These receptors are the targets of anticholinergic (antimuscarinic) drugs which inhibit contractions and increase bladder capacity. Approximately 50% of patients will benefit from medication.

- **Oxybutynin:** mixed action (antimuscarinic, local anaesthetic, and direct muscle relaxation). It is available as immediate or extended release (ER) tablets, transdermal patch, gel preparations, and can be given intravesically. It is very effective, but has a high rate of side effects, reducing patient compliance.
- **Solifenacin:** selective antimuscarinic antagonist (M3 > M2). The STAR trial[2] compared solifenacin to tolterodine ER and found higher improvements in urgency, urge incontinence, and overall incontinence with solifenacin (59% became continent vs 49%). The number of patients discontinuing treatment due to side effects was similar (3–3.5%).
- **Tolterodine:** bladder selective antimuscarinic, metabolized to 5-hydroxymethyl tolterodine (5-HMT). Extended release formulation has demonstrated good efficacy and tolerability.[3]
- **Fesoterodine:** non-selective antimuscarinic with 5-HMT active metabolite. Superior to tolerodine in reducing UUI, improving bladder

capacity and continence (64% dry vs 57% with tolterodine) with the added benefit of a flexible dosing regimen.[4]

- **Darifenacin:** highly selective M3 antagonist. Achieves significant reduction in urinary frequency, urgency, incontinence episodes (77% with 15mg dose).[5] It is well tolerated (2.1% discontinued 15mg treatment due to side effects).
- **Trospium:** non-selective for muscarinic receptors. Minimal passage across the blood brain barrier with the theoretical benefit of fewer cognitive effects. Extended release formula has good long-term results.[6]
- **Propiverine:** non-selective for muscarinic receptors.

Contraindications to anticholinergics

Uncontrolled narrow angle glaucoma, myasthenia gravis, BOO, bowel disorders (i.e. active ulcerative colitis, bowel obstruction).

Common side effects of anticholinergics

Dry mouth, constipation, blurred vision, urinary retention, cognitive impairment, skin rash with transdermal patches.

Other drugs used for OAB

- **Topical oestrogen:** can provide improvement urgency, UUI, frequency, and nocturia in post-menopausal women.[7] Relative contraindication is a history of breast cancer.

1 Milsom I, Abrams P, Cardozo L, *et al.* (2001) How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* **87**:760–6.

2 Chapple CR, Martinez-Garcia R, Selvaggi L, *et al.* (2005) A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* **48**:464–70.

3 Swift S, Garely A, Dimpfl T, *et al.* (2003) Tolterodine Study Group. A new once daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. *Int Urogynecol J Pelvic Floor Dysfunct* **14**:50–4.

4 Herschorn S, Swift S, Guan Z, *et al.* (2009) Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head to head placebo-controlled trial. *BJU Int* **105**:58–66.

5 Chapple C, Steers W, Norton P, *et al.* (2005) A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. *BJU Int* **95**:993–1001.

6 Zinner NR, Dmochowski RR, Staskin DR, *et al.* (2011) Once-daily trospium chloride 60 mg extended-release provides effective, long-term relief of overactive bladder syndrome symptoms. *Neurourol Urodyn* **30**:1214–9.

7 Cardozo L, Lose G, McClish D, *et al.* (2004) A systematic review of the effects of oestrogens for symptoms suggestive of overactive bladder. *Acta Obstet Gynecol Scand* **83**:892–7.

Overactive bladder: options for failed conventional therapy

Neuromodulation (see also 📖 p. 624)

Sacral nerve stimulation involves electrical stimulation of the bladder's nerve supply to suppress reflexes responsible for involuntary bladder muscle (detrusor) contraction.*

- The Interstim device (Medtronic) stimulates the S3 afferent nerve, which then inhibits detrusor activity at the level of the sacral spinal cord. An initial percutaneous nerve evaluation is performed, followed by surgical implantation of permanent electrode leads into the sacral foramen, with a pulse generator which is programmed externally.
- SANS™ (Stoller Afferent Nerve Stimulator) is a minimally invasive technique, which is applied near the posterior tibial nerve above the medial malleolus on the ankle.

Surgery

The aim is to increase functional bladder capacity, decrease maximal detrusor pressure, and protect the upper urinary tract (also see 📖 pp. 602–7).

Augmentation enterocystoplasty ('Clam' ileocystoplasty): relieves intractable frequency, urge, and UUI in 90% of patients. The bladder dome is cut open (bivalved) and a detubularized segment of ileum is anastomosed, creating a larger bladder volume.

Autoaugmentation (detrusor myectomy): detrusor muscle is excised from the entire dome of bladder, leaving the underlying bladder endothelium intact. A large epithelial bulge is created which augments bladder capacity. Less commonly performed now as limited long-term efficacy. Most benefit in patients with idiopathic detrusor overactivity.

Urinary diversion: a non-continent urinary outlet, reserved for intractable cases only. Typically, both ureters are anastomosed and connected to a short ileal pouch which is brought out cutaneously as a stoma.

Intravesical pharmacotherapy

Botulinum toxin-A (BTX-A): injected at multiple sites as a bleb under the bladder mucosa or into detrusor, sparing the trigone (see 📖 pp. 152–3; 604–7; 590–1). This treatment is off licence.

* Sacral nerve stimulation has National Institute of Excellence (NICE) approval for women with detrusor overactivity who have failed conservative treatments.

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Overactive bladder: intravesical botulinum toxin-A therapy

Botulinum toxin-A (BTX-A)

Botulinum toxin (BTX) is a neurotoxin produced by a Gram-positive, rod-shaped, anaerobic bacterium, *Clostridium botulinum*. There are seven subtypes. Subtypes A and B are used in urology; however, BTX-A is the more potent with longer duration of action.

Main applications for treatment in the urinary tract

- Neurogenic detrusor overactivity (NDO).[1]
- Idiopathic detrusor overactivity (IDO).[2,3]
- Detrusor sphincter dyssynergia (DSD).[4]

Children with NDO associated with myelomeningocele[5] and with IDO[6] have been safely and successfully treated with BTX-A. There is also emerging, but limited, evidence for a role in symptomatic benign prostatic enlargement and chronic pelvic pain syndromes (BPS/IC).

Mechanism of action

BTX-A acts by inhibiting the release of acetylcholine (ACh) and other neurotransmitters from presynaptic cholinergic nerve terminals, resulting in regionally decreased muscle contractility and muscle atrophy at the site of BTX-A injection. The chemical dennervation that results is a reversible process.

Adult dosing regimen for detrusor overactivity

- American BTX-A (Botox®, Allergan), 100–300 units.
- English BTX-A (Dysport®, Ipsen), up to 1000 units
- Botox® 300 is roughly equivalent to 900 units of Dysport®.

Method of intravesical administration

- Techniques include rigid cystoscopy under general anaesthetic (GA) using a flexible needle or LA flexible cystoscopy using a shealth and ultra-fine 4mm needle.
- BTX-A is diluted in normal saline (i.e. 100IU Botox® diluted in 20mL saline).
- Twenty random sites on the bladder wall are injected (i.e. ~1mL (5IU Botox®) per injection site).
- BTX-A can be injected directly into detrusor muscle or submucosally.
- General practice is usually to avoid injecting the trigone (trigone sparing)*.

Outcome

- A response is seen within 7 days (maximal response may take 30 days).
- Effects last approximately 6–9 months and repeat injections are required.
- Tolerance to the drug appears unchanged with repeated applications.

Contraindications to treatment

- Myasthenia gravis.
- Aminoglycosides/drugs interfering with neuromuscular transmission, which may enhance effects of BTX-A.
- Eaton–Lambert syndrome.**
- Breastfeeding and pregnancy.
- Bleeding disorders (haemophilia, hereditary clotting factor deficiency).

Side effects

- Urinary retention. Higher risk in NDO compared to IDO (~70% vs ~20%).[7] Risk higher (in IDO) with higher dose of BTX-A.[3]
- Haematuria.
- UTI.
- Bladder pain.
- General muscle weakness (Dysport®).
- Dysphagia.
- Diplopia, blurred vision.

* A trigone sparing technique has been used to prevent the theoretical risk of iatrogenic vesicoureteric reflux, although there is no evidence to support this.

** Eaton–Lambert syndrome: small cell bronchial carcinoma associated with defective ACh release at the neuromuscular junction causing proximal muscle weakness.

1 Schurch B, De Seze M, Denys P, *et al.* (2005) Botulinum toxin type is a safe and effective treatment for neurogenic incontinence: results of a single treatment, randomised, placebo controlled 6-month study. *J Urol* **174**:196–200.

2 Schmid DM, Suermann P, Werner M, *et al.* (2006) Experience with 100 cases treated with botulinum-A toxin injections in the detrusor for idiopathic overactive bladder syndrome refractory to anticholinergics. *J Urol* **176**:177–85.

3 Dmochowski R, Chapple C, Nitti VW**,** *et al.* (2010) Efficacy and safety of onabotulinumtoxinA for idiopathic detrusor overactivity: a double blind, placebo controlled, randomized, dose ranging trial. *J Urol* **184**:2416–22.

4 Dykstra DD, Sidi AA, Scott AB, *et al.* (1998) Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. *J Urol* **139**:919–22.

5 Riccabona M, Koen M, Schinder M, *et al.* (2004) Botulinum-A toxin injection into the detrusor: a safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflexia. *J Urol* **171**:845–8.

6 Verleyen P, Hoebeke P, Raes A, *et al.* (2004) The use of botulinum toxin A in children with a non-neurogenic overactive bladder: a pilot study. *BJU Int* **93**:69.

7 Popat R, Apostolidis A, Kalsi V, *et al.* (2005) A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum toxin-A. *J Urol* **174**:984–9.

Post-prostatectomy incontinence

Incidence

UI occurs in <1% after TURP and 0.5% after open prostatectomy (OP) performed for benign prostate disease.[1] Following radical prostatectomy (RP) for malignant disease, UI tends to improve over 12–18 months post-surgery.[2] The overall incidence in open RP is ~10–15%,[2,3] with similar risks reported for laparoscopic RP.[4] Early results from robotic-assisted laparoscopic RP suggest slightly earlier recovery of continence and improved overall continence rates.[5]

Risk factors for UI after RP

- Increasing age.
- Pre-existing bladder dysfunction.
- Previous radiotherapy (TURP following brachytherapy has a 40% risk of UI).
- Prior TURP.
- Advanced stage of disease and surgical technique.

Earlier recovery of continence after open RP is achieved using a perineal approach, nerve sparing techniques, and sphincter and bladder neck preserving procedures.

Pathophysiology

The main cause of post-radical prostatectomy incontinence is sphincter dysfunction. The proximal sphincter mechanism is removed at prostatectomy (TURP, OP, RP). Post-prostatectomy continence, therefore, requires a functioning distal (external) urethral sphincter mechanism and low bladder pressure during bladder filling. Direct damage to the external sphincter can occur during prostatectomy (at TURP, it occurs particularly during resection between 11 and 2 o'clock positions when the reference point for the position of the distal sphincter, the verumontanum, cannot be seen). Damage to the innervation of the sphincter can also occur during prostatectomy. Urodynamic studies before and after RP show that maximal urethral closure pressure (MUCP) and functional urethral length (the length of urethra over which the sphincter functions to maintain high pressures) are lower. Nerve-sparing RP (where the neurovascular bundles are specifically identified and preserved) produces better continence rates and longer functional urethral lengths and MUCPs.

A substantial proportion of men also have OAB before prostatectomy and this may remain so after surgery, contributing to UI.

Evaluation

Wait for up to 12 months for spontaneous improvement. Act sooner if symptoms are severe.

- **History:** stress-induced leakage (cough, standing from a sitting position) suggests sphincter dysfunction.
- **Examination:** observe for leakage on coughing.
- **Tests:** PVR measurement on USS (to exclude retention with overflow); (video)urodynamic studies allow the determination of

bladder and sphincter function; cystoscopy allows the identification of strictures (particularly important if artificial urinary sphincter implantation is contemplated).

Treatment

PFMT does not appear to convey benefit. In the Men After Prostate Surgery (MAPS) study, four sessions of PFMT administered by a trained physiotherapist or continence nurse over a 3-month period had no impact on continence* or QALY 12 months post-prostatectomy when compared with no intervention. In the radical prostatectomy group, 76% of incontinent men receiving PFMT remained wet compared with 77% not receiving such training; in the TURP group, 65% of incontinent men receiving PFMT remained wet compared with 62% not receiving such training.[6]

Treatment for sphincter dysfunction

- Bulbourethral sling or tapes to compress or elevate the urethra (InVance™ and AdVance™ male tapes) (see 📖 p. 143). Best results in mild to moderate incontinence (requiring <3–4 pads per day).
- Artificial urinary sphincter. Insertion is usually deferred until 1y post-prostatectomy and it is the most effective long-term treatment (80% success rates).

Treatment for bladder dysfunction

- Conservative treatment for bladder overactivity includes behavioural therapy and anticholinergic medication.
- Surgery for intractable cases includes intravesical botulinum toxin injection, augmentation cystoplasty, or urinary diversion.
- Catheterization may be considered in the older patient.

* Continence was assessed by the International Consultation on Incontinence Questionnaire (ICIQ)—Urinary Incontinence Short Form).

1 Agency for Health Care Policy and Research (AHCPR) (1994) Benign Prostatic Hyperplasia: diagnosis and treatment, Clinical Practice Guidelines No.8 [online]. Available from: www.ncbi.nlm.nih.gov.

2 Benoit RM, Naslund MJ, Cohen JK (2000) Complications after radical prostatectomy in the medicare population. *Urology* **56**:116–20.

3 Catalona WJ, Carvalhal GF, Mager DE, *et al.* (1999) Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. *J Urol* **162**:433–8.

4 Eden CG, Moon DA (2006) Laparoscopic radical prostatectomy: minimum 3-year follow-up of the first 100 patients in the UK. *BJU Int* **97**:981–4.

5 Patel VR, Thaly R, Shah K (2007) Robotic radical prostatectomy: outcomes of 500 cases. *BJU Int* **99**:1109–12.

6 Glazener C, Boachie C, Buckley B, *et al* . (2011) Urinary incontinence in men after formal one-to-one pelvic-floor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. *Lancet* **378**:328–37.

Vesicovaginal fistula (VVF)

VVF is an abnormal communication between the bladder and vagina. In 10%, there is a coexisting ureterovaginal fistula.

Aetiology

In developing countries, the majority are due to obstructed or prolonged childbirth, causing tissue pressure necrosis between the vagina and bladder. In developed countries, 75% follow hysterectomy (0.1–0.2% risk; Fig. 5.6).[1,2] Other causes include pelvic surgery or radiotherapy, pessary erosion, advanced pelvic malignancy (cervical carcinoma), pelvic endometriosis, inflammatory bowel disease, trauma, childbirth (5%), low oestrogen states, infection (urinary TB), and congenital abnormalities.

Symptoms

Immediate or delayed onset of urinary leakage from the vagina postoperatively; abdominal pain or distension; prolonged bowel ileus (due to leak of urine into the peritoneal cavity as well as through the vagina); suprapubic pain; haematuria.

Assessment

- Pelvic examination may demonstrate VVF.
- '3-swab test': give oral phenazopyridine which turns the urine orange. After 1h, place three swabs into the vagina and instill methylene blue into the bladder. If the proximal swab turns blue, it indicates VVF; if it is orange, it suggests ureterovaginal fistula.
- Cystoscopy may directly identify the fistula tract and help determine its proximity to the ureteric orifices. Biopsy the tract if history of malignancy.
- IVU and/or bilateral retrograde pyelograms to assess ureteric involvement or coexisting injury.
- Cystogram (or micturating cystourethrogram (MCUG)): best test for identifying bladder fistula.
- Contrast enhanced CT or MRI if history of previous radiotherapy or malignancy.

Management

Small, uncomplicated VVF may resolve with urethral catheterization (± anticholinergics and antibiotics) or electrocoagulation of the tract (± fibrin sealant). A coexisting ureterovaginal fistula will require ureteric stent or catheter. Most cases proceed to surgery.

Surgery

Overall surgical success for simple VVF repair is 90%. Early repair (within 2–3 weeks) is advocated in selected cases, but traditionally, surgery is delayed 3–6 months (or 6–12 months following radiation therapy). The main principles are to excise the fistula, tension-free closure, and interposition of healthy tissue.

Transvaginal approach: most commonly used. The vaginal flap technique involves incision of the fistula tract and closure with two layers of sutures.

Interpositional tissue grafts may be mobilized between the bladder and vagina (Martius fat pad graft from labia majora; peritoneal flap; gracilis flap) prior to the advancement of a vaginal flap and closure of the vaginal wall.

Abdominal approach: more often used for complex cases, patients with a VVF high in the vagina or associated ureteric injury. The bladder is bisected to the level of the fistula tract which is then completely excised. The bladder is closed and an interpositional (omental) graft created. In complex cases, urinary diversion procedures may be needed.

Suprapubic and urethral catheters are placed for 2 weeks and MCUG performed prior to catheter removal. Offer oestrogen replacement to post-menopausal women. Avoid tampons or sexual intercourse for 3 months.

Post-operative complications: vaginal bleeding; infection; bladder pain; dyspareunia due to vaginal stenosis; graft ischaemia; ureteric injury; fistula recurrence.

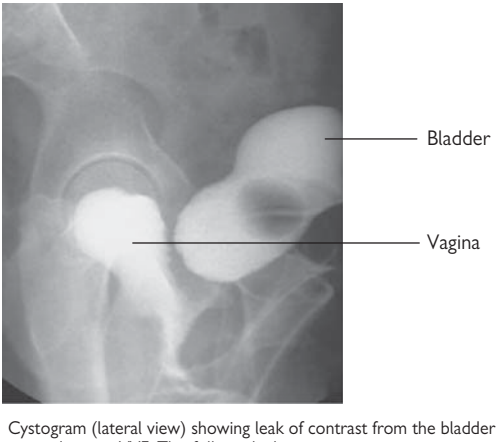

Fig. 5.6 Cystogram (lateral view) showing leak of contrast from the bladder and into the vagina due to a VVF. This followed a hysterectomy.

1 TancermL (1992) Observations on prevention and management of vesicovaginal fistula after total hysterectomy. *Surg Gynaecol Obstet* **175**:501–6.

2 Harris WJ (1995) Early complications of abdominal and vaginal hysterectomy. *Obstet Gynaecol Survey* **50**:795–805.

Incontinence in elderly patients

Prevalence

UI steadily increases with advancing age (particularly ≥70y). It affects about 10–20% of women and 7–10% of men >65y old and living at home. These figures escalate if older people are institutionalized.

Prevalence for both sexes: residential home, 25%; nursing home, 40%; long-stay hospital ward, 50–70%.[1]

Transient causes of UI ('DIAPPERS')

Delirium.
Infection.
Atrophic vaginitis or urethritis.
Pharmaceuticals (opiates and calcium antagonists cause urinary retention and constipation; anticholinergics cause increased PVR and retention; α-adrenergic antagonist cause reduced urethral resistance in women).
Psychological problems (depression; neurosis; anxiety).
Excess fluid input or output (diuretics; congestive cardiac failure (CCF); nocturnal polyuria).
Restricted mobility.
Stool impaction (constipation).

Established UI

This is unrelated to comorbid illness and persists over time. There are several types, including UUI, SUI, and incontinence associated with impaired bladder emptying (due to underactive bladder, urethral or bladder outlet obstruction). In addition, functional incontinence is associated with factors outside of the urinary tract such as permanent immobility, cognitive impairment, and environmental changes.

History

Seek out any transient causes and correct before arranging complex assessment and investigation. This can immediately improve function and quality of life and may be sufficient to restore continence, even if there is coexisting urinary tract dysfunction. Elicit full drug history; comorbid conditions; psychological, cognitive, functional, social, and environmental status.

Examination

Include mini-mental state evaluation and direct observation of patient dexterity and mobility (Barthel Index). Include abdominal assessment (distended bladder), DRE (impacted faeces), vulval inspection (POP; atrophic vaginitis), and neurological testing.

Investigations

- Measure serum creatinine.
- Frequency volume chart.
- Bladder USS for PVR volume.
- Urinalysis (screen for infection, haematuria, glycosuria, proteinuria).

- Stress test.
- Evaluation of the home environment and assess the need for modifications (occupational therapist and district nurse visits).

Urodynamics should be reserved for patients considered fit for surgery and where the results will alter clinical treatment. Renal tract USS can be undertaken where clinically indicated (i.e. large PVR, impaired renal function, haematuria, UTI).

Management

Conservative

Biofeedback, electrical stimulation of pelvic floor, and behavioural methods are appropriate only if cognition is intact. PFMT (good results if used in conjunction with anticholinergics). Treat any atrophic vaginitis (0.01% estriol cream topically). Optimize mobility and bring the toilet closer to the bed. Try timed and prompted voiding. Absorbent appliances include bed pads and body worn pad products (disposable or reuseable); body worn external urine collection devices (close fitting penile sheath); pessary for POP; indwelling catheters where UI is due to obstruction and/or no alternative intervention suitable.

Medical therapy

Ensure that BOO and significant post-void bladder residuals are adequately treated before considering treatment of OAB symptoms. Antimuscarinic drugs with fewer effects on cognitive function and good efficacy in older patients include solifenacin and trospium chloride.

Surgery

Where conservative treatments have failed, surgery can be considered for selected cases.

- In women, options include colposuspension (particularly if associated with anterior compartment prolapse), suburethral slings/tapes or periurethral bulking agents for SUI, and surgery for POP.
- In men, sphincter incompetence can be treated with bulbourethral tapes and artificial urinary sphincter in appropriately selected cases.

1 Royal College of Physicians (1995) *Incontinence: causes, management and provision of services*, Report of a working party. London: RCP 1995 [online]. Available from: www.rcplondon.ac.uk.

Initial management of urinary incontinence in women

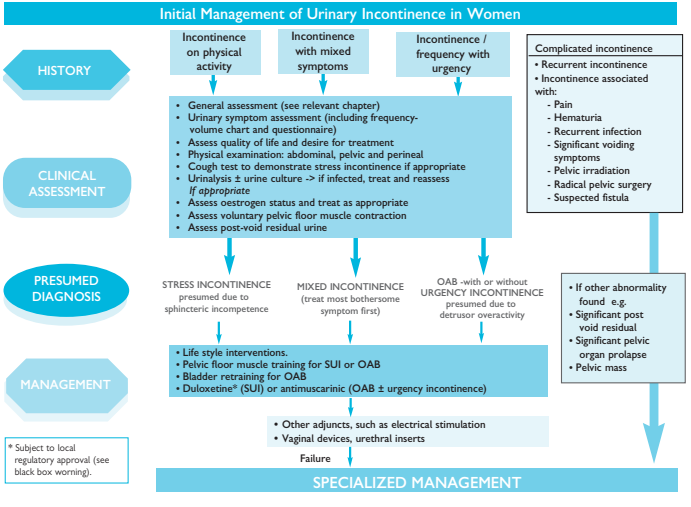

Fig. 5.7 International Continence Society (ICS) recommendations. Reproduced with permission from 4th International Consultation on Incontinence. Incontinence, 4th edition 2009. Ed. Abrams P, Cardozo L, Khoury S, Wein A. Health Publications Ltd 2009, p. 1785.

Specialized management of urinary incontinence in women

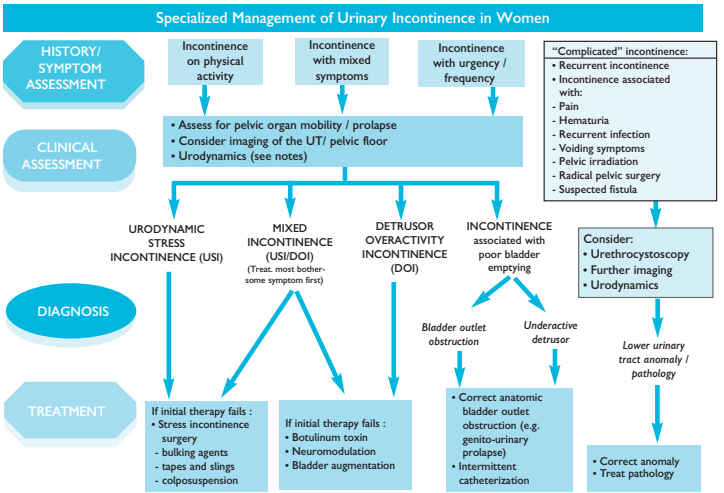

Fig. 5.8 International Continence Society (ICS) recommendations. Reproduced with permission from 4th International Consultation on Incontinence. Incontinence, 4th edition 2009. Ed. Abrams P, Cardozo L, Khoury S, Wein A. Health Publications Ltd 2009, p. 1787.

Initial management of urinary incontinence in men

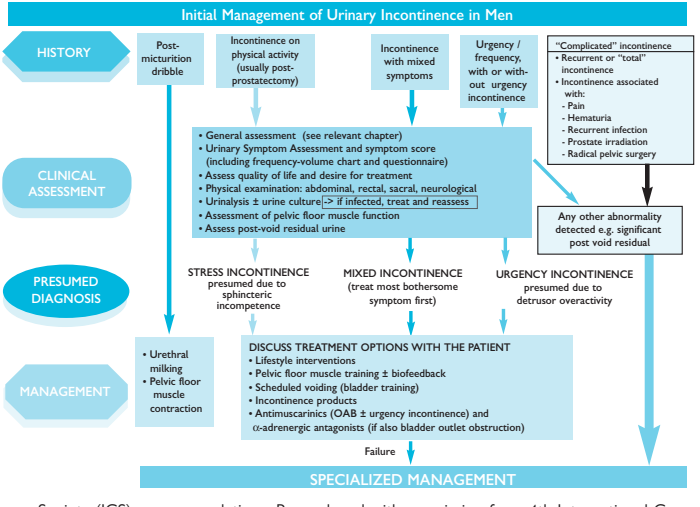

Fig. 5.9 International Continence Society (ICS) recommendations. Reproduced with permission from 4th International Consultation on Incontinence. Incontinence, 4th edition 2009. Ed. Abrams P, Cardozo L, Khoury S, Wein A. Health Publications Ltd 2009, p.1781.

Specialized management of urinary incontinence in men

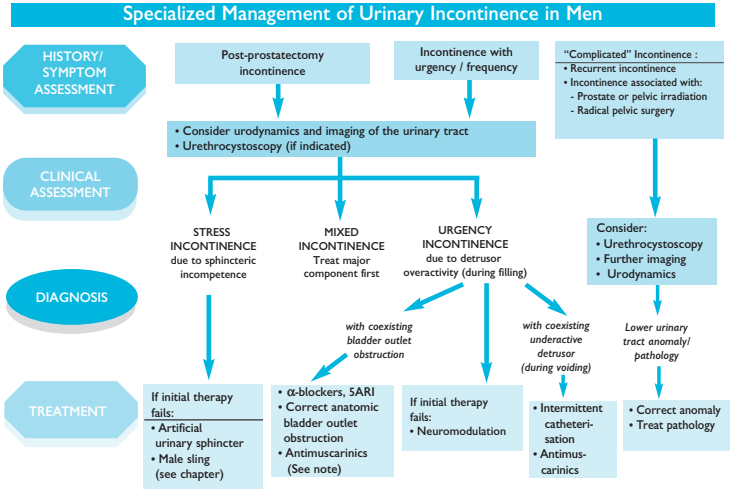

Fig. 5.10 International Continence Society (ICS) recommendations. Reproduced with permission from 4th International Consultation on Incontinence. Incontinence, 4th edition 2009. Ed. Abrams P, Cardozo L, Khoury S, Wein A. Health Publications Ltd 2009, p. 1783.

Management of urinary incontinence in frail older persons

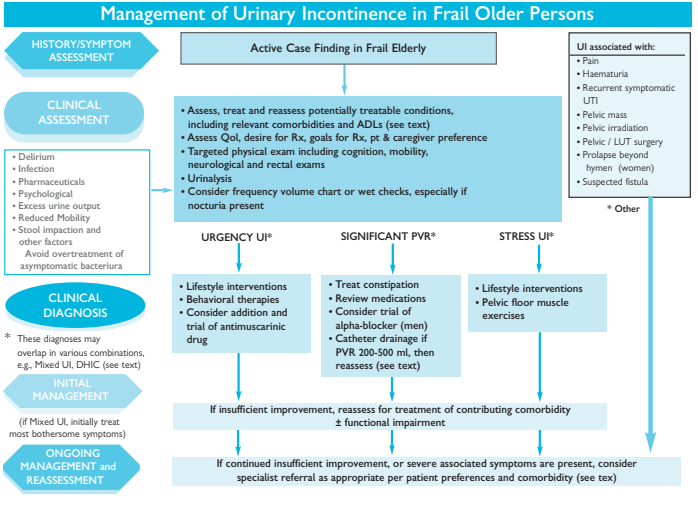

Fig. 5.11 International Continence Society (ICS) recommendations. Reproduced with permission from 4th International Consultation on Incontinence. Incontinence, 4th edition 2009. Ed. Abrams P, Cardozo L, Khoury S, Wein A. Health Publications Ltd 2009, p. 1798.

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Female urethral diverticulum (UD)

An epithelialized outpouching of urethral mucosa with a single connection (ostium) entering the urethral lumen. Affects women in the 3rd to 5th decades of life, with an incidence of 1–6%. The UK incidence has increased from 74 cases in 1998–1999 to 174 in 2009–2010, likely due to improved detected cases.[1] Some report a predilection in Afro-Caribbean races.

Aetiology

- Congenital (rare).
- Acquired.
  - Periurethral (Skene's) gland infection (by *Neisseria gonorrhoea*, *Escherichia coli*, other coliform bacteria, or normal vaginal flora) causes abscess formation and subsequent rupture into the urethral lumen. Repeated filling and stasis of urine in the cavity causes expansion of the diverticulum, recurrent infection, and epithelialization.
  - Trauma associated with childbirth (forceps delivery).
  - Previous urethral or vaginal surgery.
  - Repeated urethral instrumentation.

Classification

- Simple (most common).
- Horseshoe (or saddlebag).
- Circumferential types.

UD are single or multiple (10%) and located in the distal, middle (most common), or proximal urethra, usually seen as a midline anterior vaginal cystic swelling.

Presentation

The classical 'three Ds' (**d**ysuria, post-void **d**ribble, and **d**yspareunia) are only found in 23% of patients.[2] Patients report a wide array of symptoms, including urinary frequency, urgency, urethral discharge, recurrent UTI, incontinence, pain, obstructive symptoms, urinary retention, vaginal mass, and haematuria. Twenty percent of patients are asymptomatic.

Differential diagnoses

Skene's gland cysts or abscess, Gartner's duct cysts, vaginal wall inclusion cysts, vaginal leiomyoma, ectopic ureterocele, urethral carcinoma, and endometrioma.

Complications of UD

- Malignancy (5%).
- Stones (4–10%).
- Endometriosis.
- Rupture (can lead to fistula formation).

Assessment

History: voiding symptoms, dyspareunia, and urethral or vaginal discharge. It is common to have coexisting detrusor overactivity or SUI.

Examination: a midline anterior vaginal wall mass may be visualized or palpable in 80%[2] (Fig. 5.12). Gentle pressure can express urethral discharge in up to 40%.[2]

Investigation

- Bladder diary.
- MSU.
- Urethral pressure flowmetry may show a classical biphasic recording.
- Rigid cystourethroscopy to exclude concomitant bladder pathology.
- Twin channel urodynamics are recommended for patients with significant voiding symptoms or incontinence.

Imaging

- **MRI** (endoluminal or surface coil): is the gold standard investigation with up to 100% sensitivity. UD are identified as hyperdense areas on T2-weighted images (Fig. 5.13).
- **Micturating cystourethrography:** is up to 95% sensitive at detecting UD and useful for assessing concomitant voiding dysfunction.
- **USS** (transvaginal, transrectal, or transperineal): UD is seen as an anechoic or hypoechoic lesion with through-transmission of signal.
- **Double balloon high pressure urethrography:** involves infusion of contrast via a double balloon urethral catheter to delineate the UD cavity. It is up to 90% sensitive, but invasive and so is rarely used.

Treatment

Symptomatic UD requires surgery. The aims are dissection and excision of the diverticulum, identification and closure of the connection to the urethra (ostium), and a three-layered watertight closure ± an interpositional flap (Martius fat pad). Some advocate marsupialization for small distal third UD. A urethral catheter is placed for up to 14 days ± cystourethrogram prior to catheter removal (depending on the complexity of the repair).

The concomitant insertion of a pubovaginal sling or tape for SUI remains controversial. Many authors advocate initial UD surgery and reassessment of symptoms before proceeding with incontinence surgery.[2]

Complications and outcomes of surgery

- UTI (up to 40%).
- Recurrent UTI (23%).
- Incontinence.
- Recurrence of UD.
- Persistent or *de novo* LUTS.
- Urethrovaginal fistula (2%).
- Persistent pain or dyspareunia.
- Urinary retention.

Contemporary series report overall success rates for primary and redo surgery of 70–97%. Success rates for primary surgery are approximately 89%. [2]

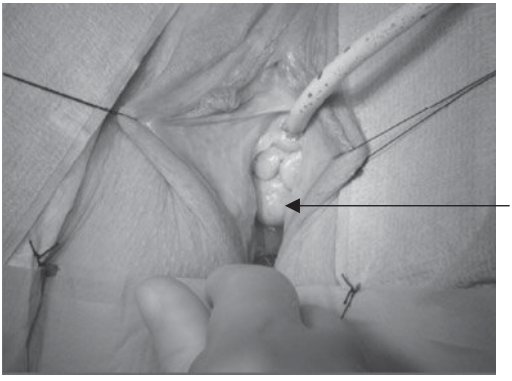

Fig. 5.12 Picture of a urethral diverticulum in a catheterized patient prior to surgery. (Kindly provided with permission from Tamsin Greenwell).

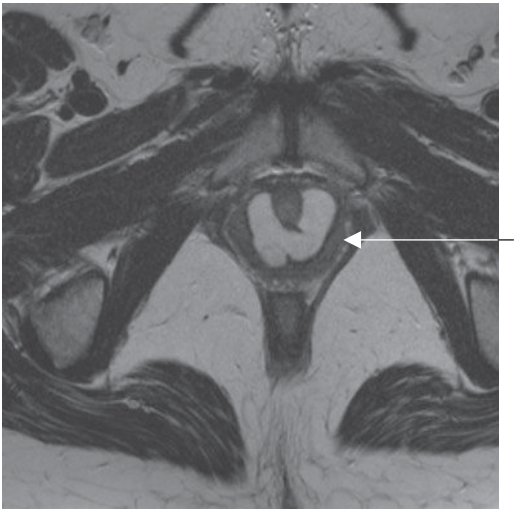

Fig. 5.13 T2-weighted axial magnetic resonance image demonstrating a horseshoe-shaped urethral diverticulum. (Kindly provided with permission from Tamsin Greenwell).

1 Department of Health, UK. Hospital Episode Statistics [online]. Available from: http://www.hesonline.nhs.uk.

2 Ockrim JL, Allen DJ, Shah PJ, Greenwell TJ (2009) A tertiary experience of urethral diverticulectomy: diagnosis, imaging and surgical outcomes. *BJU Int* **103**:1550–4.

Pelvic organ prolapse (POP)

Definitions

Anterior wall prolapse: is herniation of the bladder (cystocele) or urethra (urethrocele) through the anterior vaginal wall due to weakened pubocervical ligaments.

Posterior wall prolapse: is protrusion of the rectum through the posterior vaginal wall due to weakened perirectal fascia (rectocele) or protrusion of peritoneum (small intestine or omentum) into the vagina (enterocele).

Middle compartment prolapse: includes uterine prolapse (descent of the uterus secondary to weak cardinal or uterosacral ligaments), vault prolapse (descent of the vaginal cuff after hysterectomy) and procidentia (prolapse of the entire uterus).

Incidence

Approximately 50% of women develop prolapse after childbirth (20% is symptomatic). Lifetime risk of requiring POP or incontinence surgery is ~11% with 29% requiring repeat procedures.[1] Fifty percent are anterior, 30% posterior, and 20% uterine or vault prolapse.

Aetiology

Congenital: secondary to connective tissue abnormalities (spina bifida, exstrophy, Ehlers–Danlos syndrome).

Acquired (multifactorial): related to previous vaginal surgery (prolapse repair, colposuspension, hysterectomy); vaginal delivery; older age (decreased oestrogen levels), obesity, constipation, and chronic straining.

Staging

Pelvic organ prolapse quantification (POPQ) is a validated system which allows standardized and accurate prolapse description by measuring distances between defined anatomical points and the hymen (Fig. 5.14; Tables 5.4 and 5.5). An alternative is the Baden–Walker classification (Table 5.3).[2]

Table 5.3 Baden–Walker classification of POP[2]

Grade 0	No prolapse
Grade 1	Descent halfway to the hymen
Grade 2	Descent to hymen
Grade 3	Descent halfway past the hymen
Grade 4	Maximal descent/eversion

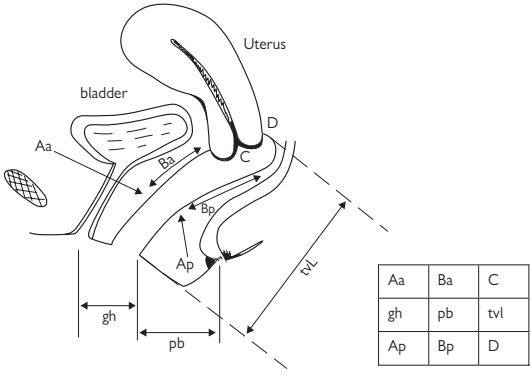

Fig. 5.14 Anatomical reference points used for POPQ.

Table 5.4 Description of anatomical points used in POPQ

Anatomical point	Description	Range of values
Anterior wall, **Aa**	Anterior vaginal wall 3cm proximal to the external meatus	–3cm to + 3cm
Anterior wall, **Ba**	Most distal part of remaining upper anterior vaginal wall	–3cm to + tvl
Cervix or cuff, **C**	Most distal edge of cervix or vaginal cuff (vault)	
Posterior wall, **Ap**	Posterior vaginal wall 3cm proximal to the hymen	–3cm to + 3cm
Posterior wall, **Bp**	Most distal position of the remaining upper posterior vaginal wall	–3cm to + tvl
Posterior fornix, **D**		
Genital hiatus, **gh**	Measured from middle of external urethral meatus to posterior midline hymen	
Perineal body, **pb**	Measured from posterior margin of gh to middle of anal orifice	
Total vaginal length, **tvl**	Depth of vagina when point D or C is returned to normal position	

Table 5.5 ICS staging of POP based on POPQ

Stage	Leading edge of POP in relation to hymen	Description
0	<–3cm	No prolapse
1	<–1cm	Prolapse >1cm above the level of the hymen
2	≤+1 and ≥+1cm	Prolapse between 1cm above or 1cm below the hymen
3	>+1cm	Prolapse >1cm below the hymen, but without complete vaginal eversion
4	≥tvl—2cm	Complete vaginal eversion. Protrusion minimally extends beyond hymen further than tvl—2cm

Presentation

History

- Vaginal pressure or bulge.
- Urinary frequency, urgency, incomplete emptying, incontinence.
- Bowel dysfunction (urgency, difficulty defecating, faecal soiling).
- Symptoms aggravated by prolonged standing.
- May need to manually reduce prolapse to void or defecate.
- Sexual dysfunction (dyspareunia, lack of sensation).

Examination

- Examine in lithotomy, left lateral position using a Sims' speculum, and standing.
- Cough or bear down when retracting the posterior wall to demonstrate anterior or middle compartment prolapse. Anterior prolapse may be due to a central fascial defect (vagina wall looks smooth) or lateral defects (vaginal has rugae).
- Retract anterior wall to visualize posterior compartment prolapse.
- Cough test for SUI. Should repeat with prolapse reduced as may unmask occult SUI.

Investigation

- MSU.
- Bladder diary.
- PVR.
- Urodynamics (if concomitant voiding dysfunction or incontinence; ICS recommends it for prolapse > stage II where surgery is planned).
- MRI (selected cases).
- Defaecography (isotope or contrast).

Treatment

Conservative

- Lifestyle intervention (treat constipation, chronic cough).
- PFMT.
- Vaginal pessary—individually fitted and changed in clinic initially every 3–6 months with inspection for vaginal ulceration or fistulae. Treat any vaginal atrophy.

Surgery

Repair may be with absorbable interrupted buttress sutures, with an on-lay mesh strip cut to size or with pre-designed mesh (i.e. AMS Elevate® and Gynecare Prolift®).There is controversy as to whether SUI should be treated at the same time as prolapse. This will be addressed by RCT CUPIDO.

Anterior compartment

Interrupted sutures are placed in remnant fascia, excise surplus vaginal skin, and close. Gynecare Prolift® is a tension-free vaginal mesh system using a trocar delivery system to guide placement of a pre-shaped mesh. AMS Elevate® has pre-shaped mesh which is positioned with a slim needle device and then held in place by self-fixing tips and also supports the middle compartment.

If there is coexisting SUI, options include prolapse repair and insertion of a tension-free vaginal tape or alternatively, a primary colposuspension (15% risk of posterior wall prolapse).

Posterior compartment

Repair with suture or mesh as above.

Middle compartment prolapse

- **Uterine prolapse:** options include vaginal or abdominal hysterectomy. An alternative for women wishing to preserve the uterus is sacrohysteropexy. An open or laparoscopic approach may be taken. A strip of mesh encircles the cervix and is then sutured to the sacrum.
- **Vault prolapse:** options include:
  - Sacrospinous fixation involves (unilateral) suspension of the vaginal vault (or cervix) to the sacrospinous ligament with two sutures via a posterior vaginal approach.
  - Sacrocolpopexy involves suspension of the anterior and posterior aspects of the vaginal vault to the sacrum by strips of mesh and non-absorbable sutures which are then covered with peritoneum to avoid bowel adhesion.
  - Uterosacral ligament suspension where the uterosacral ligament is sutured to the vaginal apex.

1 Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL (1997) Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstet Gynecol* **89**:501-6.

2 Baden WF, Walker TA, Lindsay HJ (1968) The vaginal profile. *Tex Med J* **64**:56–8.

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Chapter 6

Infections and inflammatory conditions

Urinary tract infection: definitions and epidemiology

Definitions

Urinary tract infection (UTI)

UTI is currently defined as the inflammatory response of the urothelium to bacterial invasion. This inflammatory response causes a constellation of symptoms. Bladder infection (**cystitis**) causes frequent small volume voids, urgency, suprapubic pain or discomfort, and urethral 'burning' on voiding (dysuria). Acute kidney infection (**acute pyelonephritis**) causes symptoms of fever, chills, malaise, and loin pain, often with associated LUTS of frequency, urgency, and urethral pain on voiding. The strict requirement for $>10^5$ bacteria/mL of MSU specimen is no longer required to make a diagnosis of UTI. In symptomatic patients, many clinicians will now make a diagnosis of UTI with bacterial counts of $>10^2$/mL. Current recommendations for diagnosing UTI from MSU culture is shown in Table 6.2.

Bacteriuria: is the presence of bacteria in the urine. Bacteriuria may be asymptomatic or symptomatic. Bacteriuria without pyuria indicates the presence of bacterial colonization of the urine rather than the presence of active infection.

Pyuria: is the presence of white blood cells in the urine (implying an inflammatory response of the urothelium to bacterial infection or in the absence of bacteriuria (sterile pyuria), some other pathology such as carcinoma *in situ*, TB infection, bladder stones, or other inflammatory conditions.

An uncomplicated UTI: is one occurring in a patient with a structurally and functionally normal urinary tract. The majority of such patients are women who respond quickly to a short course of antibiotics.

A complicated UTI: is one occurring in the presence of an underlying anatomical or functional abnormality (e.g. incomplete bladder emptying secondary to BOO or DSD in SCI), renal or bladder stones, colovesical fistula, etc. Other factors suggesting a potential complicated UTI are diabetes mellitus, immunosuppression, hospital-acquired infection, indwelling catheter, recent urinary tract intervention, and a failure of response to appropriate treatment. Most UTIs in men occur in association with a structural or functional abnormality and are, therefore, defined as complicated UTIs. Complicated UTIs take longer to respond to antibiotic treatment than uncomplicated UTIs and if there is an untreated underlying abnormality, they will usually recur within days, weeks, or months.

UTIs may be isolated, recurrent, or unresolved.

- **Isolated UTI:** an interval of at least 6 months between infections.
- **Recurrent UTI:** >2 infections in 6 months or 3 within 12 months. Recurrent UTI may be due to re-infection (i.e. infection by different bacteria) or bacterial persistence (infection by the same organism originating from a focus within the urinary tract). Bacterial persistence is caused by the presence of bacteria within calculi (e.g. struvite stone), within a chronically infected prostate (chronic bacterial prostatitis), within an obstructed or atrophic infected kidney, or occurs as a result of a bladder fistula (with bowel or vagina) or UD.

- **Unresolved infection:** implies inadequate therapy and is caused by natural or acquired bacterial resistance to treatment, infection by (multiple) different organisms, or rapid re-infection.

Table 6.1 Prevalence of bacteriuria

Age	Female	Male
Infants (<1y)	1%	3%
School (<15y)	1–3%	<1%
Reproductive	4%	<1%
Elderly	20–30%	10%

General risk factors for bacteriuria

- Female sex.
- Increasing age.
- Low oestrogen states (menopause).
- Pregnancy.
- Diabetes mellitus.
- Previous UTI.
- Institutionalized elderly patients.
- Indwelling catheters.
- Stone disease (kidney, bladder).
- Genitourinary tract malformation.
- Voiding dysfunction (including obstruction).

Table 6.2 Recommended criteria for diagnosing UTI[1]

Type of UTI	Urine culture (cfu/mL)
Acute uncomplicated UTI/cystitis in women	$>10^3$
Acute uncomplicated pyelonephritis	$>10^4$
Complicated UTI	$>10^5$ in women; $>10^4$ in men
Asymptomatic bacteriuria	$>10^5$ in two consecutive MSU cultures >24h apart
Recurrent UTI	$<10^3$

cfu/mL = colony forming units/mL; MSU = midstream urine.

1 Grabe M, Bjerklund-Jphansen TE, Botto H, *et al.* Guidelines on Urological Infections. European Association of Urology Guidelines 2011 edition.

Urinary tract infection: microbiology

Most UTIs are caused by faecal-derived bacteria that are facultative anaerobes (i.e. they can grow under both anaerobic and non-anaerobic conditions) (see Table 6.3).

Uncomplicated UTI

Infection in a subject with a normal functional and anatomical urinary tract. Most UTIs are bacterial in origin. The most common cause is *Escherichia coli (E. coli)*, a Gram-negative bacillus, which accounts for 85% of community-acquired and 50% of hospital-acquired infections. Other common causative organisms include *Staphylococcus saprophyticus*, *Proteus mirabilis,* and *Klebsiella*.

Complicated UTI

Infection in a subject with a functional or anatomical abnormality of the urinary tract, underlying risk factors, or failure to respond to therapy. *E. coli* is responsible for up to 50% of cases. Other causes include Enterococci, Staphylococci, *Pseudomonas*, *Proteus*, *Klebsiella,* and other enterobacteria.

Route of infection

Ascending

The vast majority of UTIs result from infection ascending retrogradely up the urethra. Bacteria, derived from the large bowel, colonize the perineum, vagina, and distal urethra. They ascend along the urethra to the bladder (increased risk in females as urethra shorter), causing cystitis. From the bladder, they may ascend via the ureters to involve the kidneys (pyelonephritis). Reflux is not necessary for infection to ascend to the kidneys, but it will encourage ascending infection as will any process that impairs ureteric peristalsis (e.g. ureteric obstruction, Gram-negative organisms and endotoxins, pregnancy). Infection that ascends to involve the kidneys is also more likely where the infecting organism has P pili (filamentous protein appendages, also known as fimbriae, which allow binding of bacteria to the surface of epithelial cells).

Haematogenous: uncommon, but is seen with *Staphylococcus (S.) aureus*, Candida fungaemia, and *Mycobacterium (M.) tuberculosis* (causing TB).

Infection via lymphatics: seen rarely in inflammatory bowel disease and from retroperitoneal abscess.

Table 6.3 Classification of bacteria and other organisms associated with the urinary tract and UTI

Cocci	Gram +ve Aerobes	Streptococcus	Non-haemolytic: Enterococcus (*E. faecalis*)
			α-haemolytic: *S. viridians*; β-haemolytic streptococcus
		Staphylococcus	*S. saprophyticus* (causes ~10% of symptomatic lower UTIs in young, sexually active women)
			S. aureus
			S. epidermidis
	Gram –ve Aerobes	Neisseria	*N. gonorrhoeae*
Bacilli (rods)	**Gram +ve** Aerobes	Corynebacteria	*C. urealyticium*
	Acid-fast	Mycobacteria	*M. tuberculosis*
	Gram +ve Anaerobes*	Lactobacillus	(i.e. *L. crispatis, L. Jensenii* are common vaginal commensal organisms)
			Clostridium perfringens
	Gram –ve Aerobes	Enterobacteriacaeae	*Escherichia coli, Proteus mirabilis, Klebsiella sp.*
		Non-fermenters	*Pseudomonas aeruginosa*
	Gram –ve Anaerobes*	Bacteroides	*Bacteroides fragilis*
Other organisms		Chlamydia	*C. trachomatis*
		Mycoplasma	*M. hominus*
		Ureaplasma	*U. urealyticum* (cause UTI in patients with indwelling catheters
		Candida	*C. albicans*

* Anaerobic infections of the bladder and kidney are uncommon—anaerobes are normal commensals of the perineum, vagina, and distal urethra. However, infections of the urinary system that produce pus (e.g. scrotal, prostatic, or perinephric abscesses) can be caused by anaerobic organisms (e.g. Bacteroides sp. such as *Bacteroides fragilis*, Fusobacterium sp., anaerobic cocci, and *Clostridium perfringens*).

Factors increasing bacterial virulence

Adhesion mechanisms

Many Gram-negative bacteria have pili (also known as fimbriae) on their cell surface, which aid attachment to urothelial cells of the host. A typical piliated cell may contain 100–400 pili. Pili are 5–10nm in diameter and up to 2μm long. *E. coli* produces a number of antigenically and functionally different types of pili on the same cell; other strains may produce only a single type and in some isolates, no pili are seen (such as Dr adhesin associated with UTI in pregnant women and children). Pili are defined functionally by their ability to mediate haemagglutination (clumping of red blood cells) of specific types of erythrocytes. Mannose-sensitive (type 1) pili are produced by all strains of *E. coli* and are associated with cystitis. Certain pathogenic types of *E. coli* also produce mannose-resistant P pili and are associated with pyelonephritis. S pili are associated with infection of both the bladder and kidneys.

Avoidance of host defence mechanisms

- **General:** an extracellular capsule reduces immunogenicity and resists phagocytosis (*E. coli*). *M. tuberculosis* resists phagocytosis by preventing phagolysosome fusion.
- **Toxins:** *E. coli* species have haemolysin activity which has a direct pathogenic effect on host erythrocytes.
- **Enzyme production:** *Proteus* species produce ureases which cause the breakdown of urea in urine to ammonia, which then contributes to disease processes (struvite stone formation).

Antimicrobial resistance

- **Enzyme inactivation:** *S. aureus*, *N. gonorrhoeae*, and enterobacteria can produce β-lactamase which hydrolyzes the β-lactam bond within the structure of some antibiotics so inactivating them. The β-lactam antibiotics are penicillins, cephalosporins, and carbapenems.
- **Altered permeability:** access of the antibiotic to the bacteria is prevented by alterations in receptor activity or transport mechanisms.
- **Alteration of binding site:** genetic variations may alter the antibiotic target, leading to drug resistance.

Host defences: factors that protect against UTI include the following.

General

- Commensal flora: protect by competing for nutrients, bacteriocin production, stimulation of immune system, and altering pH.
- Mechanical integrity of mucous membranes.
- Mucosal secretions: lysozymes split muramic acid links in cell walls of Gram-positive organisms; lactoferrin disrupts normal metabolism of bacteria.
- Urinary immunoglobulin A (IgA) inhibits bacterial adherence.

Specific

- Mechanical flushing effect of urine through the urinary tract (i.e. antegrade flow of urine).
- A mucopolysaccharide coating of bladder (Tamm–Horsfall protein) helps prevent bacterial attachment.
- Bladder surface mucin: glycosaminoglycan (GAG) layer is an anti-adherent factor, preventing bacterial attachment to mucosa.
- Low urine pH and high osmolarity reduces bacterial growth.
- Female commensal flora: *Lactobacillus acidophilus* metabolizes glycogen into lactic acid, causing a drop in pH.
- Increased rates of bladder mucosal cell exfoliation are seen during infection, which accelerates cell removal with adherent bacteria.

Lower urinary tract infection: cystitis and investigation of UTI

Cystitis: is infection and/or inflammation of the bladder.

Presentation: frequent voiding of small volumes, dysuria, urgency, offensive urine, suprapubic pain, haematuria, fever ± incontinence.

General investigation of UTI

Dipstick of MSU specimen

White blood cells (indirect testing for pyuria)

Leukocyte esterase activity detects the presence of white blood cells (WBC) in the urine. Leukocyte esterase is produced by neutrophils and causes a colour change in a chromogen salt on the dipstick. Not all patients with bacteriuria have significant pyuria (sensitivity of 75–95% for detection of infection, i.e. 5–25% of patients with infection will have a negative leukocyte esterase test, erroneously suggesting that they have no infection).

- False positives (pyuria present, negative dipstick test)—concentrated urine, glycosuria, presence of urobilinogen, consumption of large amounts of ascorbic acid.
- False negatives (pyuria absent, positive dipstick test)—contamination.

Remember, there are many causes for pyuria (and, therefore, a positive leukocyte esterase test occurring in the absence of bacteria on urine microscopy). This is so-called sterile pyuria and it occurs with TB infection, renal calculi, bladder calculi, glomerulonephritis, interstitial cystitis, and carcinoma *in situ*. Thus, the leukocyte esterase dipstick test may be truly positive in the absence of infection.

Nitrite testing (indirect testing for bacteriuria)

Nitrites are not normally found in urine and their presence suggests the possibility of bacteriuria. Many species of Gram-negative bacteria can convert nitrates to nitrites and these are detected in the urine by a reaction with the reagents on the dipstick which form a red azo dye. The specificity of the nitrite dipstick for detecting bacteriuria is >90% (false positive nitrite testing can occur with contamination). The sensitivity is 35–85% (i.e. false negatives are common—a negative dipstick in the presence of active infection) and is less accurate in urine containing $<10^5$ organisms/mL. Hence, if the nitrite dipstick test is positive, the patient probably has a UTI, but a negative test often occurs in the presence of infection.

Cloudy urine, which is positive for WBCs on dipstick and is nitrite-positive, is very likely to be infected.

Blood

Haemoglobin has a peroxidase-like activity, causing oxidation of a chromogen indicator on the dipstick, which changes colour when oxidized. False positives are seen with menstrual blood and dehydration.

pH

Urinary pH usually lies between 5.5 and 6.5 (range 4.5–8). A persistent alkaline pH associated with UTI indicates a risk of stones. Urease-producing bacteria (such as *Proteus mirabilis*) hydrolyze urea to ammonia and carbon dioxide, leading to the formation of magnesium, calcium, ammonium phosphate stones (triple phosphate or struvite calculi).

Microscopy of MSU

- False negative: low bacterial counts may make it very difficult to identify bacteria and the specimen of urine may, therefore, be deemed to be negative for bacteriuria when, in fact, there is active infection.
- False positive: bacteria may be seen in the MSU in the absence of infection. This is most often due to contamination with commensals from the distal urethra and perineum (urine from a woman may contain thousands of lactobacilli and corynebacteria derived from the vagina). These bacteria are readily seen under the microscope and although they are Gram-positive, they often appear Gram-negative (Gram-variable) if stained.

If the urine specimen contains large numbers of squamous epithelial cells (cells which are derived from the foreskin, vaginal, or distal urethral epithelium), this suggests contamination of the specimen and the presence of bacteria in this situation may indicate a false positive result. The finding of pyuria and red blood cells suggests the presence of active infection.

Further investigation

Determined by the clinical scenario. If this is a one-off infection in an otherwise healthy individual, no further investigations are required. However, further investigations are required if:

- The patient develops symptoms and signs of upper tract infection (loin pain, malaise, fever) and, therefore, acute pyelonephritis, a pyonephrosis or perinephric abscess is suspected.
- Recurrent UTIs develop (see 🕮 p. 186).
- The patient is pregnant.
- Unusual infecting organism (e.g. *Proteus*), suggesting the possibility of an infection stone.

These further investigations will include a KUB X-ray ± IVU (looking for infection stones in the kidney; avoid in pregnant women), renal USS ± cystoscopy.

Non-infective cystitis

Symptoms of cystitis can also be caused by:

- Pelvic radiotherapy (radiation cystitis—bladder capacity is reduced and multiple areas of mucosal telangiectasia are seen cystoscopically).
- Drug-induced cystitis (e.g. cyclophosphamide, ketamine).

Urinary tract infection: general treatment guidelines

Antimicrobial drug therapy

The aim is to eliminate bacterial growth from the urine. Empirical treatment involves the administration of antibiotics according to the clinical presentation and most likely causative organism before culture sensitivities are available (Table 6.4). Men are often affected by complicated UTI and may require longer treatments as may patients with uncorrectable structural or functional abnormalities (e.g. indwelling catheters, neuropathic bladders).

Bacterial resistance to drug therapy

Organisms susceptible to concentrations of an antibiotic in the urine (or serum) after the recommended clinical dosing are termed 'sensitive' and those that do not respond are 'resistant'. Bacterial resistance may be intrinsic (e.g. *Proteus* is intrinsically resistant to nitrofurantoin) via selection of a resistant mutant during initial treatment or genetically transferred between bacteria by R plasmids. Antibiotic-resistant organisms that cause complicated UTI include Gram-negative bacteria that produce AmpC enzymes or extended spectrum β-lactamases (ESBLs) (which are often multidrug resistant) and Gram-positive cocci such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCoNS), and vancomycin-resistant enterococci (VRE). To avoid increasing resistance, it is not advisable to commence antibiotics without clinical evidence of a UTI (exceptions include asymptomatic bacteriuria in pregnancy) and local microbiology guidelines should be followed.

Definitive treatment

Once urine or blood culture results are available, antimicrobial therapy should be adjusted according to bacterial sensitivities. Underlying abnormality should be corrected if feasible (i.e. extraction of infected calculus; removal of catheter; nephrostomy drainage of an infected, obstructed kidney). Post-menopausal women may benefit from topical oestrogen treatment.

General preventative advice

Encourage a good fluid intake, cranberry juice, double voiding, avoid constipation. In women—voiding before and after intercourse; wiping perineum from 'front to back' after voiding; avoid using bubble bath or washing hair in the bath (as this affects the protective commensal organisms, the lactobacilli).

Table 6.4 Recommendations for antimicrobial therapy[1]

Infection	Bacteria	Initial empirical drug	Duration
Acute, uncomplicated cystitis	*E. coli, Klebsiella, Proteus, Staphylococci*	Nitrofurantoin	55–7 days
		Alternatives:	
		Trimethoprim	55 days
		Co-trimoxazole	33 days
		Fluoroquinolone (ciproflox-acin)	33 days
Acute, uncomplicated pyelonephritis	*E. coli, Proteus, Klebsiella, other Enterobacteriacae, Staphylococci*	Fluoroquinolone	7–10 days
		Cephalosporin	
		Alternatives:	
		Aminopenicillin	
		with beta-lactamase inhibitor (BLI)	
		(amoxicillin/clavulanic acid)	
		Aminoglycoside (gentamicin)	
Complicated UTI	*E. coli, Enterococcus, Pseudomonas, Staphylococci*	Fluoroquinolone	Continue for 3–5 days after control of infection/ elimination of underlying cause. Parenteral treatment is usually followed by oral antibiotics to complete course
		Aminopenicillin/BLI	
		Cephalosporin	
Nosocomial* UTI	*Staphylococcus, Klebsiella, Proteus*	Carbapenem (meropenem)	
		±Aminoglycoside	
Acute compli-cated pye-lonephritis	*Enterobacter, Pseudomonas, (Candida)*	For Candida:	
		–Fluconazole	
		–Amphotericin B	

*Nosocomial = hospital acquired.

These are general recommendations only, adapted from EAU guidelines, to fit with common UK antibi-otic use. You should be guided by your local microbiology department whose recommendations will be based on local and regional bacterial sensitivities and resistance.

1 Grabe M, Bjerklund-Johansen TE, Botto H, *et al.* Guidelines on Urological Infections. European Association of Urology Guidelines 2011 edition.

Recurrent urinary tract infection

Recurrent UTI is defined as >2 infections in 6 months or 3 within 12 months. It may be due to re-infection (i.e. infection by different bacteria) or bacterial persistence (infection by the same organism originating from a focus within the urinary tract).

Bacterial persistence

Bacterial persistence usually leads to frequent recurrence of infection (within days or weeks) and the infecting organism is usually the same organism as that causing the previous infection(s). There is often an underlying functional or anatomical problem and infection will often not resolve until this has been corrected. Causes include kidney stones, the chronically infected prostate (chronic bacterial prostatitis), bacteria within an obstructed or atrophic infected kidney, vesicovaginal or colovesical fistula, and bacteria within a urethral diverticulum.

Re-infection

This usually occurs after a prolonged interval (months) from the previous infection and is often caused by a different organism than the previous infecting bacterium.

Women: with re-infection, do not usually have an underlying functional or anatomical abnormality. Re-infections are associated with increased vaginal mucosal receptivity for uropathogens and ascending colonization from faecal flora. These women cannot be cured of their predisposition to recurrent UTIs, but they can be managed by a variety of techniques (see 🕮 p. 176).

Men: with re-infection, may have underlying BOO (due to BPE or a urethral stricture), which makes them more likely to develop a repeat infection, but between infections, their urine is sterile (i.e. they do not have bacterial persistence between symptomatic UTIs). A flexible cystoscopy, post-void bladder USS for residual urine volume and in some cases, urodynamics or urethrography may be helpful in establishing the potential causes.

Both men and women with bacterial persistence usually have an underlying functional or anatomical abnormality and they can potentially be cured of their recurrent UTIs if this abnormality can be identified and corrected.

Management of women with recurrent UTIs due to re-infection

Imaging tests, including KUB X-ray and renal USS, and flexible cystoscopy, can be performed to check for potential sources of bacterial persistence (i.e. to confirm this is a 'simple' case of re-infection rather than one of bacterial persistence). In the absence of finding an underlying functional or anatomic abnormality, these patients cannot be cured of their tendency to recurrent urinary infection, but they can be managed in several ways.

Preventative and conservative management

- Maintain a high fluid intake.
- Avoidance of spermicides used with the diaphragm or on condoms. Spermicides containing nonoxynol-9 reduce vaginal colonization with lactobacilli and may enhance *E. coli* adherence to urothelial cells. Recommend an alternative form of contraception.
- Cranberry juice or tablets (contains proanthocyanidins which inhibit bacterial adherence).
- Oestrogen replacement. A lack of oestrogen in post-menopausal women causes loss of vaginal lactobacilli and increased colonization by *E. coli*. Oestrogen replacement (topical or systemic) can result in recolonization of the vagina with lactobacilli and help eliminate colonization with bacterial uropathogens.[1]
- Natural yoghurt applied to the vulva and vagina can help restore normal flora, thereby improving the natural resistance to recurrent infections.
- Alkalinization of the urine with potassium citrate or sodium bicarbonate can help alleviate symptoms of cystitis.

Low-dose antibiotic prophylaxis

Oral antimicrobial therapy with full-dose oral tetracyclines, ampicillin, sulphonamides, amoxicillin, and cefalexin causes resistant strains in the faecal flora and subsequent resistant UTIs. However, trimethoprim, nitrofurantoin, and low-dose cefalexin have minimal adverse effects on the faecal and vaginal flora.

- **Efficacy of prophylaxis:** recurrences of UTI may be reduced up to 90% when compared with placebo.[2] Only small doses of antimicrobial agent are required, generally given at bedtime for 6–12 months. Symptomatic re-infection during prophylactic therapy is managed with a full therapeutic dose with the same prophylactic antibiotic or another antibiotic. Prophylaxis can then be restarted. Symptomatic re-infection immediately after cessation of prophylactic therapy is managed by restarting nightly prophylaxis.
- **Trimethoprim:** the gut is a reservoir for organisms that colonize the periurethral area, which may cause episodes of acute cystitis in young women. Trimethoprim eradicates Gram-negative aerobic flora from the gut and vaginal fluid (i.e. it eliminates the pathogens from the infective source). Trimethoprim is also concentrated in bactericidal concentrations in the urine following an oral dose. *Adverse reactions:* include gastro-intestinal (GI) disturbance, rash, purities, depression of haematopoiesis, allergic reactions. *Rare side effects:* erythema multiforme, toxic epidermal necrolysis, photosensitivity. Use with caution in renal impairment as it can increase creatinine by competitively inhibiting tubular secretion.
- **Nitrofurantoin:** is completely absorbed and/or inactivated in the upper intestinal tract and, therefore, has no effect on gut flora. It is present for brief periods at high concentrations in the urine and leads to repeated elimination of bacteria from the urine. Nitrofurantoin prophylaxis, therefore, does not lead to a change in vaginal or introital colonization with Enterobacteria. The bacteria colonizing

the vagina remain susceptible to nitrofurantoin because of the lack of bacterial resistance in the faecal flora. *Adverse reactions:* include GI upset, chronic pulmonary reactions (pulmonary fibrosis), peripheral neuropathy, allergic reactions (angioedema, anaphylaxis, urticaria, rash, and pruritus). *Rare side effects:* blood dyscrasias (agranulocytosis, thrombocytopenia, aplastic anaemia), liver damage. Risk of an adverse reaction increases with age (particularly >50y old).

- **Cefalexin:** at 250mg or less nightly is an excellent prophylactic agent because faecal resistance does not develop at this low dosage. *Adverse reactions:* GI upset, allergic reactions.
- **Fluoroquinolones** (e.g. ciprofloxacin): short courses eradicate Enterobacteria from faecal and vaginal flora. The (longer term) use of ciprofloxacin is increasingly discouraged, with some hospitals not allowing its routine use in an attempt to reduce the incidence of symptomatic *Clostridium difficile*.
  - *Adverse reactions:* tendon damage (including rupture) which may occur within 48h of starting treatment. The risk of tendon rupture is increased by the concomitant use of corticosteroids.
  - *Contraindicated:* in patients with a history of tendon disorders related to quinolone use. Discontinue quinolone immediately if tendonitis suspected (elderly patients are most prone to tendonitis).
  - *Other adverse reactions:* GI upset, Stevens–Johnson syndrome, allergic reactions.

Post-intercourse antibiotic prophylaxis

Sexual intercourse has been established as an important risk factor for acute cystitis in women and women using the diaphragm have a significantly greater risk of UTI those using other contraceptive methods.[3] Post-intercourse therapy with antimicrobials, such as nitrofurantoin, cefalexin, or trimethoprim, taken as a single dose effectively reduces the incidence of re-infection.

Self-start therapy

Women keep a home supply of an antibiotic (e.g. trimethoprim, nitrofurantoin, or a fluoroquinolone) and start treatment when they develop symptoms suggestive of UTI.

Management of men and women with recurrent UTIs due to bacterial persistence

Investigation

These are directed at identifying the potential causes of bacterial persistence outlined on 📖 p. 186.

- KUB X-ray to detect radio-opaque renal calculi.
- Renal USS to detect hydronephrosis and renal calculi. If hydronephrosis is present, but the ureter is not dilated, consider the possibility of a radio-opaque stone obstructing the pelviureteric junction (PUJ) or a PUJ obstruction (PUJO).
- Determination of PVR volume by bladder USS.
- IVU or CTU where a stone is suspected, but not identified on plain X-ray or USS.

- Flexible cystoscopy to identify possible causes of recurrent UTIs such as bladder stones, an underlying bladder cancer (rare), urethral or bladder neck stricture, or fistula.

Treatment

This depends on the functional or anatomical abnormality that is identified as the cause of the bacterial persistence. If a stone is identified, this should be removed. If there is obstruction (e.g. BOO, PUJO, DSD in spinal injured patients), this should be corrected.

1 Raz R, Stamm WE (1993) A controlled trial in intravaginal estriol in postmenopausal women with recurrent urinary tract infection. *N Engl J Med* **329**:753.

2 Nicolle LE, Ronald AR (1987) Recurrent urinary tract infection in adult women: diagnosis and treatment. *Infect Dis Clin North Am* **1**:793.

3 Fihn SD, Latham RH, Roberts P, *et al.* (1985) Association between diaphragm use and urinary tract infection. *JAMA* **254**:240.

Upper urinary tract infection: acute pyelonephritis

Definition: pyelonephritis is an inflammation of the kidney and renal pelvis.

Presentation

Clinical diagnosis is based on the presence of fever, flank pain, bacteriuria, pyuria, often with an elevated white cell count. Nausea and vomiting are common. It may affect one or both kidneys. There are usually accompanying symptoms suggestive of a lower UTI (frequency, urgency, suprapubic pain, urethral burning or pain on voiding) responsible for the subsequent ascending infection to the kidney.

Differential diagnosis: includes cholecystitis, pancreatitis, diverticulitis, appendicitis.

Risk factors: females > males, VUR, urinary tract obstruction, calculi, SCI (neuropathic bladder), diabetes mellitus, congenital malformation, pregnancy, indwelling catheters, urinary tract instrumentation.

Pathogenesis and microbiology: initially, there is patchy infiltration of neutrophils and bacteria in the parenchyma. Later changes include the formation of inflammatory bands extending from the renal papilla to cortex and small cortical abscesses. Eighty percent of infections are secondary to *E. coli* (possessing P pili virulence factors). Other infecting organisms: Enterococci (*E. faecalis*), *Klebsiella*, *Proteus*, Staphylococci, and *Pseudomonas*. Any process interfering with ureteric peristalsis (i.e. obstruction) may assist in retrograde bacterial ascent from bladder to kidney.

Investigation and treatment

- For those patients who have a fever, but are not systemically unwell, outpatient management is reasonable. Culture the urine and start oral antibiotics according to your local antibiotic policy (which will be based on the likely infecting organisms and their likely antibiotic sensitivity). EAU guidelines[1] give several suggestions, including fluoroquinolones (i.e. oral ciprofloxacin, 500 mg bd) for 7–10 days. Aminopenicillin with β-lactamase inhibitor (i.e. co-amoxiclav) is an alternative.
- If the patient is systemically unwell, resuscitate, culture urine and blood, start intravenous (IV) fluids and IV antibiotics, again selecting the antibiotic according to your local antibiotic policy. EAU guideline[1] options include IV aminopenicillin with β-lactamase inhibitor ± aminoglycoside (gentamicin) with monitoring of levels. Alternatives include cephalosporins (i.e. ceftazidime) and carbapenems (i.e. meropenem).
- Arrange a KUB X-ray and renal USS to see if there is an underlying upper tract abnormality (such as a ureteric stone), unexplained

hydronephrosis, or (rarely) gas surrounding the kidney (suggesting emphysematous pyelonephritis).

- If the patient does not respond within 3 days to a regimen of appropriate IV antibiotics (confirmed on sensitivities), arrange a computed tomography urogram (CTU). Failure of response to treatment suggests possible pyonephrosis (i.e. pus in the kidney which will only respond to drainage), a perinephric abscess (which again will only respond to drainage), or emphysematous pyelonephritis. The CTU may demonstrate an obstructing ureteric calculus that may have been missed on the KUB X-ray and USS may show a perinephric abscess. A pyonephrosis should be drained by insertion of a percutaneous nephrostomy tube. A perinephric abscess should also be drained by insertion of a drain percutaneously.
- If the patient responds to IV antibiotics, change to an oral antibiotic of appropriate sensitivity when they become apyrexial (3–5 days after control of infection or after elimination of underlying problem) and continue this for approximately 10–14 days.

1 Grabe M, Bjerklund-Johansen TE, Botto H, *et al.* (2011) Guidelines on urological infections. European Association of Urology Guidelines 2011 [online]. Available from: http://www.uroweb.org/gls/pdf/15_Urological_Infections.pdf.

Pyonephrosis and perinephric abscess

Pyonephrosis

An infected hydronephrosis where pus accumulates within the renal pelvis and calyces. It is associated with damage to the parenchyma, resulting in loss of renal function. The causes are essentially those of hydronephrosis where infection has supervened (e.g. ureteric obstruction by stone, PUJ obstruction).

Presentation

Patients with pyonephrosis are usually very unwell with a high fever, flank pain, and tenderness.

Risk factors

Stone disease, previous UTI, or surgery.

Investigation

- **KUB X-ray:** may show an air urogram (secondary to gas produced by infecting pathogens).
- **USS:** shows evidence of obstruction (hydronephrosis) with a dilated collecting system, fluid–debris levels or air in the collecting system.
- **CT:** shows hydronephrosis, stranding of perinephric fat, and thickening of renal pelvis.

Treatment

IV fluids and antibiotics (as for pyelonephritis) with urgent percutaneous drainage (nephrostomy) or ureteric drainage (via ureteric catheter under endoscopic and X-ray guidance).

Perinephric abscess

Perinephric abscess develops as a consequence of extension of infection outside the parenchyma of the kidney in acute pyelonephritis, from rupture of a cortical abscess, or if obstruction in an infected kidney (i.e. pyonephrosis) is not drained quickly enough. More rarely, it is due to haematogenous spread of infection from a distant site or infection from adjacent organs (i.e. bowel). The abscess develops within Gerota's fascia.

Risk factors

Diabetes mellitus; immunocompromise; obstructing ureteric calculus may precipitate the development of a perinephric abscess.

Causes

Perinephric abscesses are caused by *S. aureus* (Gram-positive), *E. coli*, and *Proteus* (Gram-negative organisms).

Presentation

Patients present with fever, unilateral flank tenderness, and ≥5 day history of milder symptoms. Failure of a seemingly straightforward case of acute pyelonephritis to respond to IV antibiotics within a few days also arouses suspicion that there is an accumulation of pus in or around the kidney or obstruction with infection.

A flank mass with overlying skin erythema and oedema may be observed. Extension of the thigh (stretching the psoas) may trigger pain and psoas spasm may cause a reactive scoliosis.

Investigation

- **FBC**: shows raised white cell count and CRP.
- **Urine analysis and cultures**.
- **Blood cultures:** are required to identify organisms responsible for the haematogenous spread of infection (i.e. *S. aureus*).
- **USS** or **CTU**: can identify size, site, and extension of retroperitoneal abscesses and allow radiographically controlled percutaneous drainage of the abscess.

Treatment

Commence broad-spectrum IV antibiotics (i.e. aminoglycoside and aminopenicillin with β-lactamase inhibitor) until culture sensitivities are available. Drainage of the collection should be performed, either radiographically or by formal open incision and drainage if the pus collection is large. IV antibiotics should be used initially and followed by a course of oral antimicrobials until clinical review and re-imaging confirms resolution of infection. Nephrectomy may be required for extensive renal involvement or a non-functioning infected kidney.

Acute pyelonephritis, pyonephrosis, perinephric abscess, and emphysematous pyelonephritis—making the diagnosis

Maintaining a degree of suspicion in all cases of presumed acute pyelonephritis is the single most important thing in allowing an early diagnosis of complicated renal infection such as a pyonephrosis, perinephric abscess, or emphysematous pyelonephritis to be made. If the patient is very unwell, is diabetic, or has a history suggestive of stones, they may have something more than just a simple acute pyelonephritis. Specifically ask about a history of sudden onset of severe flank pain a few days earlier, suggesting the possibility that a stone passed into the ureter, with later infection supervening. Arranging a KUB X-ray and renal USS in all patients with suspected renal infection will demonstrate the presence of hydronephrosis, pus, or stones.

Clinical indicators suggesting a more complex form of renal infection are length of symptoms prior to treatment and time taken to respond to treatment. Most patients with uncomplicated acute pyelonephritis have been symptomatic for <5 days. Most with, for example, a perinephric abscess have been symptomatic for >5 days prior to hospitalization. Patients with acute pyelonephritis became afebrile within 4–5 days of treatment with an appropriate antibiotic whereas those with perinephric abscesses remained pyrexial.[1]

1 Thorley JD, Jones SR, Sanford JP (1974) Perinephric abscess. *Medicine* **53**:441.

Other forms of pyelonephritis

Emphysematous pyelonephritis (EPN)

A rare severe form of acute necrotizing pyelonephritis caused by gas-forming organisms. It is characterized by fever and abdominal pain, with radiographic evidence of gas within and around the kidney (on plain radiography or CT) (Fig. 6.1). It usually occurs in diabetics (93% in a contemporary series)[1] and, in many cases, is precipitated by urinary obstruction by, for example, ureteric stones. The high glucose levels associated with poorly controlled diabetes provides an ideal environment for fermentation by Enterobacteria, carbon dioxide being produced during this process. EPN is commonly caused by *E. coli*, less frequently by *Klebsiella* and *Proteus*.

Presentation

Severe acute pyelonephritis (high fever and systemic upset) that fails to respond to IV antibiotics within 2–3 days.

Investigation

KUB X-ray may show a crescent or kidney-shaped distribution of gas around the kidney. Renal USS often demonstrates strong focal echoes, indicating gas within the kidney. CT can help classify the disease. Type I shows parenchymal destruction, an absence of fluid collection, or streaky gas from the medulla to cortex—this has a poorer prognosis. Type II shows intrarenal gas and renal or perirenal fluid, or collecting system gas—this has a better prognosis.

Management

Patients with EPN are usually very unwell (to the extent that many are not fit enough for emergency nephrectomy) and mortality is high. Resuscitate and transfer to ITU/HDU. In recent years, management has moved away from emergency nephrectomy to an approach with IV antibiotics, IV fluids, percutaneous drainage, and careful control of diabetes.[1] Where there is no symptomatic improvement, have a low threshold for rescanning (CT) and consider additional percutaneous drainage for 'pockets' of infection that have not been adequately drained.[1] In those where sepsis is poorly controlled, emergency nephrectomy may be required.

Xanthogranulomatous pyelonephritis (XGP)

A severe renal infection, usually (although not always) occurring in association with underlying renal calculi and renal obstruction. Three forms exist: focal (XGP in the renal cortex with no pelvic communication), segmental, and diffuse. The severe infection results in the destruction of renal tissue, leading to a non-functioning kidney. *E. coli* and *Proteus* are common causative organisms. Lipid-laden, 'foamy' macrophages become deposited around abscesses within the parenchyma of the kidney. The infection may be confined to the kidney or extend to the perinephric fat. The kidney becomes grossly enlarged and macroscopically contains yellowish nodules (pus) and areas of haemorrhagic necrosis. It can be very difficult to distinguish the radiological findings from a renal cancer on imaging studies such

as CT. Indeed, in most cases, the diagnosis is made after nephrectomy for what was presumed to be a renal cell carcinoma.

Presentation

Acute flank pain, fever, haematuria, LUTS, and a tender flank mass. It affects all age groups, females more often than males.

Complications

Fistula (nephrocutaneous, nephrocolonic), paranephric abscess, psoas abscess.

Investigation

Blood tests show anaemia and leukocytosis. Bacteria (*E. coli*, *Proteus*) may be found on culture urine. Renal USS shows an enlarged kidney containing echogenic material. CT may identify (obstructing) renal or urinary tract calculi, hydronephrosis, renal cortical thinning, and perinephric fat inflammation. Non-enhancing cavities are seen, containing pus and debris. On radioisotope scanning (DMSA, MAG3 renogram), there may be some or no function in the affected kidney.

Management

On presentation, these patients are usually commenced on antibiotics as the constellation of symptoms and signs suggest infection. If systemically unwell, transfer to ITU/HDU for treatment. When imaging studies are done, such as CT, the appearances usually suggest the possibility of a renal cell carcinoma and, therefore, when signs of infection have resolved, the majority of patients will proceed to nephrectomy. Often, only following pathological examination of the removed kidney will it become apparent that the diagnosis was one of infection (XGP) rather than tumour.

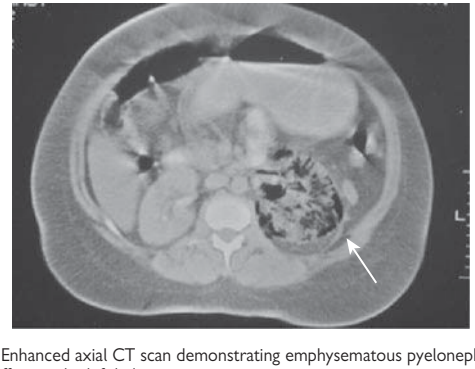

Fig. 6.1 Enhanced axial CT scan demonstrating emphysematous pyelonephritis (type I) affecting the left kidney.

Image kindly provided with permission from Professor S. Reif.

1 Aswathaman K, Gopalakrishnan G, Gnanaraj L, *et al.* (2008) Emphysematous pyelonephritis: Outcome of conservative management. *Urology* **71**:1007–9.

Chronic pyelonephritis

In essence, this describes *renal scarring* which may or may not be related to previous UTI. It is a radiological, functional, or pathological diagnosis or description.

Causes

- Renal scarring due to previous infection.
- Long-term effects of VUR, with or without superimposed infection.

A child with VUR, particularly where there is reflux of infected urine, will develop reflux nephropathy (which, if bilateral, may cause renal impairment or renal failure). If the child's kidneys are examined radiologically (or pathologically if they are removed by nephrectomy), the radiologist or pathologist will describe the appearances as those of 'chronic pyelonephritis'.

An adult may also develop radiological and pathological features of chronic pyelonephritis due to the presence of reflux or BOO combined with high bladder pressures, again particularly where the urine is infected. This was a common occurrence in male patients with SCI and DSD before the advent of effective treatments for this condition.

Pathogenesis

Chronic pyelonephritis is essentially the end result of longstanding reflux (non-obstructive chronic pyelonephritis) or of obstruction (obstructive chronic pyelonephritis). These processes damage the kidneys, leading to scarring and the degree of damage and subsequent scarring is more marked if infection has supervened.

Presentation

Patients may be asymptomatic or present with symptoms secondary to renal failure. Diagnosis is often from incidental findings during general investigation. There is usually no active infection.

Appearances on imaging

Scars can be 'seen' radiologically on a renal USS, IVU, renal isotope scan, or CT. The scars are closely related to a deformed renal calyx. Distortion and dilatation of the calyces is due to scarring of the renal pyramids. These scars typically affect the upper and lower poles of the kidneys because these sites are more prone to intrarenal reflux. The cortex and medulla in the region of a scar is thin. The kidney may be so scarred that it becomes small and atrophic.

Management

Aim to investigate and treat any infection, prevent further UTI, and monitor and optimize renal function.

Complications

Renal impairment progressing to end-stage renal failure in bilateral cases (usually only if chronic pyelonephritis is associated with an underlying structural or function urinary tract abnormality).

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Septicaemia

Bacteraemia: is the presence of pathogenic organisms in the bloodstream. This can lead to ***septicaemia*** or ***sepsis***—the clinical syndrome caused by bacterial infection of the blood. This is confirmed by positive blood cultures for a specific organism and accompanied by a systemic response to the infection known as the ***systemic inflammatory response syndrome (SIRS)***. SIRS is defined by at least two of the following:

- Fever (>38°C) or hypothermia (<36°C).
- Tachycardia (>90 beats/min in patients not on β-blockers).
- Tachypnoea (respiration >20 breaths/min or $PaCO_2$ <4.3kPa or a requirement for mechanical ventilation).
- White cell count >12 000 cells/mm^3, <4000 cells/mm^3, or >10% immature (band) forms.

Septicaemia is often accompanied by ***endotoxaemia***—the presence of circulating bacterial endotoxins.

Severe sepsis: sepsis associated with organ dysfunction (hypoperfusion or hypotension). Hypoperfusion and perfusion abnormalities may include lactic acidosis, oliguria, or acute altered mental state.

Septic shock: sepsis with hypotension[1] despite adequate fluid resuscitation with perfusion abnormalities that may include lactic acidosis, oliguria, or acute altered mental state. It results from Gram-positive bacterial toxins or Gram-negative endotoxins which trigger the release of cytokines (TNF, IL-1), vascular mediators, and platelets, resulting in vasodilatation (manifest as hypotension) and disseminated intravascular coagulation (DIC).

Refractory shock: is defined as septic shock (lasting >1h) which fails to respond to therapy (fluids or pharmacotherapy).

Causes of urinary sepsis

In the hospital setting, the most common causes are the presence or manipulation of indwelling urinary catheters, urinary tract surgery (particularly endoscopic—TURP, TURBT, ureteroscopy, PCNL), and urinary tract obstruction (particularly that due to stones obstructing the ureter). Septicaemia occurs in approximately 1.5% of men undergoing TURP. Diabetic patients, patients in ITU, and immunocompromised patients (on chemotherapy and steroids) are more prone to urosepsis.

Causative organisms in urinary sepsis: *E. coli*, Enterococci, Staphylococci, *Pseudomonas*, *Klebsiella*, and *Proteus*.

Management

The principles of management include early recognition, resuscitation, localization of the source of sepsis, early and appropriate antibiotic administration, and removal of the primary source of sepsis. From a urological perspective, the clinical scenario is usually a post-operative patient who has undergone TURP or surgery for stones. On return to the ward, they become pyrexial, start to shiver (chills) and shake, and are tachycardic and tachypnoea (leading initially to respiratory alkalosis). They may be confused and oliguric. They may initially be peripherally vasodilated (flushed appearance with warm peripheries). Consider the possibility of a

non-urological source of sepsis (e.g. pneumonia). If there are no indications of infection elsewhere, assume the urinary tract is the source of sepsis.

Investigations

- **FBC**: the white blood count is usually elevated. The platelet count may be low—a possible indication of impending DIC.
- **Coagulation screen**: this is important if surgical or radiological drainage of the source of infection is necessary.
- **Urea and electrolytes**: as a baseline determination of renal function and CRP which is usually elevated.
- **Arterial blood gases**: to identify hypoxia and the presence of metabolic acidosis.
- **Urine culture**: an immediate Gram stain may aid in deciding which antibiotic to use.
- **Blood cultures**.
- **Imaging**: guided by clinical findings (i.e. CXR looking for pneumonia, atelectasis, and effusions; renal USS may be helpful to demonstrate hydronephrosis or pyonephrosis; CT if suspicious of renal calculi, urinary tract anomalies, or infected pelvic collections, etc.).

Treatment

- A (**A**irway), B (**B**reathing), C (**C**irculation).
- 100% oxygen via a face-mask.
- Establish IV access with two wide-bore cannulae.
- IV crystalloid (e.g. normal saline) or colloid (e.g. Gelofusin®).
- Catheterize to monitor urine output.
- Empirical antibiotic therapy (see 📖 p. 200). This should be adjusted later when cultures are available.
- If there is septic shock, the patient needs to be transferred to ITU. Inotropic support may be needed with invasive monitoring (central line, arterial line). Steroids may be used as adjunctive therapy in Gram-negative infections. Naloxone may help revert endotoxic shock. Blood glucose is carefully controlled and recombinant activated protein C has proven benefit in severe sepsis. This should all be done under the supervision of an intensivist.
- Treat the underlying cause. Drain any obstruction and remove any foreign body. If there is a stone obstructing the ureter, preferably arrange for nephrostomy tube insertion to relieve the obstruction. If the patient is stable, an alternative is to take the patient to theatre for JJ ureteric stent insertion. Send any urine specimens obtained for microscopy and culture.

1 Hypotension in septic shock is defined as a sustained systolic BP <90mmHg, or a drop in systolic pressure of >40mmHg for >1h, when the patient is normovolaemic, and other causes have been excluded or treated.

Empirical treatment of septicaemia

This is 'blind' use of antibiotics based on an educated guess of the most likely pathogen that has caused the sepsis. Gram-negative aerobic rods are common causes of urosepsis (e.g. *E. coli*, *Klebsiella*, *Citrobacter*, *Proteus*, and *Serratia*). The enterococci (Gram-positive aerobic non-haemolytic Streptococci) may sometimes cause urosepsis. In urinary tract operations involving the bowel, anaerobic bacteria may be the cause of urosepsis and in wound infections, staphylococci (e.g. *S. aureus* and *S. epidermidis*) are the usual cause.

Recommendations for treatment of urosepsis[1]

Refer to your local microbiology guidelines. Options include:

- A third-generation cephalosporin (e.g. IV cefotaxime or ceftriaxone). These are active against Gram-negative bacteria, but have less activity against staphylococci and Gram-positive bacteria. Ceftazidime also has activity against *Pseudomonas*.
- Fluoroquinolones (e.g. ciprofloxacin) are an alternative to cephalosporins. They exhibit good activity against enterobacteriaceae and *Pseudomonas*, but less activity against staphylococci and enterococci. GI tract absorption of ciprofloxacin is good so oral administration is as effective as IV.
- (Consider metronidazole if there is a potential anaerobic source of sepsis.)
- If no clinical response to these antibiotics, consider a combination of antipseudomonal acylaminopenicillin and β-lactamase inhibitor (i.e. piperacillin and tazobactam; trade name Tazocin®). This combination is active against enterobacteriaceae, enterococci, and *Pseudomonas*.
- Carbapenems (i.e. meropenem, imipenem, ertapenem). Broad-spectrum with good activity against Gram-positive and Gram-negative bacteria, including anaerobes. Meropenem and imipenem are also active against *Pseudomonas*.
- Aminoglycoside (i.e. gentamicin) is used in conjunction with other antibiotics. It has a relatively narrow therapeutic spectrum against Gram-negative organisms. Close monitoring of therapeutic levels and renal function is important. It has good activity against enterobacteriaceae and *Pseudomonas* with poor activity against streptococci and anaerobes and, therefore, should ideally be combined with β-lactam antibiotics or ciprofloxacin.

If there is clinical improvement, parenteral treatment (IV) should continue for 3–5 days after the infection has been controlled (or complicating factor has been eliminated), followed by a course of oral antibiotics. Make appropriate adjustments when sensitivity results are available from urine cultures (which may take about 48h).

Mortality rate: 13% with septicaemia alone; 28% with septicaemia and shock; 43% with septicaemia followed by septic shock.[2]

1 Grabe M, Bjerklund-Johansen TE, Botto H, *et al.* (2011) Guidelines on urological infections. European Association of Urology Guidelines [online]. Available from: http://www.uroweb.org/gls/pdf/15_Urological_Infections.pdf.

2 Bone RC, Fisher CJ Jr, Clemmer TP, *et al.* (1989) Sepsis syndrome: a valid clinical entity. Methyl-prednisolone Severe Sepsis Study Group. *Crit Care Med* **17**:389–93.

Fournier's gangrene

A necrotizing fasciitis of the external genitalia and perineum, primarily affecting males and causing necrosis and subsequent gangrene of infected tissues. Also known as spontaneous fulminant gangrene of the genitalia, it is a urological emergency.

Causative organisms

Culture of infected tissue reveals a combination of aerobic (*E. coli*, enterococci, *Klebsiella*) and anaerobic organisms (*Bacteroides*, *Clostridium*, micro-aerophilic streptococci) which are believed to grow in a synergistic fashion.

Predisposing factors

- Diabetes mellitus.
- Chronic alcohol excess.
- Local trauma to the genitalia and perineum (e.g. zipper injuries to the foreskin, periurethral extravasation of urine following traumatic catheterization, or instrumentation of the urethra).
- Surgical procedures such as circumcision.
- Paraphimosis.
- Perianal and perirectal infections.

Pathophysiology

Fournier's gangrene is usually related to an initial genitourinary tract infection, skin trauma, or from direct extension from a perirectal focus. Spread of infection is through the local fascia (Buck's fascia in the penis, Darto's fascia in the scrotum, Colle's fascia in the perineal region, and Scarpa's fascia of the anterior abdominal wall). Infection produces tissue necrosis that can spread rapidly and pus produced by anaerobic pathogens (*Bacteroides*) produces the typical putrid smell.

Presentation

A previously well patient may become systemically unwell following a seemingly trivial injury to the external genitalia. Early clinical features include localized skin erythema, tenderness and oedema, and sometimes with LUTS (dysuria, difficulty voiding, urethral discharge). This progresses to fever and sepsis with cellulitis and palpable crepitus in the affected tissues, indicating the presence of subcutaneous gas produced by gas-forming organisms. As the infection advances, blisters (bullae) appear in the skin and within a matter of hours, areas of necrosis may develop, which spread to involve adjacent tissues (e.g. lower abdominal wall).

Diagnosis

The diagnosis is a clinical one and is based on the awareness of the condition and a high index of suspicion. In early stages of disease, abdominal X-ray, and scrotal USS, or CT may demonstrate the presence of air in tissues. CT can also indicate the extent of disease, however, most surgeons would not delay to image the patient, but progress directly to surgical treatment.

Management

- Do not delay.
- Resuscitate the patient: obtain IV access and take bloods (FBC, U & E, LFT, CRP, clotting, group & save) and blood cultures. Start IV fluids, administer oxygen, check and control blood sugars in diabetics.
- Broad-spectrum parenteral antibiotics are given immediately to cover both Gram-positive and Gram-negative aerobes and anaerobes (e.g. combination of aminopenicillin with β-lactamase inhibitor plus gentamicin plus clindamycin or metronidazole). Refer to your local microbiology guidelines.
- Inform ITU/HDU.
- Transfer the patient to theatre as quickly as possible for debridement of necrotic tissue until healthy bleeding tissue margins are found. Extensive areas may have to be removed, but it is unusual for the testes or deeper penile tissues to be involved and these can usually be spared. Send tissue for culture.
- If there is extensive perineal/perianal involvement, faecal diversion with colostomy may be required.
- Wound irrigation with hydrogen peroxide may be used at the end.
- A suprapubic catheter is inserted to divert urine and allow monitoring of urine output.
- Repeat examination under anaesthetic ± further debridement to remove residual necrotic tissue is required at 24h and then guided by clinical progress.
- Where facilities allow, treatment with hyperbaric oxygen therapy can be beneficial.[1]
- Treat the underlying comorbidity or cause, i.e. optimize diabetic control.
- Vacuum-assisted closure of wounds can hasten patient recovery.
- Reconstruction can be contemplated when wound healing is complete.

Mortality is in the order of 20–30%. Mortality rates are reported to be higher in patients with a degree of immunocompromise (diabetics, alcohol excess) and those with anorectal or colorectal disease/involvement. Mortality risk can be assessed by the Fournier's gangrene severity index (FGSI)[2] based on nine clinical parameters: respiratory rate, heart rate, temperature, WBC count, haematocrit, sodium, potassium, creatinine, and sodium bicarbonate levels. Each parameter was valued between 0 and 4, with the higher value given to the greatest deviation from normal. FGSI >9 correlates with increased mortality (46–75%);[2,3] FGSI <9 has a reported 78–96% chance of survival.[2,3]

1 Pizzorno R, Bonini F, Donelli A, *et al.* (1997) Hyperbaric oxygen therapy in the treatment of Fournier's gangrene in 100 male patients. *J Urol* **158**:837–40.

2 Laor E, Palmer LS, Tolia BM, *et al.* (1995) Outcome prediction in patients with Fournier's gangrene. *J Urol* **154**:89.

3 Corcoran AT, Smaldone MC, Gibbons EP, *et al.* (2008) Validation of the Fournier's gangrene severity index in a large contemporary series. *J Urol* **180**:944–8.

Peri-urethral abscess

Peri-urethral abscess can occur in patients with urethral stricture disease following urethral catheterization and in association with gonococcal urethritis. The bulbar urethra is a commonly affected site in men. These conditions predispose to bacteria (Gram-negative rods, enterococci, anaerobes, gonococcus) gaining access through Buck's fascia to the peri-urethral tissues. If not rapidly diagnosed and treated, infection (necrotizing fasciitis) can spread to the perineum, buttocks, and abdominal wall. In immunocompromised patients (i.e. patients with HIV infection), *M. tuberculosis* is also a causative organism.

Presentating features

- Scrotal swelling.
- Tender, inflamed area on the perineum or under the penis.
- Fever.
- Urinary retention (>20%).
- Urethral discharge (10%).
- Spontaneous discharge of abscess through the urethra (10%).

Complications

Extravasation of urine from the abscess cavity may result in cellulitis and a risk of fistula formation.

Management

Emergency treatment is required. The abscess should be incised and drained, a suprapubic catheter placed to divert the urine away from the urethra, and broad-spectrum parenteral antibiotics commenced (gentamicin and cephalosporin) until antibiotic sensitivities are known. Any devitalized and necrotic tissue requires immediate surgical debridement.

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Epididymitis and orchitis

Acute epididymitis

An inflammatory condition of the epididymis, often also involving the testis, and usually caused by bacterial infection. It has an acute onset and a clinical course lasting <6 weeks, presenting with epididymal pain, swelling, and tenderness. It can occur in all age groups.

Pathogenesis

Infection ascends from the urethra or bladder. In sexually active men aged <35y, the infective organism is usually *N. gonorrhoeae*, *C. trachomatis*, or coliform bacteria (causing a urethritis which then ascends to infect the epididymis). In older men and children, the infective organisms are usually common uropathogens (i.e. *E. coli*). *M. tuberculosis* (TB) is a rarer cause of epididymitis where the epididymis feels like a 'beaded' cord (see 📖 p. 220).

A rare, non-infective cause of epididymitis is the antiarrhythmic drug, amiodarone, which accumulates in high concentrations within the epididymis, causing inflammation.[1] It can be unilateral or bilateral and resolves on discontinuation of the drug. Some cases of epididymitis in children are also non-infective (idiopathic or as a result of trauma).

Presentation

Fever; testicular swelling; scrotal pain that may radiate to the groin (spermatic cord) and lower abdomen; erythema of scrotal skin; thickening of spermatic cord; reactive hydrocele; evidence of underlying infection (urethral discharge, symptoms of urethritis, cystitis, or prostatitis).

Differential diagnosis

- Testicular torsion is the main differential diagnosis. In torsion, pain and swelling are more acute and localized to the testis whereas epididymitis is mainly preceded by infective symptoms with pain, tenderness, and swelling tending to be confined to the epididymis.

If any doubt in the diagnosis exists, exploration is the safest option. Although radionuclide scanning can differentiate between a torsion and an epididymitis, this is not widely available. Colour Doppler USS, which provides a visual image of blood flow, can differentiate between a torsion and epididymitis, but its sensitivity for diagnosing torsion is only 80% (i.e. it 'misses' the diagnosis in 20% of cases). Its sensitivity for diagnosing epididymitis is about 70%.

- Torsion of testicular appendage.
- Acute haemorrhage within a testicular tumour.
- Testicular trauma.
- Mumps orchitis.

Investigation

- FBC, U & E, CRP, and blood cultures (if systemically unwell).
- Urine dipstick ± culture (PCR of first void urine to detect chlamydia).
- Urethral swab/culture of any urethral discharge.
- Scrotal USS.

Treatment

Bed rest, analgesia, scrotal elevation, and antibiotics.

Until culture sensitivities are available and where *C. trachomatis* is a possible infecting organism, prescribe a 14-day course of doxycycline 100mg twice daily (an alternative is a single dose of azithromycin 1g). If gonorrhoea is suspected or confirmed, prescribe ciprofloxacin (500mg bd for 14 days). An alternative is a single dose of oral cefixime (400mg). Patients should be referred for genitourinary medicine (GUM) input and tracing of sexual contacts.

For non-sexually transmitted infection of the epididymis, prescribe antibiotics empirically (until culture results are available) according to your local microbiology department advice. Our empirical antibiotic regimen is ciprofloxacin for 2 weeks. When the patient is systemically unwell, we admit them for IV cephalosporin and IV gentamicin (initially 3–5mg/kg, then adjusted according to serum gentamicin concentration). When the patient becomes apyrexial, we change to oral ciprofloxacin for 2 weeks. Any underlying cause of infection should be identified and treated (i.e. BOO) to prevent further episodes.

Complications

These include abscess formation (requiring incision and drainage), infarction of the testis, chronic pain and infection, and infertility.

Chronic epididymitis

Diagnosed in patients with long-term pain in the epididymis (± testicle). It can result from recurrent episodes of acute epididymitis. Clinically, the epididymis is thickened and may be tender. Treatment is with the appropriate antibiotics (guided by cultures) and analgesia. Epididymectomy is reserved for severe refractory cases.

Orchitis

Orchitis is inflammation of the testis, although it often occurs with epididymitis (epididymo-orchitis). Causes include the mumps virus, *M. tuberculosis*, syphilis, autoimmune processes (granulomatous orchitis). The testis is swollen and tense, with oedema of connective tissues and inflammatory cell infiltration. Treat the underlying cause.

Mumps orchitis occurs in 30% of infected post-pubertal males. It manifests 3–4 days after the onset of parotitis and can result in tubular atrophy. Ten to thirty percent of cases are bilateral and are associated with testicular atrophy and infertility.

1 Gasparich JP, Mason JT, Greene HL, *et al.* (1984) Non-infectious epididymitis associated with amiodarone therapy. *Lancet* **2**:1211–2.

Prostatitis: classification and pathophysiology

Prostatitis is infection and/or inflammation of the prostate, which is described as acute or chronic and bacterial or abacterial. The classification system is from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institute of Health (NIH) in the United States. Chronic abacterial prostatitis is further divided into inflammatory and non-inflammatory types, guided by the results of segmented urine cultures.

NIKKD/NIH classification of prostatitis[1]

- **I** Acute bacterial prostatitis.
- **II** Chronic bacterial prostatitis.
- **III** Chronic pelvic pain syndrome (CPPS): chronic abacterial prostatitis.
- **III_A** Inflammatory CPPS: WBC in expressed prostatic secretions (EPS), post-prostatic massage urine (VB_3), or semen.
- **III_B** Non-inflammatory CPPS: no WBC in EPS, VB_3, or semen.
- **IV** Asymptomatic inflammatory prostatitis (histological prostatitis).

Segmented urine cultures

Technique described by Meares and Stamey (1968) to help classify the type of prostatitis. It localizes bacteria to a specific part of the urinary tract by sampling different parts of the urinary stream with prostatic massage which produces EPS. Where cultures are negative, increased numbers of leukocytes per high powered field (>10) on microscopy favours a diagnosis of inflammatory CPPS.

Thirty minutes before the test, the patient should drink 400mL of fluid. Retract foreskin and cleanse the glans before specimen collection.

- **VB1**: first 10–15mL of urine voided. Positive culture indicates urethritis or prostatitis.
- **VB2**: MSU collection of 10–15mL (the patient is asked to void 100–200mL in total). Positive culture indicates cystitis.
- **EPS**: the prostate is massaged whilst holding a sterile container below the glans to catch secretions. Positive culture indicates prostatitis.
- **VB3**: first 10–15mL of urine voided following prostatic massage. Positive culture indicates prostatitis.

Epidemiology

Prostatitis is estimated to affect 50% of men at some point in their lives. The overall prevalence is reported at 5–14%. Age groups at increased risk are 20–50y and >70y.

Pathophysiology

Bacterial prostatitis

The most common infective pathogens are Gram-negative Enterobacteriaceae (*E. coli* in 80% of cases, *Klebsiella*, *Proteus*, *Pseudomonas*). Both type 1 and P pili are important bacterial virulence factors that facilitate

infection. Five to ten percent of infections are caused by Gram-positive bacteria (*S. aureus* and *S. saprophyticus*, *E. faecalis*). Acute bacterial prostatitis is often secondary to infected urine refluxing into prostatic ducts that drain into the posterior urethra. The resulting oedema and inflammation may then obstruct the prostatic ducts, trapping uropathogens and causing progression to chronic bacterial prostatitis in ~5%.

Inflammatory and non-inflammatory prostatitis

The underlying aetiology is not fully understood, but is likely to be multifactorial. The Multidisciplinary Approach to Pelvic Pain (MAPP) research project has been set up to evaluate the importance and impact of various 'clinical phenotypes' for CPPS. Essentially, patients may have a predominance of certain symptoms or conditions that feature in their disease, suggestive of the main underlying aetiology (i.e. neurological, endocrine, immunological, infectious, neuromuscular, and psychosocial components). The MAPP study aims to identify potential biomarkers relating to these 'clinical phenotypes' which will ultimately help with the diagnosis and direct patient specific management.

1 Krieger JN, Nyberg LJ, Nickel JC (1999) NIH consensus definition and classification of prostatitis. *JAMA* **282:**236–7.

Bacterial prostatitis

Acute bacterial prostatitis

Acute infection of the prostate associated with lower urinary tract infection and generalized sepsis. The underlying focus or cause of initial infection should be identified and also treated (i.e. BOO, urethral stricture, voiding dysfunction, urinary tract stones).

Risk factors

Factors that predispose to genitourinary tract and then prostatic colonization with bacteria are:

- UTI.
- Acute epididymitis.
- Indwelling urethral catheters.
- Transurethral surgery.
- Intraprostatic ductal reflux.
- Phimosis.
- Prostatic stones.

Presentation

- Acute onset of fevers, chills, nausea, and vomiting.
- Pain: perineal/prostatic, suprapubic, penile, groin, external genitalia.
- Urinary symptoms: 'irritative'—frequency, urgency, dysuria; 'obstructive'—hesitancy, strangury, intermittent stream, urinary retention.
- Signs of systemic toxicity: fever, tachycardia, hypotension.
- Suprapubic tenderness and a palpable bladder if urinary retention.
- DRE: prostate is usually swollen and tender (but may also be normal).

Investigation

- Serum blood tests: FBC, U & E, CRP.
- Urinalysis, urine culture ± cytology.
- Blood cultures if high pyrexia/systemically unwell.
- Urethral swabs (if indicated to exclude STI).
- PVR urine measurement (and flow rate).

Further investigation is guided by individual patient presentation and clinical suspicion. Although segmented urine cultures are recommended in some guidelines, prostatic massage should be avoided in the acute, painful phase of prostatitis.

Treatment

- **Antibiotics**: if the patient is systemically well, use an oral fluoroquinolone (i.e. ciprofloxacin 500mg bd) for 2–4 weeks. For a patient who is systemically unwell, IV antibiotics options include a broad-spectrum penicillin or a third-generation cephalosporin, combined with an aminoglycoside (gentamicin) for initial treatment. When infection parameters normalize, IV antibiotics can change to oral therapy which is continued for a total of 2–4 weeks.
- **Pain relief**.
- **Treat urinary retention**: urethral, suprapubic, or in-and-out catheter.

Complications

Prostatic abscess

Failure to respond to treatment (i.e. persistent symptoms and fever while on appropriate antibiotic therapy) suggests the development of a prostatic abscess. The majority are due to *E. coli* infection. Risk factors include diabetes mellitus, immunocompromise, renal failure, transurethral instrumentation, and urethral catheterization. Rectal examination demonstrates a tender, boggy-feeling prostate or an area of fluctuance. A transrectal USS or CT scan (if the former proves too painful) is the best way of diagnosing a prostatic abscess. Transurethral resection or deroofing of the abscess is the optimal treatment. Alternatively, percutaneous drainage may be attempted.

Chronic bacterial prostatitis

Defined as bacterial prostatitis where symptoms persist for ≥**3 months.** Caused by recurrent UTI. Chronic episodes of pain, voiding dysfunction, and ejaculatory problems may be a feature.

Assessment

Enquire about factors that may be contributing to infection: urinary symptoms, history of renal tract stones, symptoms suggesting a colovesical fistula in at-risk patients (pneumaturia, history of diverticular disease, pelvic surgery, or radiotherapy). DRE may reveal a tender, enlarged, and boggy prostate.

Investigation

- Urinalysis, urine culture ± cytology.
- Segmented urine cultures (see 📖 p. 208).
- Semen culture.
- Urethral swabs (to exclude STI).
- Flow rate and PVR urine measurement.
- Individualized further investigation as indicated (e.g. renal tract imaging to identify stones).

Treatment

- Prescribe a 2-week course of antibiotics (fluoroquinolone or trimethoprim)* and then reassess. If initial cultures are positive or the patient has reported positive effects from the treatment, antibiotics can be continued for a total course of 4–6 weeks.
- α-adrenoceptor blockers may provide some benefit. They act on the prostate and bladder neck α-receptors, causing smooth muscle relaxation, improved urinary flow, and reduced intraprostatic ductal reflux.

* The use of fluoroquinolones is restricted in many hospitals due to the risk of *Clostridium difficile* infection. Hospitals now have their own antibiotic protocols for most infections, or alternatively, discuss with your local microbiologist. Alternative antibiotics include trimethoprim which has good prostatic penetration. However, trimethoprim has no activity against *Pseudomonas*, some Enterococci, and some Enterobacteriaceae.

Chronic pelvic pain syndrome

Chronic prostatitis / chronic pelvic pain syndrome (CP/CPPS)

Refers to abacterial prostatitis (i.e. inflammatory (III_A) and non-inflammatory (III_B) types of prostatitis). Also referred to as 'prostate pain syndrome'. The aetiology and pathophysiology is unknown.

Presentation

- ≥3 months of localized pelvic pain (prostate/perineum, suprapubic, penile, groin, external genitalia, lower back).
- Pain with ejaculation.
- LUTS (dysuria, frequency, urgency, poor flow).
- May be associated with erectile dysfunction.
- Symptoms can be difficult to treat. They can recur over time and severely affect the patient's quality of life. Younger men have a higher risk of suffering severe symptoms.

Basic evaluation

- History, including enquiry into associated disorders and psychosocial assessment.
- Physical exam, pelvic floor assessment (including tenderness), and DRE.
- NIH-CPSI questionnaire (National Institute of Health Chronic Prostatitis Symptom Index). This scores three main symptom areas: pain (location, frequency, severity), voiding (obstructive and irritative symptoms), and impact on quality of life.
- Uroflowmetry and PVR urine volume.
- Segmented urine cultures and EPS. These specimens may or may not reveal leucocytes, but for the diagnosis, EPS and post-prostatic massage urine (VB3) cultures should not identify any bacteria.

Further evaluation (where clinically indicated)

- Semen analysis and culture.
- Urethral swab for culture (to exclude STI).
- Urine cytology (if suspicion of bladder malignancy).
- Urodynamics (to investigate voiding dysfunction).
- Cystoscopy (if suspicion of urethral stricture, BOO, or bladder pathology).
- TRUS.
- PSA.

Treatment

Some groups of patients will benefit more from specific therapies than others. Patients require a multimodal approach to treatment, guided by their main clinical features.[1] Options include:

- **Conservative therapy**: counselling, biofeedback, education, anxiety/stress reduction, psychotherapy, focused pelvic physiotherapy for tenderness of skeletal muscles, gentle exercise, avoid aggravating factors (i.e. certain foods or activities).
- **α-adrenoceptor blockers**: most useful for those with associated voiding symptoms and in newly diagnosed disease.

- **Antibiotics**: some benefit in patients presenting early with a new diagnosis of inflammatory CPPS (i.e. ciprofloxacin, levofloxacin for 4–6 weeks). Antibiotics do not appear effective for longstanding, refractory disease.
- **Anti-inflammatory drugs**: NSAIDs (i.e. ibuprofen).
- **5α-reductase inhibitors**: anti-androgens (i.e. finasteride, dutasteride) have the ability to reduce prostatic glandular tissue and improve intraductal reflux and symptoms in selected cases.
- **Phytotherapies**: Quercetin (polyphenolic bioflavonoid with antioxidant and anti-inflammatory properties); Cernilton (pollen abstract).
- **Pentosan polysulphate sodium (PPS)**.
- **Analgesics**: opioids may be trialled in collaboration with the pain team.
- **Neuromodulatory therapies**: amitriptyline, gabapentinoid (pregabalin)—shown to improve mean NIH-CPSI and pain scores.
- **Muscle relaxants**: diazepam.
- **Prostatic massage**: 2/3 times per week for 6 weeks with antibiotic therapy.
- **Local heat therapy**.

If no pathology is identified and there is no response to initial treatments, referral to the pain team is advised.

1 Nickel JC, Shoskes DA (2010) Phenotypic approach to the management of the chronic prostatitis/chronic pelvic pain syndrome. *BJU Int* **106**:1252–63.

Bladder pain syndrome (BPS)

A chronic and debilitating disorder characterized by urinary frequency, urgency, nocturia, and bladder and pelvic pain. It remains a diagnosis of exclusion after all other causes for the symptoms have been ruled out (Table 6.5). The 'classic' form is associated with bladder ulceration (Hunner's ulcers) and destructive inflammation, with some developing a small-capacity fibrotic bladder or upper urinary tract outflow obstruction. 'Non-ulcer' forms do not show the same progression.

Definitions

Terminology has changed a number of times. It was formally known as interstitial cystitis (IC). The ICS, the European Society for the Study of Bladder Pain Syndrome/Interstitial Cystitis (ESSIC), and the EAU use the term 'BPS'.[1,2] The AUA use the term 'IC/BPS'.[2,3]

ESSIC: 'chronic (>6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder, accompanied by at least one other urinary symptom such as persistent urge to void or frequency'. [1,2]

AUA: 'an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with LUTS >6 weeks, in the absence of infection or other identifiable causes'.[2,3]

Epidemiology

Predominantly affects females (female : male ratio is >5:1). Reported prevalence varies widely, but is estimated to be 300 per 100 000 women and 30–60 per 100 000 men.[2]

Associated disorders

Irritable bowel syndrome, allergies, fibromyalgia, chronic fatigue syndrome, focal vulvitis, Sjögren's syndrome, inflammatory bowel disease.

Aetiology

BPS is now considered a generalized somatic disorder with multifactorial contributing factors, including:

- **Mast cells**: frequently associated with the BPS bladder, located around detrusor, blood vessels, nerves, and lymphatics. Activated mast cells release histamine, causing pain, hyperaemia, and fibrosis in tissues.
- **C-fibre activation** and substance P release.
- **Defective bladder epithelium**: an abnormal GAG layer may allow urine constituents (including potassium) to leak past the luminal surface, causing inflammation in muscle layers.
- **Neurogenic mechanisms**: abnormal activation of sensory nerves causes release of neuropeptides, resulting in neurogenic inflammation.
- **Reflex sympathetic dystrophy of the bladder**: excessive sympathetic activity.
- **Bladder autoimmune response**.
- **Urinary toxins or allergens**.

- **Urine antiproliferative factor (APF)**: is made by bladder urothelium. It inhibits bladder cell propagation and may predispose susceptible individuals to BPS following other bladder insults.

Presentation

Urinary frequency, urgency and nocturia with associated suprapubic pain, pressure or discomfort related to bladder filling (and typically relieved by bladder emptying). Patients often describe pelvic pain (urethra, vagina, vulva, rectum) and pain in the lower abdomen and back.

Evaluation

The first priority is to exclude other causes for symptoms (Table 6.5).

- **History**.
- **Focused physical examination**.
- **Frequency–volume chart**.
- **Urinalysis and urine culture** (treat any infection and reassess).
- **O'Leary–Sant Symptom Index** is useful in assessing baseline symptoms and effectiveness of treatments.

Further investigations (if clinically indicated):

- **Urine cytology**.
- **Urodynamics**.
- **Cystoscopy**: indicated for investigation of haematuria and to exclude malignancy. Bladder biopsy is only indicated to rule out other pathologies.
- Around 10% of patients may have Hunner's ulcers, seen as pink or red areas on the bladder mucosa, often associated with small vessels radiating towards a central scar, occasionally covered by fibrin deposit or clot. The scar ruptures with increasing bladder distension, producing 'waterfall' type bleeding. It is clinically significant as it is directly related to symptoms of pain and sensory urgency and destruction of the lesion can provide symptomatic relief.
- **Low-pressure hydrodistension**: under anaesthesia, the bladder is distended twice (to around 80cmH_2O for 1–2min) and then reinspected for diffuse glomerulations (petechiae); >10 per quadrant in three of four bladder quadrants previously being described as diagnostic. Hydrodistension can have some therapeutic benefit, but it is now thought that neither the presence nor severity of post-distension glomerulations correlates with any of the primary symptoms of BPS. It is still used to help classify disease.[1]

First-line treatment

There should be a multidisciplinary team approach throughout from physicians, dieticians, physiotherapists, pain specialists, psychologists, and patient support groups.

- **Patient education and support**: bladder training, stress management, pelvic floor relaxation techniques (avoid pelvic floor exercises), referral to the pain team. Avoid triggers individual to the patient (i.e. coffee, citrus fruits). Aims are to optimize the quality of life and encourage realistic patient expectations.

- **Multimodal pain management**: initially use simple analgesia (low potency NSAIDs), progressing to more potent forms if no benefit. Opiates may be used when all other reasonable treatments have been tried and failed. Pain control should be reassessed throughout treatment, with input from specialist pain clinics.

Second-line treatment

- **Oral medications**: tricyclics (amitriptyline) have anticholinergic, antihistamine, and sedative effects; pentosan polysulphate is an anti-inflammatory synthetic GAG analogue; cimetidine (H_2 histamine receptor anatagonist); hydroxyzine (H_1 antagonist); gabapentin (antiepileptic used as an adjuvant in pain disorders). Try one drug at a time. Stop ineffective treatments and try an alternative. If there is only moderate improvement with one drug, add an adjuvant therapy.
- **Repeated intravesical drug installation**: dimethyl sulphoxide (DMSO); (alkalinized) lignocaine; heparin. Sodium hyaluronate and pentosan polysulphate both repair the GAG layer (the potassium sensitivity test can help to predict the response to GAG treatment). Instillation of lignocaine and dexamethsone can be given by electromotive drug administration (EMDA) which enhances drug penetration across the urothelium.

Third-line treatment

- **Surgery**: transurethral resection, laser coagulation or diathermy of Hunner's ulcers, bladder hydrodistension.

Fourth-line treatment

- **Sacral nerve neuromodulation**.
- **Botulinum toxin A injection** into the bladder.
- **Oral cyclosporine A**.
- **Reconstruction**: urinary diversion (ileal conduit) with or without cystectomy. This can be considered earlier in the treatment strategy for end-stage, small fibrotic bladders. Augmentation cystoplasty can be used for small capacity bladders due to classical Hunner's ulcer disease, with complete relief of pain in 63% and improvement in 25%. However, warn patients that they may experience recurrence of pain in their augmented bladder or continent diversion (neobladder).

Of note, it is recommended that patients are **not** given: long-term antibiotics in the absence of proven infection or effectiveness; intravesical BCG; intravesical resiniferatoxin; high-pressure, long duration hydrodistension; or long-term oral glucocorticoids.

Table 6.5 NIDDK diagnostic criteria for 'interstitial cystitis'[4]

Diagnostic criteria	1. Cystoscopic evidence of Hunner's ulcer
Positive factors (supporting diagnosis)	1. Pain on bladder filling, relieved by emptying 2. Pain (suprapubic, pelvic, urethral, vaginal, or perineal) 3. Glomerulations on cystoscopy 4. Decreased compliance on urodynamics
Exclusion criteria	1. <18y old (controversial— children can be affected) 2. Benign or malignant bladder tumours 3. Radiation cystitis 4. Tuberculous cystitis 5. Bacterial cystitis 6. Vaginitis 7. Cyclophosphamide cystitis 8. Symptomatic urethral diverticulum 9. Uterine, cervical, vaginal, or urethral cancer 10. Active herpes 11. Bladder or lower ureteral calculi 12. Daytime frequency <5 times in 12h 13. Nocturia <2 times 14. Symptoms relieved by antibiotics, urinary antiseptics and analgesics, e.g. phenazopyridine hydrochloride 15. Duration <12 months (definitions now suggest shorter durations of >6 weeks **are** associated with BPS) 16. Involuntary bladder contractions (on urodynamics) 17. Bladder capacity >400 mL (absence of sensory urgency)

NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases.

Of note, it is recommended that these criteria are only used within the context of clinical trials as they are felt to be too restrictive for clinical use.

1 Van De Merwe J, Nordling J, Bouchelouche K, *et al.* (2008) Diagnostic criteria, classification and nonmenclature for painful bladder syndrome/interstitial cystitis: An ESSIC proposal. *Eur Urol* **53**:60–7.

2 Hanno P, Lin A, Nordling J, *et al.* (2010) Bladder Pain Syndrome International Consultation on Incontinence. *Neurourol Urodyn* **29**:191–8.

3 Hanno PM, Burks DA, Clemens JQ, *et al.* (2011) AUA guidelines for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol* **185**:2162–70.

4 Gillenwater JY, Wein AJ (1988) Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29,1987. *J Urol* **140**:203–6.

Urological problems from ketamine misuse

Ketamine is a sedative and an analgesic used clinically for the induction and maintenance of anaesthesia. Increasingly, it is being misused as a recreational drug (its class C status is under review). It is a non-competitive N-methyl-D-aspartate receptor antagonist, excreted with its metabolites into the urine. It has hallucinogenic effects, producing an out-of-body experience known as the 'K-hole'.

Pathology

Inflammation of bladder epithelium, denuding of urothelium, and neovascularization and petechial haemorrhage of the bladder are reported.[1] Histologically, it may mimic the characteristics of carcinoma *in situ*.[2] The exact mechanism of damage is not known. Theories include a direct toxic effect of ketamine and its metabolites on the genitourinary tract, microvascular reactions and damage, and autoimmune processes.[5]

Presentation

- **Lower urinary tract**: ketamine-induced cystitis is a recognized phenomenon, comprising severe urinary frequency, urgency, urge incontinence, dysuria, and painful haematuria. Bladder emptying and urinary flow rates appear unaffected.
- **Upper urinary tract**: unilateral and bilateral hydronephrosis secondary to ureteric transmural inflammation and stricture formation, VUR, papillary necrosis, and renal failure.

An association of these symptoms with hepatic dysfunction is reported.[3]

Assessment

A full history of urinary symptoms and recreational drug use is essential, including doses and duration of use, as they impact on prognosis. Patients often use other substances at the same time.

Investigation

- Renal function (U & E; GFR).
- MSU dipstick ± microscopy and culture to detect and guide treatment of UTI.
- Urodynamics: demonstrated detrusor overactivity and reduced bladder compliance.
- CT urogram: to assess for upper urinary tract involvement.
- Cystoscopy and biopsy: clearly document any pathology (i.e. denuded urothelium) and measure bladder capacity.

Treatment

- Patients must be strongly encouraged to stop using ketamine. Taking the drug >3 times per week is associated with significantly lower voided volumes.[4] Pelvic pain, urgency, and frequency are reported to be significantly higher for ketamine use for >24 months, compared to use for short durations.[4] Symptoms scores improve, directly related to

the length of abstinence from the drug,[4] and early functional changes have the potential to normalize after 1y of ketamine cessation.[4] Reduced benefit from abstinence is seen if ketamine is used at higher frequencies or for longer durations. Symptoms can persist for up to 1y after stopping.

- Analgesia to control the symptoms. Pain control strategies that have been described include buprenorphine patches, co-codamol, and amitriptyline.[3] Symptoms are often refractory to treatment with antibiotics, anticholinergics, and NSAIDs.
- Local support from drug and addiction services.
- Where indicated, nephrostomy or ureteric stents to preserve renal function until definitive surgical correction of ureteric stricture.
- Surgery is undertaken for refractory end-stage disease. Techniques include cystectomy (± reconstruction with neobladder)[3] or substitution cystoplasty to increase bladder capacity. These procedures should be reserved for patients who have abstained from ketamine use.

1 Chu PS, Ma WK, Wong J, *et al.* (2008) The destruction of the lower urinary tract by ketamine abuse: a new syndrome? *BJU Int* 2008;**102**:1616-22.

2 Oxley JD, Cottrell AM, Adams S, *et al.* (2009) Ketamine cystitis is a mimic of carcinoma in situ. *Histopathology* **55**:705–8.

3 Wood D, Cottrell A, Baker S, *et al.* (2011) Recreational ketamine: from pleasure to pain. *BJU Int* **107**:1881–4.

4 Mak SK, Chan MT, Bower WF, *et al.* (2011) Lower urinary tract changes in young adults using ketamine. *J Urol* **186**:610–4.

Genitourinary tuberculosis

Tuberculosis (TB) of the genitourinary tract is caused by *Mycobacterium (M.) tuberculosis*. TB was formerly predominantly seen in Asian populations, but is now seen with increasing incidence in those from other ethnic groups and immunocompromised patients (i.e. with HIV infection). It has a higher incidence in males than females.

Pathogenesis

Primary TB: the primary granulomatous lesion forms in the mid to upper zone of the lung. It consists of a central area of caseation surrounded by epitheloid and Langhans' giant cells, accompanied by caseous lesions in the regional lymph nodes. There is early spread of bacilli via the bloodstream to the genitourinary tract, but immunity rapidly develops and the infection remains quiescent. Acute diffuse systemic dissemination of tubercle bacilli can result in symptomatic miliary TB.

Post-primary TB: reactivation of infection is triggered by immune compromise (including HIV). It is at this point that patients develop clinical manifestations.

Effects on the genitourinary tract

- **Kidney**: the most common site of extrapulmonary TB. Haematogenous spread causes granuloma formation in the renal cortex, associated with caseous necrosis of the renal papillae and deformity of the calyces, leading to the release of bacilli into the urine. This is followed by healing fibrosis and calcification, which causes destruction of the renal architecture, resulting in a small, distorted kidney. In severe cases, this ultimately results in autonephrectomy.
- **Ureters**: spread is directly from the kidney and can result in stricture formation (VUJ, PUJ, and mid-ureteric) and ureteritis cystica. VUR may develop due to distortion of the ureteric orifices.
- **Bladder**: usually secondary to renal infection, although iatrogenic TB can be caused by intravesical Bacillus Calmette–Guérin (BCG), the treatment given for bladder cancer. The bladder wall becomes oedematous, red, and inflamed, with ulceration and tubercles (yellow lesions with a red halo). Disease progression causes fibrosis and contraction (resulting in a small capacity 'thimble' bladder), obstruction, calcification, and fistula formation.
- **Prostate and seminal vesicles**: haematogenous spread causes cavitation and calcification, with palpable, hard-feeling structures. Fistulae may form to the rectum or perineum.
- **Epididymis**: results from descending renal infection or haematogenous spread. Features include a 'beaded' cord which may be tender or asymptomatic and is usually unilateral. Complications include abscess, spread of infection to the testis, and infertility.
- **Fallopian tubes**: may then spread to involve the uterus. It can present with infertility, pelvic pain, mass, or abnormal bleeding.
- **Penis**: rare manifestation transmitted from sexual contact or local contamination, resulting in ulceration of the glans or a penile nodule. Biopsy confirms the diagnosis.

Presentation

Early symptoms include fever, lethargy, weight loss, night sweats, and UTI not responding to treatment. Later manifestations include LUTS, haematuria, and flank pain.

Investigation

- **Urine dipstick test**: may show blood and leukocytes, but no nitrites.
- **Urine culture**: at least three early morning urines (EMUs) are required. A typical finding is sterile pyuria (leukocytes, but no growth). Ziehl–Neelsen staining will identify these acid- and alcohol-fast bacilli (cultured on Lowenstein–Jensen medium). Polymerase chain reaction (PCR) of urine, where available, is useful for TB detection.
- **Urine cytology**: to exclude other causes of sterile pyuria (i.e. bladder malignancy/carcinoma *in situ*).
- **CXR** and **sputum culture**.
- **Tuberculin skin test**: a negative test excludes TB; a positive test suggests TB exposure.
- **Renal tract imaging**: X-ray and USS of kidneys, ureters, and bladder initially. Further investigation into urinary tract involvement and complications can include CTU or IVU.
- **Cystoscopy** and **biopsy**.

Treatment

Medical

A multidisciplinary team approach is required, involving colleagues from respiratory, infectious diseases, and microbiology departments. Treatment is with 2 months of isoniazid, rifampicin, and pyrazinamide and ethambutol, followed by a continuation phase of 4 months of isoniazid and rifampicin. Longer treatments or modification of drugs is needed for complications and resistant organisms.

Surgical

A non-functioning, calcified kidney may need nephrectomy. Regular follow-up imaging with IVU is recommended to monitor for ureteric strictures which may need stenting, nephrostomies, or ureteric reimplantation. Severe bladder disease may require surgical augmentation, urinary diversion or cystectomy, and neobladder reconstruction. For epididymal involvement, epididymectomy ± orchidectomy is considered if pharmacotherapy fails or extensive disease is present.

Parasitic infections

Urinary schistosomiasis (bilharzia)

This is caused by the parasitic trematode (or flatworm) called ***Schistosoma (S.) haematobium***. It occurs in Africa (Egypt) and the Middle East. Other causes of schistosomiasis include *S. mansoni, S. japonicum*, *S. mekongi*, and *S. intercalatum.* They are mainly responsible for intestinal forms of disease.

Life cycle of S. haematobium (Fig. 6.2)

Infection is acquired by exposure to contaminated water. The parasite (**cercariae** form) penetrates the skin of the human host, shed their tails, and become **schistosomula**. They migrate first to the lung via venous circulation, then to the liver to mature. The **adult worms** couple (sexual reproductive phase), migrate to veins of the vesical plexus, and lay fertilized eggs. Most **eggs** (which typically have a terminal spine) leave the body by penetrating the bladder and entering the urine. Some eggs are trapped in the tissues and those not destroyed by host responses can become calcified. The released eggs hatch in fresh water, releasing **miracidia** which find and enter the intermediate host, a fresh water *Bulinus* species snail. Through an asexual reproductive phase, **sporocytes** are created in the snail. These produce and later release larvae called **cercariae**, the free-swimming, infective form of the parasite, and the cycle is continued, with penetration into the human host. The disease has two main stages: **active** (when adult worms are laying eggs) and **inactive** (when the adults have died and there is a reaction to the remaining eggs).

Pathology

Lesions occur due to calcification of dead eggs trapped in tissues, triggering a fibrotic reaction. A T-cell-mediated immune response is stimulated also by the presence of the eggs, resulting in eosinophilic granuloma in the bladder, uterus, and genitalia.

Clinical presentation

- **Maculopapular eruption** (cercarial dermatitis): may arise on the skin at the site of cercarial penetration (within hours, lasting up to 3 days). 'Swimmer's itch' may occur in individuals who are already sensitized and become re-infected.
- **Acute schistosomiasis** (Katayama fever): is a generalized immune reaction associated with the onset of egg-laying. Symptoms may include fever, malaise, non-productive cough, lymphadenopathy, hepatosplenomegaly, haematuria, urinary frequency, and terminal dysuria (onset 3 weeks–4 months).
- **Chronic and advanced disease**: chronic local inflammatory response to eggs trapped in host tissues results in inflammatory and obstructive urinary tract sequelae, usually after several years. Obstructive features include fibrosis and 'eggshell' calcification of the bladder, urinary retention, ureteric stenosis, hydronephrosis, renal failure, and stones. Seminal vesicle involvement can produce 'lumpy semen'.

Investigation

- **Midday urine specimen**: may contain eggs (distinguished by having a *terminal spine*). Eggs may also be identified in the faeces.
- **FBC**: eosinophilia in acute infection; anaemia and thrombocytopenia in chronic and advanced disease.
- **U & E**: raised creatinine in advanced disease (renal impairment).
- **Serology tests (ELISA)**: identify specific antibodies.
- **Cystoscopy**: identifies eggs in the trigone ('sandy patches').
- **Bladder and rectal biopsies**: may identify eggs (if not already found in urine or faeces).
- **X-ray, CT, or IVU**: may show a calcified, contracted bladder and evidence of obstructive uropathy.
- **USS**: in established disease may show hydronephrosis and a thickened bladder wall.

Treatment

Praziquantel 40mg/kg as a single or divided oral doses. Corticosteroids are an adjuvant therapy used to treat Katayama fever (within 2 months of freshwater contact). Patients should be followed up at 2 and 6 months with urinalysis and clinical assessment.

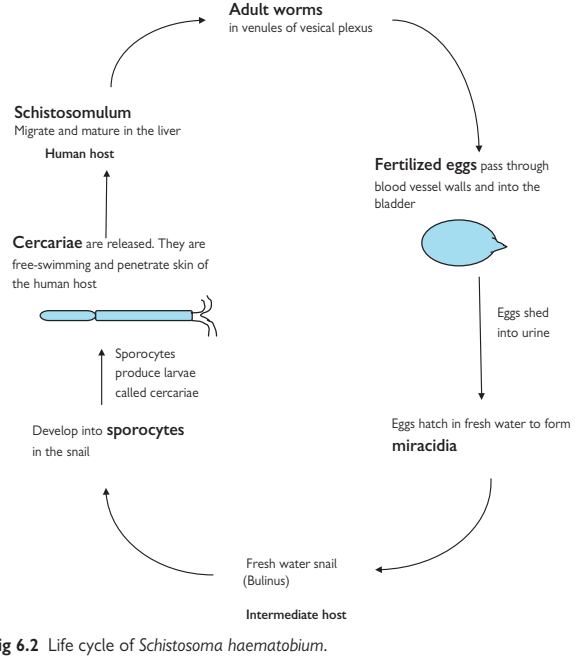

Fig 6.2 Life cycle of *Schistosoma haematobium*.

Complications

- SCC of the bladder—there can be a lag period of around 20y between infection and the development of malignancy.
- Bladder contraction, calcification, and ulceration.
- Obstructive uropathy.
- Renal failure.
- Secondary bacterial UTI.

Genitourinary hydatid disease

- Infection occurs after ingestion of the dog parasite, *Echinococcus granulosus* (tapeworm). Sheep are the intermediate hosts. Occurs in the Middle East, Australia, and Argentina. Eggs come to rest in the genitourinary tract after passage through the portal system, heart, and pulmonary circulation.
- Large (hydatid) cysts form, which can be asymptomatic or present with pain. They can affect the kidneys, bladder, prostate, seminal vesicles, and epididymis.
- A peripheral eosinophilia is seen, with a positive hydatid complement fixation test.
- USS is usually diagnostic; X-rays and CT scans show a thick-walled, fluid-filled spherical cyst with a calcified wall.
- Medical treatment is with albendazole, mebendazole, or praziquantel.
- Where surgical excision is indicated, cysts can be first sterilized with chlorhexidine, alcohol, or hydrogen peroxide.
- Medical therapy is recommended preoperative and post-operatively to reduce recurrence rates.
- Cyst rupture or spillage of cyst contents perioperatively can provoke systemic anaphylaxis.

Genital filariasis

Lymphatic filariasis caused by *Wuchereria bancrofti* infection is common in the tropics and is transmitted by mosquitoes. Genitourinary manifestations, which may be delayed up to 5y, include funiculoepididymitis, orchitis, hydrocoele, scrotal and penile elephantitis, and lymph scrotum (oedema). Diagnosis is on thick film, serology, or biopsy. Medical treatment is with diethylcarbamazine. Surgical excision of fibrotic and oedematous tissue may be needed for genital elephantitis.

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HIV in urological surgery

Human immunodeficiency virus (HIV)

Causes a spectrum of illness related to immune system deficiency. HIV-1 is pandemic and accounts for significant mortality in developing countries. HIV-2 has less pathogenicity and is predominant in West Africa. Transmission is via unprotected sexual intercourse, contaminated needles, mother-to-fetus transmission, infected blood, and blood products (blood transfusion risks are now minimal).

Pathogenesis

HIV is a retrovirus. It possesses the enzyme, reverse transcriptase, that enables viral RNA to be transcribed into DNA, which is then incorporated into the host cell genome. HIV binds to CD4 receptors on helper T-lymphocytes (CD4 cells), monocytes, and neural cells. After an extended latent period (8–10y), CD4 counts decline. Acquired immunodeficiency syndrome (AIDS) is defined as HIV positivity and CD4 lymphocyte counts $<200 \times 10^6$/L. The associated immunosuppression increases the risk of opportunistic infections and tumours.

Diagnosis

ELISA testing of serum detects antibodies against HIV antigens. The second confirmatory test is Western blot. Informed consent is required for the test.

Urological sequelae of HIV infection

Renal

- **Opportunistic infections**: including cytomegalovirus (CMV), aspergillosis, mycobacteria, and cryptococcus infections. Can lead to pyelonephritis, acute tubular necrosis, and abscess formation.
- **Renal impairment and failure**: HIV and AIDS-associated nephropathy.
- **Renal stones**: secondary to indinavir (antiretroviral treatment).
- **Tumours**: Kaposi's sarcoma, lymphoma.

Bladder

- **Voiding dysfunction**: urinary retention (associated with toxoplasmosis), bladder overactivity or underactivity.
- **Opportunistic infections** causing UTI.
- **Tumours**: squamous cell carcinoma, Kaposi's sarcoma, lymphoma.

Urethra

- Reiter's syndrome (urethritis, conjunctivitis, arthritis) is associated with AIDS.
- Bacterial urethritis.

Prostate

- Bacterial prostatitis and abscesses (including opportunistic organisms).
- Reported increased progression rate for prostatic carcinoma.

External genitalia

- Chronic or recurrent genital herpes.
- Atypical syphilis.
- Opportunistic infections of testicle and epididymis.
- Testicular cancers (increased risk of germ cell and non-germ cell tumours, lymphoma).
- Testicular atrophy ± hypogonadism.
- Scrotal and penile Kaposi's sarcoma (seen as purple/red lesions).
- Fournier's gangrene.
- Sexual dysfunction: due to the underlying HIV pathology (HIV neuropathy, encephalopathy, or lipodystrophy) and/or due to HIV drug therapies (antiretroviral therapy).

Of note, circumcision has been shown to reduce the risk of acquiring HIV infection in heterosexual men.

Occupational needle stick injury

The risk of HIV transmission after percutaneous exposure to HIV-infected blood is 3 per 1000 injuries.[1] Risks are increased if the patient has terminal HIV-related illness, a deep injury, visible blood on the device causing the injury, and injury with a needle previously placed in the source patient's vein or artery.[1] After mucocutaneous exposure, the risk is <1 in 1000.[1]

Management

Immediately wash the area well and encourage free bleeding of puncture wounds. Irrigate exposed mucous membranes with water. Report to occupational health (A & E or equivalent out-of-hours service) for a risk assessment and baseline blood sample for storage. The source patient will be approached and counselled on undergoing HIV testing. Health care worker follow-up testing is recommended at 12 and 24 weeks post-exposure (or 24 weeks after antiretroviral prophylaxis if prescribed). Occupational HIV exposure is reported to the HPA Centre for Infections.

Post-exposure prophylaxis (PEP) is recommended if there has been significant occupational exposure to blood or another high-risk body fluid from a patient or other source, either known to be HIV-infected or considered high risk of HIV infection (but where the result of a HIV test has not or cannot be obtained). PEP should be initiated ideally within 1h and continued for at least 28 days. The PEP starter pack contains one Truvada tablet (tenofovir and emtricitabine) taken once a day *plus* two Kaletra tablets (lopinavir and ritonavir) taken twice a day.[1]

1 Department of Health (2008) HIV post exposure prophylaxis: Guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS [online]. Available from: http://www.dh.gov.uk/publications.

Phimosis

A condition where the contracted foreskin (prepuce) has a tight, narrowed orifice and cannot be retracted back over glans of the penis. A physiological phimosis is present at birth due to adhesions between the epithelium of inner foreskin and glans. Penile growth, erections, and accumulation of epithelial debris (smegma) under the foreskin causes gradual separation. Ninety percent of foreskins are retractile at age 3.[1] Few persist into adulthood (<1% phimosis at age 17).[2] Recurrent balanitis and inflammatory conditions such as BXO in uncircumcised males can cause new pathological phimosis (see 📖 p. 230).

Presentation

Physiological phimosis is usually asymptomatic. Patients may describe ballooning of the foreskin on voiding and an inability to fully retract the foreskin which, in sexually active men, may also cause skin trauma during sexual intercourse. Inflammation or infection (balanitis and balanoposthisis) may cause bleeding, pain, discharge, or dysuria (see 📖 p. 230). Phimosis associated with BXO presents with white, itching plaques affecting the foreskin and glans and may have associated voiding problems.

Treatment

Adults: treat any associated infection. If symptomatic or a pathological phimosis, surgical treatment is circumcision (see 📖 p. 750). Preputioplasty (longitudinal incision on foreskin which is closed transversely) is an alternative for milder cases. It is effective in around 50%; a circumcision is then required for those who do not respond. It is not suitable for BXO.

Children: older children with phimosis suffering infection (balanitis) can be treated with antibiotics and a course of topical 0.1% betamethasone (betnovate) cream which acts to soften the phimosis and allow foreskin retraction. The recommendations are to avoid circumcision where possible.[1]

Indications for circumcision in children include phimosis associated with recurrent balanitis, BXO, (recurrent) UTI associated with an underlying abnormality (i.e. VUR,[3] posterior urethral valves, neuropathic bladder dysfunction), recurrent UTI,[3] failed medical therapy for UTI, stone disease, and for religious reasons.

Contraindications to (neonatal) circumcision include the presence of hypospadias (± chordee or hooded foreskin), small penis, or large hernia or hydrocele (where repair after circumcision may cause a buried penis or secondary phimosis).

Complications of phimosis

- **Paraphimosis**: the foreskin is retracted behind the glans, but cannot be replaced again. An existing degree of phimosis and/or prolonged retraction produces a tight ring of tissue at the corona, leading to venous congestion, oedema, and swelling of the glans, which can progress to arterial occlusion and necrosis (see 📖 p. 533).
- **Recurrent balanitis**.

- **Balanoposthitis**: severe balanitis and infection of the foreskin, where inflammatory secretions and pus are trapped in the foreskin by the phimotic band.
- **Chronic inflammation**.
- **Penile cancer (squamous cell carcinoma)**: increased risk in uncircumcised males.
- **Sexually transmitted infection**: increased risk (including HIV transmission) in uncircumcised males (see 📖 p. 227).

1 Gairdner D (1949) The fate of the foreskin. A study in circumcision. *BMJ* **2**:1433–7.

2 Oster J (1968) Further fate of the foreskin. Incidence of preputial adhesions, phimosis, and smegma among Danish schoolboys. *Arch Dis Child* **43**:200–3.

3 Singh-Grewal D, Macdessi J, Craig J (2005) Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. *Arch Dis Child* **90**:853–8.

Inflammatory disorders of the penis

Balanitis and balanoposthitis

Balanitis is inflammation of the glans penis. Balanoposthitis is inflammation of the prepuce (foreskin) and glans. Increased risk with phimosis and uncircumcised males. Causes are shown in Table 6.6. Clinical features include pain, erythema, discharge, difficulty retracting the prepuce, and voiding dysfunction. Treat any proven infection, instruct on good hygiene, and avoid irritants. A short course of topical steroid cream (i.e. 0.1% betham-ethasone) can be applied to improve retractability of the prepuce. Surgical options for recurrent infections include circumcision.

Table 6.6 Causes of balanitis

Lifestyle-related	Poor hygiene, local irritants (soaps, spermicides)
Fungal infection	Candida
Bacterial infection	Non-sexually transmitted: coliforms, group B streptococci
	Sexually transmitted: *N. gonorrhoeae, C. trachomatis, syphilis, Herpes simplex*
Inflammatory dermatoses	Lichen sclerosis, Lichen planus, Zoon's balanitis, Reiter's syn-drome, psoriasis, eczema, irritant contact dermatitis
Drugs	Examples: amoxicillin, paracetamol, salicylates, tetracyclines, propranolol, quinine, chlordiazepoxide

Lichen sclerosis

- A chronic inflammatory skin condition of unknown aetiology. On the penis, it is called **balanitis xerotica obliterans (BXO)**.
- Presentation: phimosis, itching, and discomfort with itchy, flat-topped white papules that coalesce to form white patches on the glans penis and prepuce. May be associated with voiding dysfunction.
- Complications include meatal stenosis, urethral strictures, and dense adhesions, causing fusion between the prepuce and glans.
- Pathological features are thinning and hyperkeratosis of the epithelium, hyalinization of keratin in the upper dermis, infiltration of lymphocytes and plasma cells in the dermis, and degeneration of the basal cell layer.
- BXO is thought to be a premalignant condition in adults, although progression to SCC is rare. BXO is an associated finding in around 28% of patients presenting with penile carcinoma in contemporary series,[1] although larger series report lower rates (2%).[2]
- Treatment: a trial of topical corticosteroids may be tried for mild conditions, but generally, men require circumcision (± meatal dilatation).
- The prepuce should be sent for histological analysis. Surgery is usually curative, but any residual BXO after circumcision should be followed

up, with further topical therapy (steroid, antibiotic, or antifungal) as indicated. Biopsy may be needed if the lesion persists, progresses, or changes (despite appropriate treatment).

Zoon's balanitis

Also referred to as 'plasma cell balanitis'. It tends to occur in older, uncircumcised men. Patients present with well-circumscribed, shiny, moist, erythematous plaque on the glans (sometimes described as having a 'cayenne pepper' appearance), with a corresponding lesion on the prepuce. Pathological features are chronic inflammatory cell (plasma cell) infiltrate in the dermis. It is usually asymptomatic, but may present with irritation, pain, or discharge. Differential diagnosis is erythroplasia of Queyrat, lichen planus, fixed drug eruption, or psoriasis and a skin biopsy is often indicated to confirm the diagnosis. A swab should be taken for microbiological analysis as secondary infection is common and requires antibiotic treatment. Conservative therapies include advice on hygiene, topical corticosteroids (± antibiotics or antifungals as clinically indicated), but the disorder tends to persist or recur. Definitive treatment is with circumcision. Carbon dioxide laser therapy also has reported success.

Lichen planus

It affects all age groups and can occur in isolation on the penis or as part of a generalized eruption. It presents as an itchy, papular rash. It consists of mauve papules which have a flat top covered in white streaks (Wickham's striae). It affects flexor surfaces (wrists, elbows), genitalia (appearing as a white annular lesion or erythematous plaques on the glans penis), buccal mucosa, lumbar region, and ankles. The diagnosis is made clinically; biopsy can be used if the diagnosis is unclear or the lesions fail to respond to appropriate treatment. It is often self-limiting, but topical steroids can be prescribed for symptomatic lesions.

Psoriasis

Chronic papulosquamous inflammatory skin disease, presenting with itchy pink plaques covered in silver white scales on hair-bearing areas and extensor surfaces (knees and elbows). It also causes pitting of the nails. Lesions may be guttate (raindrop-shaped), circinate (rings), or geographic. Genital psoriasis may present as itching and soreness of the groins and glans and a red penile rash. It may also involve the prepuce. It is treated with topical emollients, soap substitutes, and short courses of topical low-dose steroid creams.

Reiter's syndrome

The typical triad of symptoms is urethritis, conjunctivitis, and seronegative arthritis. It tends to present in younger men. It can be caused by STI (*Chlamydia trachomatis*) and there is an association with HIV. Penile, oral, and skin lesions may occur, which can be confused for psoriasis. Genital manifestations include circinate balanitis (ring-shaped eroded lesions on the glans penis) in uncircumcised men, which can appear as a crust lesion in circumcised patients. Patients should be under STI screening. The condition is self-limiting and usually resolves spontaneously.

Behçet's syndrome

An uncommon disorder of unknown cause characterized by painful genital (scrotum, prepuce, glans) and oral (aphthous) ulceration, polyarthritis, uveitis, and neurological syndromes. Treatment of genital lesions is with topical steroids (corticosteroids).

1 Pietrzak P, Hadway P, Corbishley CM, *et al.* (2006) Is the association between balanitis xerotica obliterans and penile carcinoma underestimated? *BJU Int* **98**:74–6.

2 Depasquale I, Park AJ, Bracka A (2000) The treatment of balanitis xerotica obliterans. *BJU Int* **86**:459–65.

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Chapter 7

Urological neoplasia

Basic pathology and molecular biology

Neoplasia (the formation and growth of a tumour) may be a **benign or malignant** process. Malignant neoplasms, characterized by local invasion of normal tissue or distant spread (metastasis) via lymphatic or vascular channels, may be **primary or secondary**. Neoplasms are considered to arise by clonal expansion of a single abnormal cell through uncontrolled aberrant divisions. This cell may be a **stem cell** rather than a terminally differentiated cell. Tumour formation results from the loss of balance between cell division and withdrawal from the cell cycle by differentiation or programmed cell death (apoptosis). Signals regulating cell proliferation and interactions come from proteins encoded by messenger RNA that is in turn transcribed from genomic DNA. An identifiable precursor lesion may exist.

Urological neoplasms most commonly arise from the lining epithelium of the genitourinary tract. Benign epithelial neoplasms from glandular or transitional epithelium are, respectively, termed **adenoma** or **transitional cell papilloma**. **Malignant epithelial neoplasms are carcinomas**; they may be further characterized histologically by prefixing either **adeno** if the neoplasm is glandular or **squamous cell** or **transitional cell**, according to the epithelium from which it has arisen. Carcinomas arise from non-invasive epithelial lesions, some of which are identifiable histologically: in the bladder, it is **flat carcinoma *in situ* (CIS)** while in the prostate, it is **prostatic intraepithelial neoplasia (PIN)**. **Connective tissue neoplasms** are described according to their components, adding benign (-oma) or malignant (-sarcoma) suffixes. For example, a benign neoplasm composed of blood vessels, fat, and smooth muscle is an **angiomyolipoma**; a malignant neoplasm composed of smooth muscle is a **leiomyosarcoma**. Genitourinary sarcomas are rare, constituting 1% of all neoplasms.

There are exceptions. In the testis, the most common primary neoplasms arise from seminiferous tubules and are termed **germ cell tumours**. Rarely, primary malignant **lymphoma** can arise in the testis. In the kidney, the childhood **Wilms' tumour** arises from the embryonic mesenchyme of the metanephric blastema while the benign **oncocytoma** is thought to arise from cells of the collecting ducts.

Secondary malignant neoplasms within urological tissues are uncommon; they may arise by direct invasion from adjacent tissues (for example, adenocarcinoma of the sigmoid colon may invade the bladder) or haematogenous metastasis from a distant site such as the lung.

Neoplasia is a genetic disease: it may be **hereditary** or **sporadic**, depending on whether the genetic abnormalities are constitutional (germ-line) or somatic (acquired). Hereditary tumours tend to appear at a younger age than their sporadic counterparts and are often multifocal due to an underlying constitutional genetic abnormality.

Genetic and epigenetic abnormalities may promote tumour development or growth in a number of ways.

- Activation (overexpression) of **oncogenes** encoding transcription factors, e.g. c-myc.
- Inactivation (reduced expression) of **tumour suppressor genes**; their diverse protein products stabilize the cell, ensuring differentiation

and a finite lifespan in which it performs its function. Inactivation of such genes by deletion or mutation may result in loss of this negative growth control. For example, PTEN (chromosome 10q) is a prostate tumour suppressor gene, encoding a phosphatase that is active against protein and lipid substrates. It is present in normal epithelium, but is commonly reduced in prostate cancer due to allele loss of chromosome 10q. It inhibits one of the intracellular signalling pathways, PI3 kinase-Akt, that is essential for cell cycle progression and cell survival. Inactivation of PTEN, therefore, promotes cell immortalization and proliferation.

- Overexpression of **peptide growth factors**, e.g. insulin-like growth factor type 1 in prostate cancer or the highly angiogenic vascular endothelial growth factor in renal cancer.
- **Promoter methylation or acetylation** inactivating genes encoding detoxification enzymes, e.g GSTP1.
- **Gene fusions**: a translocation occurs during mitosis to bring a promoter gene adjacent to a transcription factor gene on a particular chromosome, resulting in overexpression of this factor and abnormal positive growth control, e.g. TMPRSS2-ERG fusions are found in 50% of prostate cancers.
- **MicroRNA**: tissue-specific, non-coding, short ssRNA; regulate gene expression by interacting with mRNA; multifunctional, measurable, and potentially reversible; postulated to be the key to individualized cancer treatment.

Interest in the molecular pathology of urological neoplasia has begun to result in the development of screening tests for hereditary diseases, diagnostic or prognostic gene profiling, and new strategies for treatment. Examples include the PCA3 test for prostate cancer and the development of targeted therapies for advanced renal cancer.

Wilms' tumour and neuroblastoma

Wilms' tumour (nephroblastoma)

First described by the German surgeon, Max Wilms (1867–1918), this is a rare childhood tumour, affecting 1 in 10 000 children. It is, however, the commonest intra-abdominal tumour of childhood (20% of all childhood malignancies) and it represents 80% of all genitourinary tumours affecting children under 15y. Male and female are equally affected, 20% are familial, and 5% are bilateral. Seventy-five percent present under the age of 5y. Children of African descent are at greatest risk.

Pathology and staging

Wilms' tumour is a soft pale grey tumour (it looks like brain). It contains metanephric blastema, primitive renal tubular epithelium, and connective tissue components. Two distinct histological subtypes are described: *favourable* (well differentiated) and *anaplastic* (poorly differentiated).

In at least 20% of cases, mutation or deletion of both copies (alleles) of the chromosome 11p13 WT1 tumour suppressor gene results in tumourigenesis. The familial disease exhibits autosomal dominant inheritance, but is recessive at the cellular level. Affected family members harbour a germ-line WT1 mutation, conferring susceptibility. One further 'hit' is required while two 'hits' are required to cause the sporadic disease. This explains why hereditary Wilm's tumours tend to develop multifocally and at a slightly younger age than its sporadic counterpart. Mutations of three further genes, WT2 (11p15.5), WTX (on the X chromosome), and CTNNB1 account for a further 30% of cases. Loss of chromosome 1p and 16q alleles defines a subgroup with worse prognosis.

Stage I Wilms' tumour (43% of patients)—at least one of the following criteria must be met.

- Tumour is limited to the kidney and is completely excised.
- The surface of the renal capsule is intact.
- The tumour is not ruptured or biopsied (open or needle) prior to removal.
- No involvement of extrarenal or renal sinus lymph–vascular spaces.
- No residual tumour apparent beyond the margins of excision.
- Metastasis of tumour to lymph nodes not identified.

Stage II Wilms' tumour (23% of patients)—at least one of the following criteria must be met.

- Tumour extends beyond the kidney, but is completely excised.
- No residual tumour apparent at or beyond the margins of excision.
- Any of the following conditions may also exist.
  - Tumour involvement of the blood vessels of the renal sinus and/or outside the renal parenchyma.
  - The tumour has been biopsied prior to removal or there is local spillage of tumor during surgery, confined to the flank.
  - Extensive tumour involvement of renal sinus soft tissue.

Stage III Wilms' tumour (23% of patients)—at least one of the following criteria must be met.

- Unresectable primary tumour.
- Lymph node metastasis.
- Tumour is present at surgical margins.
- Tumour spillage involving peritoneal surfaces, either before or during surgery, or transected tumour thrombus.

Stage IV Wilms' tumour (10% of patients) is defined as the presence of haematogenous metastases (lung, liver, bone, or brain) or lymph node metastases outside the abdominopelvic region.

Stage V Wilms' tumour (5% of patients) is defined as bilateral renal involvement at the time of initial diagnosis.

Presentation

Ninety percent have a mass, 33% complain of abdominal or loin pain, 30–50% develop haematuria, 50% are hypertensive. Fifteen percent of patients exhibit other anomalies such as hemihypertrophy/macroglossia (Beckwith–Wiedemann syndrome), gonadal dysgenesis/nephropathy (Denys–Drash syndrome) aniridia/retardation (WAGR), and fetal overgrowth (Perlman's syndrome).

Investigations

The first-line investigation for a child with an abdominal mass or haematuria is ultrasound which will reveal a renal tumour. Further to diagnostic imaging, staging is obtained by CT, including the chest. Needle biopsy is avoided.

Treatment and prognosis

Children with renal tumours should be managed by a specialist paediatric oncology centre. Staging nephrectomy, with or without preoperative or post-operative chemotherapy, remains the mainstay of treatment. The chemotherapy most frequently used is vincristine and doxorubicin. Flank irradiation may be used in higher stage tumours. Survival is generally good at 92% overall, ranging from 55% to 97%, according to stage at presentation and histology.

Neuroblastoma

The most common extracranial solid tumour of childhood. Eighty percent are diagnosed <4y old. The tumour is of neural crest origin; 50% occur in the adrenal gland and most of the remainder arise along the sympathetic trunks.

Presentation

Systemic symptoms and signs are common: fever, abdominal pain/distension, mass, weight loss, anaemia, and bone pain. Retro-orbital metastases may cause proptosis.

Imaging and staging

Ultrasound initially; CT of chest and abdomen. Calcification in tumour helps distinguish neuroblastoma from Wilms' tumour. MIBG scans are very sensitive for detection of neuroblastomas (Table 7.1).

Table 7.1 Imaging and staging

Stage 1	Tumour confined to organ of origin and grossly complete excision
Stage 2	Unilateral tumour with residual disease post-resection or lymphadenopathy
Stage 3	Tumour crossing midline or contralateral nodes
Stage 4	Metastatic disease beyond regional nodes; survival 6%
Stage 4S	Unilateral tumour with metastasis limited to liver, skin, or bone marrow; survival 77%

Treatment and prognosis

Surgical excision; radiotherapy; combination chemotherapy, possibly with autologous bone marrow transplantation. Stage 4S tumours may resolve with little or no treatment. Prognosis is poor, except for stages 1 and 4S disease.

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Radiological assessment of renal masses

Abdominal *USS* is the first-line investigation for a patient with loin pain or a suspected renal mass. The size resolution for renal masses is 1.5cm, exhibiting variable echo patterns. Ultrasound may also detect renal cysts, most of which are simple: smooth-walled, round or oval, without internal echoes, and complete transmission with a strong acoustic shadow posteriorly. If the cyst has a solid intracystic element, septations, an irregular or calcified wall, further imaging with *CT* is indicated. Ten to twenty-five percent of RCC contain cysts. Yale radiologist, Morton Bosniak, developed the following radiological classification of renal cysts in Table 7.2.[1]

Table 7.2 Radiological classification of renal cysts

I	Uncomplicated simple (see above criteria); benign; no follow-up if asymptomatic
II	Minimally complicated; septa, calcification, hyperdense (contain blood); benign, but require radiological follow-up
III	Complicated; irregular margin, thickened septa, thick irregular calcification; indeterminate, surgical exploration indicated unless there is history of trauma or infection
IV	Large, irregular cyst margins with solid components internally; cystic renal carcinoma until proven otherwise; surgery required

If a renal mass is detected by USS, a thin slice or helical *CT scan* before and after IV contrast is the most important investigation for characterization and staging. Around 90% of solid-enhancing renal masses will be RCC. Ten percent of RCC will contain calcifications or fat. Even relatively avascular renal carcinomas enhance by 10–25* Hounsfield units. Occasionally, an isodense, but enhancing, area of kidney is demonstrated: this is termed 'pseudotumour' and may correspond to a harmless hypertrophied cortical column (of Bertin) or dysmorphic segment. CT may mislead with respect to liver invasion (rare) due to 'partial volume effect'; real-time ultrasound is more accurate. Lymphadenopathy >2cm is invariably indicative of metastasis.

MRI with gadolinium contrast may be used for imaging the IVC, locally advanced disease, renal insufficiency, or for patients allergic to iodinated contrast. Doppler USS may also evaluate IVC tumour thrombus. *Renal arteriography* is seldom used in the diagnostic setting, but may be helpful to delineate the number and position of renal arteries in preparation for nephron-sparing surgery or surgery for horseshoe kidneys.

* Hounsfield units are a measure of X-ray attenuation applied to CT scanning: –1000 units equates with air, 0 units equates with water, and +1000 equates with bone.

Ultrasound or CT-guided fine needle aspiration (FNA) or needle biopsy

This is increasingly indicated due to the trend in managing small masses with surveillance or minimally invasive ablative therapies. Also, a histological diagnosis is usually required prior to treating inoperable patients with systemic therapies. Needle biopsy is highly specific, but less sensitive for detecting malignancy: 80% of biopsy cores are diagnostic, of which 75% are RCC. Repeat biopsy is diagnostic in 80%. There are also risks of haemorrhage (5%) and tumour spillage (rare). FNA is useful for aspiration of renal abscess or infected cyst or to diagnose suspected lymphoma or metastatic lesions. Table 7.3 shows a practical radiological classification of renal masses.

Table 7.3 Classification of renal masses by radiographic appearance

Simple cyst	Complex cyst	Fatty mass	Others (excluding rarities)
Cyst	Renal carcinoma	Angiomyolipoma	Renal cell carcinoma
Multiple cysts	Cystic nephroma	Lipoma	Metastasis
Parapelvic cyst	Haemorrhagic cyst	Liposarcoma	Lymphoma
Calyceal diverticulum	Metastasis		Sarcoma
	Wilms' tumour		Abscess
	Infected cyst		Tuberculosis
	Lymphoma		Oncocytoma
	Tuberculosis		Xanthogranulomatous pyelonephritis
	Renal artery aneurysm		Phaeochromocytoma (adrenal)
	Arteriovenous malformation		Wilms' tumour
	Hydrocalyx		Transitional cell carcinoma

It has been suggested that abdominal USS could be used as a *screening* test for early detection and treatment of RCC; this has been piloted in Germany and Japan. While there is currently no plan for population screening in the UK, it would be appropriate to offer USS to high-risk individuals such as relatives of VHL syndrome patients.

1 Bosniak MA (1986) The current radiological approach to renal cysts. *Radiology* **158**:1–10.

Benign renal masses

The most common (70%) are *simple cysts*, present in >50% of those aged >50y. Rarely symptomatic, treatment by aspiration or laparoscopic de-roofing is seldom considered.

Most benign renal tumours are rare; the two most clinically important are *oncocytoma* and *angiomyolipoma*.

Oncocytoma

This is uncommon, accounting for 3–7% of renal tumours. Males are twice as commonly affected as females. They occur simultaneously with RCC in 7–32% of cases.

Pathology

Oncocytomas are spherical, capsulated, brown/tan colour, mean size 4–6cm. Half contain a central scar. They may be multifocal and bilateral (4–13%) and 10–20% extend into perinephric fat. Histologically, they comprise aggregates of eosinophillic cells thought to arise from intercalated cells of the collecting duct. Cells are packed with mitochondria, mitoses are rare, large nucleoli are present; they are considered benign, not known to metastasize. There is often loss of the Y chromosome.

Presentation

Oncocytomas often (83%) present as an incidental finding or with loin pain or haematuria.

Investigations

Oncocytoma cannot often be distinguished radiologically from RCC; they may coexist with RCC. Rarely, they exhibit a 'spoke-wheel' pattern on CT scanning, caused by stellate central scar. Percutaneous biopsy is not usually recommended since there is often continuing uncertainty about the diagnosis. The main *differential diagnosis* of renal oncocytoma is *chromophobe RCC oncocytic variant* which, like the renal oncocytoma, has eosinophilic cytoplasm, but has perinuclear clearing and typically, some degree of *nuclear atypia*.

Treatment

Radical or partial nephrectomy is indicated as for renal carcinoma. Minimally invasive techniques such as radiofrequency ablation (RFA) or high intensity focused ultrasound (HIFU) could be considered for smaller tumours. No follow-up is necessary.

Angiomyolipoma (AML)

Eighty percent of these benign clonal neoplasms (PEComa, formerly considered as a hamartoma) occur sporadically, mostly in middle-aged females. Twenty percent are in association with tuberous sclerosis (TS), an autosomal dominant syndrome characterized by mental retardation, epilepsy, adenoma sebaceum, and other hamartomas. Up to 80% of TS patients develop AMLs, mean age 30y, 66% female, frequently multifocal, and bilateral.

Pathology

AML is composed of perivascular epithelioid cells (PEC) containing blood vessels, immature smooth muscle, and fat. They are always considered benign although extrarenal AMLs have been reported in venous system, hilar lymph nodes, and liver. Macroscopically, it looks like a well circumscribed lump of fat. Solitary AMLs are more frequently found in the right kidney.

Presentation

AMLs frequently present as incidental findings (>50%) on USS or CT scans. They may present with flank pain, palpable mass, or painless haematuria. Massive and life-threatening retroperitoneal bleeding occurs in up to 10% of cases (Wunderlich's syndrome).

Investigations

Ultrasound reflects from fat, hence a characteristic bright echo pattern. This does not cast an 'acoustic shadow' beyond, helping to distinguish an AML from a calculus. CT shows fatty tumour as low density (Hounsfield units <10) in 86% of AMLs. If the proportion of fat is low, a definite diagnosis cannot be made as other renal tumours may contain fat. Measurement of the diameter is relevant to treatment.

Treatment

In studies, 52–82% of patients with AML >4cm are symptomatic compared with only 23% with smaller tumours. Therefore, asymptomatic AMLs can be followed with serial USS if <4cm while those bleeding or >4cm should be treated surgically. Emergency nephrectomy or selective renal artery embolization may be life-saving. Patients with kidney loss should be monitored for hypertension (and treated for it if discovered) and avoid nephrotoxic drugs such as certain pain relievers and IV contrast agents. In patients with TS, in whom multiple bilateral lesions are present, annual renal USS and conservative treatment should be attempted. HIFU could be considered for asymptomatic tumours.

Renal cell carcinoma: pathology, staging, and prognosis

RCC is adenocarcinoma of the renal cortex, believed to arise from the proximal convoluted tubule (although the majority of VHL gene deletions occur in the distal tubule). Usually tan-coloured, lobulated, and solid, 7% are multifocal, 1–2% bilateral, 10–20% contain calcification, and 10–25% contain cysts or are predominantly cystic. There may be zones of haemorrhage, necrosis, and scarring. Rarely grossly infiltrative, they are usually circumscribed by a pseudocapsule of compressed tissue.

Spread is by: direct extension to adrenal gland (7.5% in tumours >5cm), through the renal capsule (25%), into renal vein (up to 44%), IVC (5%), right atrium; by lymphatics to hilar and para-aortic lymph nodes; haematogenously to lung (75%), bone (20%), liver (18%), and brain (8%).

Histological classification of RCC

- **Conventional (80%)**: arise from the proximal tubule; highly vascular; clear cells (glycogen, cholesterol) or granular (eosinophillic cytoplasm, mitochondria); involves loss of VHL, PBRM1, and others genes on chromosome 3.
- **Papillary (10–15%)**: papillary, tubular, and solid variants; 40% multifocal; small incidental tumours could equate with Bell's legendary 'benign adenoma'; trisomy 7, 16, 17.
- **Chromophobe (5%)**: arises from the cortical portion of the collecting duct; possesses a perinuclear halo of microvesicles; hypodiploid with loss of chromosomes 1, 2, 6, 10, 13, 17, 21.
- **Collecting duct (Bellini)**: rare, young patients, poor prognosis.
- **Medullary cell**: rare, arises from calyceal epithelium; young sickle cell sufferers; poor prognosis.

'Sarcomatoid" describes an infiltrative poorly differentiated variant of any type in 5–25%. Coagulative necrosis is seen in 30%. Array-based karyotyping performs well on paraffin-embedded tumours and can be used to identify characteristic chromosomal aberrations in renal tumours with challenging morphology.

Genetic changes associated with RCC are described on 📖 p. 250. RCC is an unusually immunogenic tumour, expressing numerous antigens (e.g. RAGE-1, MN-9). Reports of spontaneous regression, prolonged stabilization, and complete responses to immunotherapy support this. Tumour-infiltrating lymphocytes are readily obtained from RCCs, including T-helper, dendritic, natural killer, and cytotoxic T cells. RCC is also unusually vascular, overexpressing angiogenic factors, principally VEGF, but also bFGF and TGF-β.

Grading is by the *Fuhrman system* (1 = well differentiated; 2 = moderately differentiated; 3 and 4 = poorly differentiated), based on nuclear size, outline, and nucleoli. It is an independent prognostic factor.

Staging

Staging is by the TNM classification following histological confirmation of the diagnosis (see Table 7.4 and Fig. 7.1). All rely upon physical examination and imaging; the pathological classification (prefixed 'p') corresponds to the TNM categories. *Staging is the most important prognostic indicator for RCC.*

Table 7.4 UICC 2009 TNM staging of RCC

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤7cm, limited to the kidney a. ≤4cm b. –7cm
T2	Tumour >7cm, limited to the kidney 7–10cm >10cm
T3	Tumour extends outside the kidney, but not into ipsilateral adrenal or beyond Gerota's (perinephric) fascia
T3a	Tumour invades renal sinus, renal vein, or perinephric fat
T3b	Tumour grossly extends into subdiaphragmatic IVC
T3c	Tumour grossly extends into supradiaphragmatic IVC, atrium or invades wall of vena cava
T4	Tumour directly invades beyond Gerota's fascia into surrounding structures, e.g. ipsilateral adrenal, liver
Nx	Regional (para-aortic) lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional node
N2	Metastasis in 2 or more regional nodes
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Prognosis (Table 7.5)

Factors for RCC survival include:

- TNM stage.
- Fuhrman grade, necrosis, or sarcomatoid features.
- Performance status and systemic symptoms.
- Molecular factors (under investigation: VEGF, HIF-1, p53, gene expression profiling).

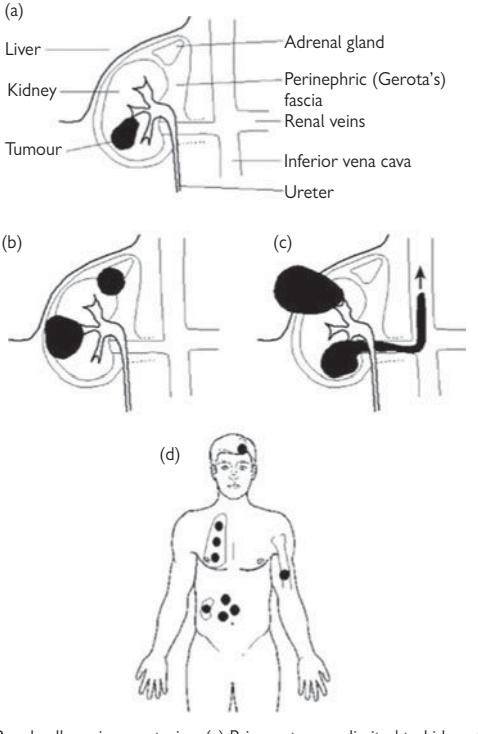

Fig. 7.1 Renal cell carcinoma staging. (a) Primary tumour limited to kidney (T1/T2). (b) Primary tumour invading perinephric fascia or adrenal gland (T3a). (c) Primary tumour extends into renal veins or IVC below diaphragm (T3b); above diaphragm/into right atrium (T3c); outside perinephric fascia (e.g. into liver, bowel, or posterior abdominal wall) (T4). (d) N and M staging: multiple para-aortic/para-caval nodes; pulmonary, bone, or brain metastases (T1–4N2M1).

Table 7.5 RCC: 5y survival

Organ-confined T1 N0M0 (AJCC stage I)	70–94%(depends on grade)
Organ-confined T2 N0M0 (AJCC stage II)	50–75%
Locally advanced T3 or N1 (AJCC stage III)	22–70% (25% in T3c IVC wall invasion)
Metastatic T4, N2 or M1 (AJCC stage IV)	5–40%

A prognostic nomogram has been developed to predict 5y probability of treatment failure for patients with newly diagnosed RCC. It is available for download at: http://www.mskcc.org/mskcc/html/6156.cfm.

Renal cell carcinoma: epidemiology and aetiology

Renal cell carcinoma (RCC) (also known as hypernephroma since it was erroneously believed to originate in the adrenal gland, clear cell carcinoma, and Grawitz tumour) is the commonest of renal tumours, constituting 2–3% of all cancers. It is an adenocarcinoma, accounting for 85% of renal malignancies; the remainder are TCC (10%), sarcomas, Wilms', and other rarities (5%). It occurs in sporadic (common) and hereditary (rare) forms.

Incidence, mortality, and survival

In the UK, both incidence and mortality are rising, with 8228 patients diagnosed (compared with 3676 patients in 1999) and 3848 deaths in 2008. RCC is the most lethal of all urological tumours, approximately 50% of patients dying of the condition; it is the tenth most common cause of cancer death. Relative 5y survival, heavily dependent on stage at diagnosis, is 50% while 10y survival fell to 43% for UK patients. Survival has increased since the 1970's. As with most cancers, there is a steady fall in survival with advancing age at diagnosis: rates for patients under 50y are twice that for patients over 80.

Aetiology

Males are affected 1.5 times as commonly as females; peak incidence of sporadic RCC is between 60–70y of age.

Environmental

Studies have shown associations with cigarette pipe or cigar *smoking* (1.4–2.3-fold risk), *renal failure and dialysis* (30-fold risk), *obesity*, *hypertension* (1.4–2-fold risk), urban dwelling, low socio-economic status, tobacco chewing, occupational *asbestos and cadmium exposure*, the analgesic *phenacitin,* thorium dioxide, and sickle cell trait (medullary carcinoma only). *Nutrition* is considered important: Asian migrants to western countries are at increased risk of RCC; vitamins A, C and E, and fruit/vegetable consumption are protective. Anatomical risk factors include polycystic and horseshoe kidneys.

Genetic

VHL syndrome: 50% of individuals with this autosomal dominant syndrome, characterized by phaeochromocytoma, renal and pancreatic cysts, and cerebellar haemangioblastoma, develop RCC, often bilateral and multifocal. Patients typically present in 3rd, 4th, or 5th decades. VHL syndrome occurs due to loss of both copies of a tumour suppressor gene at chromosome 3p25–26; this and other 3p genes (RASSF1A; PBRM1) are implicated in causing >80% of sporadic RCCs. Inactivation of the VHL gene leads to effects on gene transcription, including dysregulation of hypoxia inducible factors 1 and 2, intracellular proteins that play an important role in the cellular response to hypoxia and starvation. This results in an upregulation of VEGF, the most prominent angiogenic factor in RCC, explaining why some RCCs are highly vascular and enabling targeted treatment approaches (see 🕮 p. 258).

A *papillary variant* of RCC also has an autosomal dominant familial component, characterized by trisomy 7 and 17, with activation of the c-MET proto-oncogene. c-MET is the receptor tyrosone kinase for hepatocyte growth factor which regulates epithelial proliferation and differentiation in a wide variety of organs, including the normal kidney.

Mutations of the *FLCN* gene on chromosome 17p results in the autosomal dominant Birt–Hogg–Dubé syndrome. This rare disease is characterized by benign tumours of hair follicles (mainly facial), pulmonary cysts, pneumothoraces, and renal tumours, including oncocytomas and RCC.

Screening for RCC

Aside from investigating the upper urinary tracts for non-visible asymptomatic haematuria, there is little to support population screening for RCC using USS, given that a large study of 10 000 men aged >40y yielded RCC in only 0.1%.

Renal cell carcinoma: presentation and investigation

At least half of all RCCs are detected incidentally on abdominal imaging carried out to investigate vague or unrelated symptoms. Thus, there has been a downward stage migration at diagnosis since ultrasound and CT scanning came into routine use in the 1980's.

Presentation

History: of the symptomatic RCCs diagnosed, 50% of patients present with haematuria, 40% with loin pain, 25% of patients notice a mass, and 30% have symptoms or signs of metastatic disease, including bone pain, night sweats, fatigue, weight loss, and haemoptysis. Less than 10% of patients exhibit the classic triad of haematuria, pain, and abdominal mass. Less common presenting features include pyrexia of unknown origin (9%), acute varicocoele due to obstruction of the testicular vein by tumour within the left renal vein (2–5%), and lower limb oedema due to venous obstruction. Paraneoplastic syndromes due to ectopic hormone secretion by the tumour occur in 30% of patients; these may be associated with any disease stage (Table 7.6).

Table 7.6 Paraneoplastic syndromes

Syndrome associated with RCC	Cause
Anaemia (30%)	Haematuria, chronic disease
Polycythaemia (5%)	Ectopic secretion of erythropoeitin
Hypertension (25%)	Ectopic secretion of renin, renal artery compression, or AV fistula
Hypoglycaemia	Ectopic secretion of insulin
Cushing's syndrome	Ectopic secretion of ACTH
Hypercalcaemia (10–20%)	Ectopic secretion of parathyroid hormone-like substance
Gynaecomastia, amenorrhoea, reduced libido, baldness	Ectopic secretion of gonadotrophins
Stauffer's syndrome: hepatic dysfunction, fever, anorexia	Unknown; resolves in 60–70% of patients post-nephrectomy

Clinical examination: may reveal abdominal mass, cervical lymphadenopathy, non-reducing varicocele, or lower limb oedema (both suggestive of venous involvement).

Investigations

- **Radiological evaluation**: of haematuria, loin pain, and renal mass is described on 📖 pp. 242 and 270, together with discussion of the role of ***needle biopsy***.
- **Urine cytology and culture**: should be normal.
- **FBC**: may reveal polycythaemia or anaemia.
- **Serum creatinine and electrolytes, calcium, and liver function tests**: are essential.

When RCC is diagnosed radiologically, staging *chest CT* will follow and *bone scan*, if clinically indicated. Any suggestion of renal vein or IVC involvement on CT may be further investigated with *Doppler USS or MRI*. *Angiography* may be helpful in planning partial nephrectomy or surgery for horseshoe kidneys. Contralateral kidney function is assessed by the uptake and excretion of CT contrast and the serum creatinine. If doubt persists, *isotope renography* is used.

Renal cell carcinoma (localized): surgical treatment I

Surgery is the mainstay of treatment for RCC. Increasing diagnosis of smaller, early stage RCC and the concept of cytoreductive surgery for advanced RCC has impacted on investigation and surgical treatment strategies while reduction in mortality remains elusive.

Localized disease—partial nephrectomy (PN) is now the gold standard

Nephron-sparing surgery without adrenalectomy is indicated as follows.

- **Absolute**: tumour in single anatomical/functioning kidney; bilateral tumours.
- **Relative**: multifocal RCC, particularly if the patient has VHL syndrome, aiming to avoid renal replacement therapy; contralateral kidney threatened by another condition.
- **Elective**: T1 (up to 7cm) tumours with a normal contralateral kidney unless the tumour is close to the pelvicalyceal system.

Three-dimensional CT reconstructions provide the surgeon with preoperative identification of the arterial anatomy. Open transperitoneal or loin approaches are used. The renal artery is clamped and the kidney packed with crushed ice to avoid warm ischaemia. If the surgical margin is clear of tumour, the depth of the margin (>1mm) does not influence risk of local recurrence (which is up to 10%). PN for T2 RCC carries increased risk of local recurrence. Specific complications include urinary leak from the collecting system and hyperfiltration renal injury which may eventually require renal replacement therapy; proteinuria is a prognostic sign. *Oncological outcomes are comparable with radical surgery.*

Robot-assisted or laparoscopic PN is becoming the standard approach in centres with expertise for small peripheral RCC. Oncological outcomes are comparable with open PN. Disadvantages include a longer (up to 30min) warm ischaemia time (this is less with the Da Vinci®) and increased peroperative complications. Functional recovery is within hours after 20min of warm ischaemia and days after 30min; it may take several weeks after 60min of clamping. Attempts at achieving cold ischaemia using renal artery or retrograde ureteric infusions or crushed ice in endo-bags have proved difficult and laborious. Some enthusiasts are performing 'zero ischaemia' laparoscopic PN and accepting significant blood loss.

Radical nephrectomy

This remains the gold standard treatment of T2–4 RCC and in T1 RCC in patients unsuitable for PN. There is no difference in outcome favouring a specific surgical approach so the default is now laparoscopic for localized RCC. In the case of upper pole or T2 tumours, adrenalectomy is also necessary.

- **Laparoscopic approach**: has become a widely available option in centres treating RCC. Approaches are either transperitoneal or retroperitoneal. The specimen is removed whole or morselated in a bag through an iliac incision. Advantages over open surgery include

less pain, reduced hospital stay, and quicker return to normal activity. Morbidity is reported in 8–38% of cases, including PE and poorly understood effects on renal function. Long-term (10y) results are equivalent to those obtained by open surgery; cancer-specific survival (CSS) was 92% in a mixed US series.

- **Open approach**: this should be carried out only for large or locally advanced RCCs. The aim is to remove all tumour with adequate surgical margins by excising the kidney with Gerota's fascia, vein tumour thrombus, adrenal gland (if invasion indicated by imaging), and limited regional nodes for staging. Surgical approach is transperitoneal (good access to hilar vessels) or thoracoabdominal (for very large or T3c tumours). Following renal mobilization (avoiding tumour manipulation), the ureter is divided; ligation and division of the renal artery or arteries should ideally take place prior to ligation and division of the renal vein to prevent vascular swelling of the kidney. Complications include mortality up to 2% from bleeding or embolism of tumour thrombus; bowel, pancreatic, splenic, or pleural injury.

Post-operative follow-up aims to detect local or distant recurrence to permit additional treatment, if indicated; incidence is 7% for T1N0M0 RCC, 20% for T2N0M0, and 40% for T3N0M0. After partial nephrectomy, concern will also focus on recurrence in the remnant kidney. There is no consensus regarding the optimal regime, typically stage-dependent 6-monthly clinical assessment and annual CT imaging of chest and abdomen for 5–10y.

Post-operative prognosis

The Leibovich scoring system groups patients into low, intermediate, or high risk for development of metastasis at 1, 3, 5, 7, and 10y according to tumour stage, size, nuclear grade, presence of necrosis, and regional nodal status. This is particularly useful when selecting patients for trials of adjuvant therapy.[1]

A nomogram combining prognostic factors for prediction of 5y recurrence risk following surgery can be downloaded at: http://www.mskcc.org/mskcc/html/6156.cfm

1 Leibovich BC, Blute ML, Cheville JC, *et al.* (2003) Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer* **97**:1663–71.

Renal cell carcinoma: surgical treatment II and non-surgical alternatives for localized disease

Localized RCC—lymphadenectomy

Lymph node involvement in RCC is a poor prognostic factor. Incidence ranges from 6% in T1–2 tumours, 46% in T3A, and 62–66% in higher stage disease. Lymphadectomy at time of nephrectomy may add prognostic information, especially if there is obvious lymphadenopathy, but therapeutic benefit remains unclear. Extended lymphadenectomy adds time and increases blood loss while nodes are clear in about 95% of cases so is not recommended.

Localized RCC: adjuvant therapy

To date, no adjuvant therapy has been shown to improve survival after nephrectomy.

Localized RCC: treatment of local recurrence

Though uncommon, if there is local recurrence in the renal bed after radical nephrectomy, surgical excision remains the preferred treatment choice, provided there are no signs of distant disease. Local recurrence is more common after partial nephrectomy where it can be treated by a further partial or radical nephrectomy.

Localized RCC: alternatives to surgery

- **Renal artery embolization**: indicated for patients with gross haematuria who are unfit for curative surgery.
- **Active surveillance**: small (T1a; <4cm) solid renal masses may be followed with repeat scans in elderly or unfit individuals. Metastasis is rare in masses <3cm. For every 1cm size increase, the estimated prevalence of metastasis increases by 3.5%. Of 178 patients, 101 had renal biopsy, of which 55% were malignant, 12% benign, and 33% non-diagnostic. Average growth rate was similar for these histological groups, ~0.15cm per year. Over a minimum 2y period, 25 (12%) progressed locally (i.e. grew to ≥4cm or volume doubled in ≤12 months) and only 2 (1.1%) developed bone/lung metastases.[1]
- **Cryosurgery**: this minimally invasive treatment (MIT) performed using intraoperative ultrasound by open, percutaneous, or laparoscopic routes, is gaining popularity as a nephron-sparing treatment option.
- **HIFU**: this MIT delivered percutaneously or extracorporeally, is under evaluation as a nephron-sparing treatment option.
- **Image-guided percutaneous RFA**: this MIT, delivered by extracorporeal or laparoscopic routes, remains under evaluation as a nephron-sparing treatment option.

Cryosurgery, HIFU, and Image-guided percutaneous RFA have the advantage of being outpatient-based, low morbidity, and repeatable; they are currently

recommended only for those patients unfit or unwilling to undergo surgery (since current data show recurrence rates are higher), ideally within clinical trials.

Locally advanced RCC

Disease involving the IVC, right atrium, liver, bowel, or posterior abdominal wall demand special surgical skills. In appropriate patients, an aggressive surgical approach involving a multidisciplinary surgical team to achieve negative margins appears to provide survival benefit.

Adjuvant treatment: To date no adjuvant therapy has demonstrated any survival benefit, even in those who are predicted to have a higher risk of recurrence. With the advent of the newer tyrosine kinase inhibitors that have demonstrated a benefit in metastatic disease, multiple randomized trials are ongoing and results are awaited.

Metastatic RCC

Nephrectomy has long been indicated for *symptom palliation* (pain, haematuria) in patients with metastatic RCC (if inoperable, arterial embolization can be helpful) and is also performed *prior to systemic therapy*, if appropriate. A median survival benefit of 10 months for patients with good performance status treated with cytoreductive nephrectomy prior to immunotherapy (interferon-α) has been reported. Studies are ongoing to investigate whether there is a similar benefit to cytoreductive nephrectomy with the tyrosine kinase inhibitors. Currently, the standard practice is to recommend it, extrapolating from the cytokine era. Patients should be recruited to the studies that are investigating cytoreductive nephrectomy.

Resection of a solitary metastasis is an appropriate option for a small number of patients, usually a few months after nephrectomy, to ensure the lesion has remained solitary.

1 Jewett MA, Mattar K, Basiuk J, *et al.* (2011) Active surveillance of small renal masses: progression patterns of early stage kidney cancer. *Eur Urol* **60**:39–44.

Renal cell carcinoma: management of metastatic disease

Approximately 25% of patients with RCC have metastatic disease at presentation; a further 30% progress subsequently to this stage following nephrectomy.

Prognostic risk stratification: The MSKCC (Motzer) criteria may be used, based on Karnofsky performance status <80%; absence of prior nephrectomy; haemoglobin subnormal; LDH >1.5 times upper limit; corrected calcium > normal. No factors confers favourable risk, median time to death—20 months; one to two factors carry intermediate risk (10 months median survival); >3 factors carry poor risk (4 months median survival).

Surgery: despite the rare possibility of spontaneous metastatic regression (<5%) following nephrectomy, it was rarely undertaken except to relieve local symptoms of pain or haematuria. The role of nephrectomy in metastatic RCC is discussed on 📖 p. 257.

Metastasectomy may be of benefit to the 1.5–3% of patients who develop a solitary metastasis (particularly in lung, adrenal, or brain) following nephrectomy.

Angiogenesis (signal transduction) inhibitors

As discussed earlier (see 📖 p. 250), most RCCs are highly angiogenic so fortunately become good therapeutic targets for angiogenesis inhibitors. Via its cell surface receptor (VEGFR), VEGF is a pro-angiogenic peptide growth factor that activates the PI3kinase/AKT signal transduction pathway, which is one of three major receptor tyrosine kinase (RTK) signalling pathways. VEGF is overexpressed in most sporadic RCC as a result of HIF-1 overexpression caused by inactivation of the VHL tumour suppressor gene. In randomized trials, two well-tolerated oral multi-RTK inhibitors, sunitinib and pazopanib, have demonstrated significant benefit in the first-line metastatic setting, prolonging progression-free survival (PFS) in metastatic RCC patients by 3–8 months compared with interferon alpha (IFNα) or placebo. The UK NICE approved both in 2009 and 2011, respectively. Complete responses are rare, partial responses modest (30–40%), they also stabilize the disease in approximately 30% of patients.[1] Pazopanib is effective as second-line treatment (prior cytokine therapy).

A further randomized trial demonstrated >3-month survival advantage of temsirolimus, an inhibitor of cytoplasmic mTOR kinase (a downstream component of the same pathway) in metastatic RCC patients compared with IFNα.[2] This is currently recommended for first-line treatment of poor risk disease. For second-line, everolimus is an orally available mTOR inhibitor: it confers a 2-month PFS over placebo when used for patients failing the treatments. However, NICE has not approved its use (2011).

VEGF antibodies

Bevacizumab is a humanized monoclonal antibody that binds to VEGFR. A phase III randomized trial demonstrated a median 31% response with bevacizumab + IFNα compared with IFNα alone, with a 4.8-month PDS

advantage for low and intermediate risk patients. This combination is an option for first-line treatment.

These agents represent a major advance in the first- and second-line treatment of metastatic RCC. *There are multiple newer thymidine kinase inhibitors (TKI) that are also currently being investigated.*

Immunotherapy

The immunogenicity of RCC is discussed on 📖 p. 246. The first cytokines to be used therapeutically to activate anti-tumour immune response were interferons and subsequently IL-2. Randomized studies in the 1990's demonstrated modest response rates (10–20%) after *systemic immunotherapy* using these cytokines alone and in combination; toxicity could be severe. Responses were more likely in patients with good performance status, prior nephrectomy, and small-volume metastatic burden. An MRC trial of IFNα vs medroxyprogesterone demonstrated a 2.5-month survival advantage in the immunotherapy group. The use of immunotherapy has been overshadowed recently by the development of RTK inhibitors, although there may still be a role for IL-2 in a very select group of patients and is still being used for appropriate patients (excellent performance status, small volume lung only metastases, and no prior treatment).

Chemotherapy: little role in RCC; ineffective due to high multidrug resistance P glycoprotein expression.

Radiotherapy: useful for palliation of metastatic lesions in bone and brain and in combination with surgery for spinal cord compression.

Palliative care

Steroids (e.g. dexamethazone 4mg qds) improve appetite and mental state, but are unlikely to impact on tumour growth. The involvement of multidisciplinary uro-oncology, palliative, and primary care teams is essential to support these patients and their relatives.

1 Motzer RJ, Hutson TE, Tomczak P, *et al.* (2007) Sunitimib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* **356**:115–24.

2 Sternberg CN, Davis ID, Mardiak J, *et al.* (2010) Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* **28**:1061–8.

3 Hudes G, Carducci M, Tomczak P, *et al.* (2007) Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* **356**:2271–81.

Upper urinary tract transitional cell carcinoma (UUT-TCC)

UUT-TCC accounts for 90% of upper urinary tract tumours, the remainder being benign inverted papilloma, fibroepithelial polyp, squamous cell carcinoma (associated with longstanding staghorn calculus disease), adenocarcimona (rare), and various rare non-urothelial tumours, including sarcoma.

TCC of the renal pelvis is uncommon, accounting for 10% of renal tumours and 5% of all TCC. Ureteric TCC is rare, accounting for only 1% of all newly presenting TCC. Half are multifocal; 75% located distally while only 3% are located in the proximal ureter.

Risk factors are similar to those of bladder TCC (see 📖 p. 264).

- *Males* are affected three times as commonly as females.
- Incidence increases with *age*.
- *Smoking* confers a 2-fold risk and there are various occupational causes.
- Phenacetin ingestion.
- There is a high incidence of UUT-TCC in families from some villages in Balkan countries *('Balkan nephropathy')* that remains unexplained.
- Lynch syndrome (hereditary non-polyposis colon cancer) is an autosomal dominant condition caused by a DNA mismatch repair defect; it is associated with various cancers, including UUT-TCC, most in middle-aged females.

Pathology and grading

The tumour usually has a papillary structure, but occasionally solid. It is bilateral in 2–4%. It arises within the renal pelvis, less frequently in one of the calyces or ureter. Histologically, features of TCC are present; grading is as for bladder TCC. Spread is by direct extension, including into the renal vein and vena cava; lymphatic spread to para-aortic, para-caval, and pelvic nodes; bloodborne spread, most commonly to liver, lung, and bone.

Presentation

- Painless total haematuria (80%).
- Loin pain (30%), often caused by clots passing down the ureter ('clot colic').
- Asymptomatic when detected, associated with synchronous bladder TCC (4%).

At follow-up, approximately 50% of patients will develop a metachronous bladder TCC and 2% will develop contralateral upper tract TCC.

Investigations

Ultrasound is excellent for detecting the more common renal parenchymal tumours, but not sensitive in detecting tumours of the renal pelvis or ureter.

Diagnosis is usually made on *urine cytology* and *CTU*, respectively, revealing malignant cells and a filling defect in the renal pelvis or ureter. If doubt exists, selective ureteric urine cytology, *retrograde ureteropyelgraphy*, or

flexible *ureterorenoscopy* with *biopsy* are indicated. Some surgeons prefer to have histological proof of malignancy prior to treatment. Additional staging is obtained by chest CT and occasionally, isotope bone scan.

Staging uses the TNM (2009) classification (Table 7.7) following histological confirmation of the diagnosis. All rely on physical examination and imaging, the pathological classification corresponding to the TNM categories.

Table 7.7 TNM 2009 staging of carcinomas of the renal pelvis and ureter

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis propria
T3	Tumour invades beyond muscularis propria into perinephric or perureteric fat or renal parenchyma
T4	Tumour invades adjacent organs or through kidney into perinephric fat
Nx	Regional (para-aortic) lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node ≤2cm
N2	Metastasis in a single lymph node >2–5cm or multiple nodes up to 5cm
N3	Metastasis in a single lymph or multiple nodes >5cm
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Treatment

If staging indicates non-metastatic disease in the presence of a normal contralateral kidney, the gold standard treatment with curative intent is *nephroureterectomy with excision of the bladder cuff and node sampling* (if possible).

The open approach uses either a long transperitoneal midline incision or separate loin and iliac fossa incisions. The entire ureter is taken with a cuff of bladder because of the 50% incidence of subsequent ureteric stump recurrence.

The laparoscopic approach focuses on mobilizing the kidney and upper ureter extraperitoneally; the lower ureter with bladder cuff is dissected via a Gibson-type open incision through which the entire specimen is retrieved. As for laparoscopic nephrectomy, benefits include reduced

post-operative pain and faster recovery. Tumour spillage and port site metastases are theoretical hazards. Long-term results are equivalent with the open approach.

Percutaneous, segmental, or ureterorenoscopic resection/laser ablation of the tumour are the minimally invasive options for patients with a single functioning kidney, bilateral disease, unilateral low-grade tumours <1cm, or those who are unfit. Topical BCG or chemotherapy (for example, mitomycin C) may subsequently be instilled through the nephrostomy or ureteric catheters, though benefit has not been proven. This nephron-sparing approach is less likely to be curative than definitive surgery.

Follow-up should continue at least 5y:

- **T1-2**: cystoscopy at 3 months, then annually, plus annual CTU to detect metachronous TCC development.
- **T3-4 and minimally invasive management**: cystoscopy and CTU should be at 3 months, then 6-monthly for the first 2y, together with urine cytology.

Metastatic disease

- **Systemic combination chemotherapy (platinum-based)**: for unresectable or metastatic disease is associated with a 30% total or partial response at the expense of moderate toxicity.
- **Palliative surgery or arterial embolization**: may be necessary for troublesome haematuria. Radiotherapy is generally ineffective.

Prognostic factors (Table 7.8)

Muscle-invasive UUT-TCC, constituting 60% of new presentations, have a poor prognosis. The following are recognized prognostic factors, in descending order of importance:

- Tumour grade and stage.
- Associated Tis.
- Age.
- Lymphovascular invasion.
- Tumour architecture.
- Extensive tumour necrosis.
- Tumour location.
- Molecular markers, e.g. epithelial cadherin, HIF-1α, telomerase RNA, TK MET.

Table 7.8 5y survival

Organ-confined (T1, 2)	60–100%
Locally-advanced (T3, 4)	10–50%
Node-positive (N+)	10%
Pulmonary, bone metastases (M+)	10%

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Bladder cancer: epidemiology and aetiology

Incidence, mortality, and survival

Bladder cancer is the second most common urological malignancy and the fourth most common cancer in men. UK incidence has fallen since the mid-1990s in all age groups; 10 091 patients diagnosed in 2008. Mortality has fallen since the early 1990s, more pronounced in men than women (in fact, mortality of elderly women is still increasing), accounting for 5002 UK deaths in 2007. This represents 3% of all cancer deaths. Perhaps the reduction in smoking accounts for such trends. These data indicate about half of patients diagnosed have curable or controllable disease; hence, 10y survival is ~50% for women and approaching 60% in men.

Risk factors

- **Men**: are 2.5 times more likely to develop the disease than women, the reasons for which are unclear, but may be associated with greater urine residuals in the bladder
- **Age**: increases risk, most commonly diagnosed in the eighth decade and rare below age 50y.
- **Smoking**: is the major cause of bladder cancer in the developed world. Smokers have a 2–5-fold risk of developing bladder cancer, subsequent recurrences, and higher mortality compared to non-smokers. Estimates suggest that 30–50% of bladder cancer is caused by smoking. Cigarette smoke contains the carcinogens 4-aminobiphenyl (4-ABP) and 2-naphthylamine (Fig. 7.2). Slow hepatic acetylation (detoxification) of 4-ABP by N-acetyltransferase and glutathione S-transferase M1 (GSTM1) or induction of the cytochrome P450 1A2 demethylating enzyme appear to increase urothelial carcinogenic exposure. There is a slow (20y) risk reduction following cessation of smoking.
- **Occupational exposure**: to carcinogens, in particular aromatic hydrocarbons like aniline, is a recognized cause of bladder cancer. Examples of 'at risk' occupations are shown in Box 7.1. A latent period of 25–45y exists between exposure and carcinogenesis.
- **Environmental carcinogens**: found in urine are the major cause of bladder cancer.
- **Chronic inflammation of bladder mucosa**: bladder stones, long-term catheters, and notoriously the ova of *Schistosoma haematobium* (bilharziasis) are implicated in the development of SCC of the bladder.
- **Drugs**: phenacitin and cyclophosphamide.
- **Race**: Black people have a lower incidence than white people, but inexplicably they appear to carry a poorer prognosis.
- **Pelvic radiotherapy**: either for prostate cancer (external beam or brachytherapy) or a gynaecological malignancy, a relative risk of 1.4–4 exists for the later development of a second primary malignancy in the bladder.

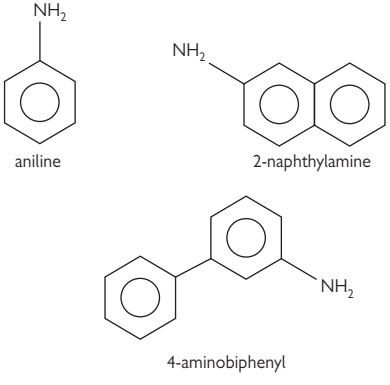

Fig. 7.2 Carcinogens known to increase risk of bladder cancer.

Box 7.1 Occupations associated with TCC

- Rubber manufacture, e.g. tyres or electric cable.
- Paint and dye manufacture.
- Fine chemical manufacture, e.g. auramine.
- Gas and tar manufacture.
- Iron and aluminium processing.
- Hairdressers.
- Leather workers.
- Plumbers.
- Painters.
- Drivers exposed to diesel exhaust.

No evidence for a hereditary genetic aetiology exists, though many somatic genetic abnormalities have been identified. The most common cytogenetic abnormality is loss of chromosomes 9p, 9q, 11p 13q, and 17q. Activation/amplification of oncogenes (p21 ras, c-myc, c-jun, erbB-2), inactivation of tumour suppressor genes (p53 mutations appear to worsen survival after treatment, retinoblastoma, p16 cyclin-dependent kinase inhibitor), and increased expression of angiogenic factors (for example, VEGF) are reported in TCCs.

Bladder cancer: pathology, grading, and staging

Benign tumours of the bladder, including inverted urothelial papilloma and nephrogenic adenoma, are uncommon.

The vast majority of primary bladder cancers are malignant and epithelial in origin.

- >90% are TCC, usually high-grade.
- 1–7% are SCC; 75% are SCC in areas where schistosomiasis is endemic.
- 2% are adenocarcinoma.
- Small cell and spindle cell carcinomas (rare).
- Other rare primary tumours include phaeochromocytoma, melanoma, lymphoma, and sarcoma arising within the bladder muscle.
- Secondary bladder cancers are mostly directly spread by adenocarcinomas from the gut, prostate, kidney or ovary, or squamous carcinoma of the urerine cervix.

Tumour spread is:

- **Direct**: tumour growth to involve the detrusor, the ureteric orifices, prostate, urethra, uterus, vagina, perivesical fat, bowel, or pelvic side walls.
- **Implantation**: into wounds/percutaneous catheter tracts.
- **Lymphatic**: infiltration of the iliac and para-aortic nodes.
- **Haematogenous**: most commonly to liver (38%), lung (36%), adrenal gland (21%), and bone (27%). Any other organ may be involved.

Histological grading has traditionally (1973 WHO Classification) been divided into: benign urothelial papilloma; well, moderately, and poorly differentiated (G1, G2, and G3, respectively) carcinoma. Most retrospective studies, clinical trials, and guidelines are based on this classification. The 2004 WHO grading uses cytological/architectural criteria to distinguish flat lesions (hyperplasia, dysplasia, carcinoma *in situ*) and raised lesions (urothelial papilloma, papillary urothelial neoplasms of low malignant potential (PUNLMP), low-grade and high-grade urothelial carcinomas). The 2004 system is more reproducible, but is as yet not proven to be of better prognostic value than the 1973 system. Hence, both systems are used in contemporary clinical practice, with G2 tumours being called either low-grade or high-grade.

Staging is by the TNM (2009) classification (Table 7.9 and Fig. 7.3). All rely upon physical examination and imaging, the pathological classification (prefixed 'p') corresponding to the TNM categories.

TCC: may be single or multifocal. Because 5% of patients will have a synchronous upper tract TCC and metachronous recurrences may develop after several years, the urothelial 'field change' theory of polyclonality has been favoured over the theory of tumour monoclonality with transcoelomic implantation (seeding).

Primary TCC is either *non-muscle invasive* (formerly known as 'superficial') or *muscle-invasive*.

- 70% of tumours are *papillary*, usually G1 or G2, exhibiting at least seven transitional cell layers covering a fibrovascular core (normal transitional epithelium has approximately five cell layers). *Papillary* TCC is usually *superficial,* confined to the bladder mucosa (Ta) or submucosa (T1); 10% of patients subsequently develop muscle-invasive or metastatic disease. However, G3T1 tumours are more aggressive, with 40% subsequently upstaging.
- 10% of TCC have *mixed papillary and solid* morphology and 10% are *solid*. These are usually G3, half of which are *muscle-invasive* at presentation.
- 10% of TCC is flat CIS. This is poorly differentiated carcinoma, but confined to the epithelium and associated with an intact basement membrane; 50% of CIS lesions occur in isolation; the remainder occurs in association with muscle-invasive TCC. CIS usually appears as a flat red velvety patch on the bladder mucosa; 15–40% of such lesions are CIS, the remainder being focal cystitis of varying aetiology. The cells are poorly cohesive, up to 100% of patients with CIS exhibiting positive urine cytology in contrast to much lower yields (17–72%) with G1/2 papillary TCC; 40–83% of untreated CIS lesions will progress to muscle-invasive TCC, making CIS the most aggressive form of superficial TCC.
- 5% of patients with G1/2 TCC and at least 20% with G3 TCC (including CIS) have vascular or lymphatic spread. *Metastatic lymph node disease* is found in: 0% Tis, 6% Ta, 10% T1, 18% T2 and T3a, 25–33% T3b and T4 TCC.

SCC: is usually solid or ulcerative and muscle-invasive at presentation. SCC accounts for only 1% of UK bladder cancers. SCC in the bladder is associated with chronic inflammation and urothelial squamous metaplasia rather than CIS. In Egypt, 80% of SCC is induced by the ova of *Schistosoma haematobium*. Five percent of paraplegics with long-term catheters develop SCC. Smoking is also a risk factor for SCC. The prognosis is better for bilharzial SCC than for non-bilharzial disease, probably because it tends to be lower-grade and metastases are less common in these patients.

Adenocarcinoma: is rare, usually solid/ulcerative, G3, and carry a poor prognosis. One-third originate in the urachus, the remnant of the allantois, located deep to the bladder mucosa in the dome of the bladder. Adenocarcinoma is a long-term (10–20+ year) complication of bladder exstrophy and bowel implantation into the urinary tract, particularly bladder substitutions and ileal conduits after cystectomy. There is association with cystitis glandularis rather than CIS. Secondary adenocarcinoma of the bladder may arise.

Table 7.9 The 2009 UICC TNM staging of bladder carcinoma

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ* (flat disease)
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis propria (detrusor): T2a = inner half T2b = outer half
T3	Tumour invades beyond muscularis propria into perivesical fat: T3a = microscopic T3b = macroscopic
T4a	Tumour invades any of: prostate, uterus, vagina, bowel
T4b	Tumour invades pelvic or abdominal wall
Nx	Regional (iliac and para-aortic) lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node below the common iliac bifurcation
N2	Metastasis in a group of lymph nodes below the common iliac bifurcation
N3	Metastasis in a common iliac node
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

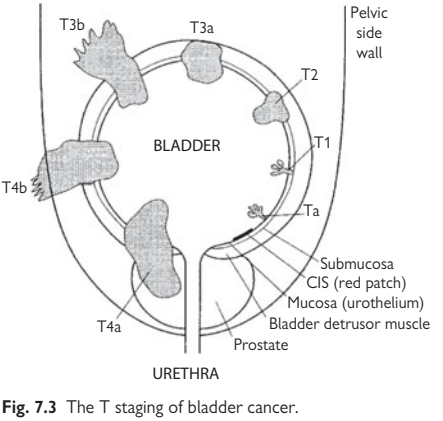

Fig. 7.3 The T staging of bladder cancer.

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Bladder cancer: clinical presentation

Symptoms

- The commonest presenting symptom (85% of cases) is ***painless visible haematuria***. Haematuria may be initial or terminal if the lesion is at the bladder neck or in the prostatic urethra. Thirty-four percent of patients >50y and 10% <50y with macroscopic haematuria have bladder cancer. A history of smoking or occupational exposure is relevant.
- ***Asymptomatic non-visible haematuria*** found on routine urine stick-testing accounts for an important minority of presentations. Up to 16% of females and 4% of males have stick-test haematuria: <5% of those <50y and 7–13% of those >50y will have a malignancy.
- ***Filling-type LUTS*** such as urgency or suprapubic pain. There is almost always microscopic or macroscopic haematuria. This so-called 'malignant cystitis' is typical in patients with CIS.
- Recurrent ***UTIs*** and ***pneumaturia*** due to malignant colovesical fistula, though less common than benign causes (diverticular and Crohn's disease).
- Urachal adenocarcinomas may present with a blood or mucus ***umbilical discharge*** or a deep subumbilical mass.
- More advanced cases may present with ***lower limb swelling*** due to lymphatic/venous obstruction, ***bone pain***, ***weight loss***, ***anorexia***, ***confusion***, and ***anuria*** (renal failure due to bilateral ureteric obstruction).
- ***Pain*** is unusual, even if the patient has obstructed upper tracts since obstruction and renal deterioration arise gradually.

Signs

General examination may reveal ***pallor***, indicating anaemia due to blood loss or chronic renal impairment. Abdominal examination may reveal a ***suprapubic mass*** in the case of locally advanced disease; DRE may reveal a pelvic ***mass*** above or involving the prostate.

Although the likelihood of diagnosing bladder cancer in patients <50y is low, all patients with these presenting features should be investigated (see 🕮 p. 272).

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Bladder cancer: haematuria, diagnosis, and transurethral resection of bladder tumour (TURBT)

Investigation of haematuria

After a UTI has been excluded or treated and menstruation ruled out as the cause, ***all*** patients with persistent microscopic (2 out of 3 dipstick tests) or macroscopic haematuria require investigation of their upper tracts, bladder, and urethra. *Visible haematuria* (VH, otherwise referred to as 'macroscopic haematuria' or 'gross haematuria') requires consideration of other (rare) causes of discoloured urine (myoglobinuria, haemoglobinuria, beeturia, drug discoloration—rifampicin, doxorubicin). Twenty-two percent of patients with VH will harbour a urological malignancy. *Non-visible haematuria* (NVH, otherwise referred to as 'microscopic haematuria' or 'dipstick-positive haematuria') is further subdivided as follows:

- **Symptomatic NVH (s-NVH)**: symptoms such as voiding LUTS, hesitancy, frequency, urgency, dysuria.
- **Asymptomatic NVH (a-NVH)**: incidental detection in the absence of LUTS or upper urinary tract symptoms.
- Five percent of patients with NVH will harbour urological malignancy, more frequently in patients >40y.

Dipstick vs microscopy

Urine dipstick of a fresh voided urine sample, containing no preservative, is considered a sensitive means of detecting the presence of haematuria. Community-based urine samples sent for microscopy have a significant false negative rate; the procedure is more labour intensive and adds little to establishing the diagnosis of haematuria. Routine microscopy for confirmation of dipstick haematuria is not necessary. Whilst the sensitivity of urine dipsticks may vary from one manufacturer to another, significant haematuria is considered to be 1+ or greater. Trace haematuria should be considered negative. There is no distinction in significance between non-haemolysed and haemolysed dipstick-positive haematuria. A 1+ positive for either should be considered of equal significance.[1]

Urological investigations are tailored according to patient age and symptoms:

- **Over 40y old with macroscopic haematuria**: urgent CTU, cystoscopy, and cytology.
- **Under 40y with macroscopic haematuria**: urgent USS renal tract followed by CT-KUB, cystoscopy, and cytology.
- **Over 40y with NVH**: CT-KUB followed by USS renal tract, cystoscopy ± urine cytology.
- **Under 40y with NVH**: USS renal tract alone for a-NVH and with cystoscopy for s-NVH.

CTU is faster and more sensitive than ultrasound or IVU in the detection of renal (parenchymal and urothelial) and ureteric tumours. However, it carries a higher radiation dose and is more expensive. CTU also detects

some bladder tumours, but may overcall bladder wall hypertrophy as tumour and will miss flat CIS and urethral pathology so it cannot replace cystoscopy. CT-KUB requires less radiation dose and is preferred in patients who are more likely to have stone than malignancy.

If all investigations are normal, consideration should be given to nephrological disorders that may cause haematuria such as glomerulonephritis. Annual monitoring of BP, urinalysis, and eGFR is recommended. Cross-referral to a renal physician is advised in patients with persisting microscopic haematuria ± proteinuria and hypertension or eGFR <60mL/min.

Referral back for further urological investigation is required if haematuria becomes visible (CTU indicated) or NVH persists, but becomes symptomatic. Patients with predominantly filling-type LUTS, suprapubic pain, or recurrent UTI/pneumaturia should also have urine cytology and cystoscopy.

Causes of persistent NVH

Urological causes

Common

- Benign prostatic hyperplasia.
- Cancer (bladder, kidney, prostate, ureter).
- Calculus disease or nephrolithiasis.
- Cystitis or pyelonephritis.
- Prostatitis or urethritis.
- *Schistosoma haematobium* infection.

Less common

- Radiation cystitis.
- Urethral strictures.
- TB.
- Medullary sponge kidney.
- Cyclophosphamide-induced cystitis.

Rare

- Arteriovenous malformation.
- Renal artery thrombosis.
- Polycystic kidney disease.
- Papillary necrosis of any cause.
- Loin pain haematuria syndrome.

Nephrological causes

Common

- IgA nephropathy (Berger's disease).
- Thin basement membrane disease.

Less common/rare

- Acute glomerular disease.
  - Post-infectious glomerulonephritis.
  - Rapidly progressive glomerulonephritis.
  - Systemic lupus nephritis.
  - Vasculitis.
  - Goodpasture's disease.

- Henoch–Schönlein purpura syndrome.
- Haemolytic uraemic syndrome.

- Chronic primary glomerulonephritis.
  - Focal segmental glomerulonephritis.
  - Mesangiocapillary glomerulonephritis
  - Membranous nephropathy.
  - Mesangial proliferative glomerulonephritis.
- Familial causes.
  - Hereditary nephritis (Alport's syndrome).
- Polycystic kidney disease (autosomal dominant or recessive).

Urine cytology

Examination of voided urine for exfoliated cells is most sensitive (90–100%) in patients with high-grade TCC and CIS, anywhere in the urinary tract. It is costly and <1% of cancers are detected by cytology alone when other investigations are normal. False-negative cytology is frequent (40–70%) in patients with papillary TCC while false-positive cytology can arise due to infection, inflammation, stones, instrumentation, and intravesical instillations such as chemotherapy. Guidelines do not specify if and when to use it so practices vary.

Urine molecular markers

ELISA tests for detecting tumour-specific urinary markers such as *bladder tumour antigen (BTA)* or *nuclear matrix protein 22 (NMP22)* tend to have greater sensitivity, but reduced specificity for detecting TCC, compared with urine cytology. *ImmunoCyt* has the highest sensitivity for detection of low-grade tumours and is less affected by other urological diseases. However, with a 60% detection rate for low-grade tumours, the test remains largely inadequate to replace cystoscopy. The absence of clinical trials and the costs involved mean that it is unclear whether these tests, alone or in combination, may replace any of the standard investigations for haematuria.

Diagnosis and initial treatment of bladder cancer

TURBT usually provides definitive histological diagnosis, grade, and clinical and pathological stage and is the first (sometimes sole) treatment. This is undertaken under general or spinal anaesthesia; bimanual examination is mandatory before and after bladder tumour resection to assess size, position, and mobility. If possible, the surgeon should resect the tumour(s) completely. The pathologist should report on the tumour type, grade, and stage; in particular, the presence or absence of muscularis propria should be noted since its absence will preclude reliable T staging. Red areas are biopsied separately; the prostatic urethra is biopsied if cystectomy with bladder reconstruction is under consideration. Particular care is taken when resecting tumours at the dome since intraperitoneal bladder perforation may occur, especially in women with thin-walled bladders. Care is also taken when resecting posterolateral tumours due to the proximity of the obturator nerve; stimulation may result in a 'kick' unless the patient is under full paralysis, which may lead to bladder perforation and/or troublesome bleeding.

Narrow-band imaging (NBI) and photodynamic detection (PDD)

- **NBI**: is an optical image enhancement technology in which the narrow bandwidth of light is strongly absorbed by haemoglobin and penetrates only the surface of tissue, increasing the visibility of capillaries and other delicate tissue surface structures by enhancing contrast between the two. A number of small studies have demonstrated NBI to be superior to standard white light cystoscopy for the detection of new and recurrent tumours.
- **PDD (fluorescence cystocopy)**: uses blue light in combination with a porphyrin-based photosensitizer, hexaminolevulinic acid (HAL; Hexvix®). Several randomized studies have revealed CIS lesions and developing papillary tumours which cannot be seen using standard white light for tumour detection and resection. For example, a total of 113 CIS lesions in 58 patients 104 (92%) were detected by PDD, 77 (68%) were detected by white light cystoscopy, while 5 were detected only by biopsy of visually normal mucosa.[2] The 1y risk of papillary recurrence is reduced by 9–27% This technique is gaining popularity, but is expensive; however, it has been suggested that improved tumour detection leads to better patient management and reduced long-term recurrence rates and costs. The value of PDD for improvement of the outcome in relation to progression rate or survival remains to be demonstrated, though it has gained a place in routine management of selected patients, particularly in those with positive urine cytology, but normal-looking bladder mucosa.

Staging investigations are usually reserved for patients with biopsy-proven muscle-invasive bladder cancer unless clinically indicated since non-muscle-invasive TCC and CIS are rarely associated with metastases.

1 Kelly JD, Fawcett DP, Goldberg LC (2009) Assessment and management of non-visible haematuria in primary care. *BMJ* **338**:a3021.

2 Fradet Y, Grossman HB, Gomella L, *et al.* (2007) A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. *J Urol* **178**:68–73.

Bladder cancer (non-muscle invasive TCC): surgery and recurrence

TURBT

The diagnostic role of TURBT has been discussed on 📖 p. 274. As a primary treatment, a visually complete tumour resection is adequate for 70% of newly presenting patients with Ta/T1 superficial disease. The remaining 30% of patients experience early recurrence, 15% with upstaging. Because of this, it is standard care that all new patients receive adjuvant treatment with a single dose of post-operative intravesical chemotherapy (usually mitomycin; see 📖 p. 280). ***Complications*** of TURBT are uncommon, including bleeding, sepsis, bladder perforation, incomplete resection, and urethral stricture.

Alternatives to TURBT

Transurethral cystodiathermy or laser are accepted, quicker and less morbid procedure for ablating small superficial recurrences when obtaining tissue for histology is not considered necessary.

Fluorescence and NBI cystocopy are discussed on 📖 p. 275.

Follow-up after TURBT

Second resection: an early repeat TUR (within 2–6 weeks) should be undertaken: (a) if the first resection was incomplete, (b) when the pathologist reports that the resected specimen contains no muscularis propria, or (c) if a high-grade, but apparently non-invasive, T1 tumour has been reported since perhaps 10% (3–25%) of these G3pT1 tumours are understaged T2 tumours. This strategy improves recurrence-free survival and prognosis while complications include bladder perforation.

In the absence of these indications for a second resection, review cystoscopy is performed at 3 months. If this demonstrates recurrence, 70% will recur further. If not, only 20% will recur further. If the bladder is clear at follow-up, subsequent cystoscopies are performed under local anaesthetic at 9 months and thereafter annually for 5y (patients with low-risk TCC) or until the patient is no longer fit to undergo treatment (patients with high-risk disease).

Patients with G3T1 TCC, and CIS are at significantly higher risk of recurrence and 40% subsequently upstage. Some patients experience persistent symptomatic multifocal G1/2, Ta/1 recurrent TCC, demanding frequent follow-up procedures. In these circumstances, ***adjuvant treatment*** is indicated (see 📖 p. 280).

There is no accepted protocol for ***upper tract surveillance*** in patients with a history of bladder TCC, although EAU guidelines[1] recommend yearly imaging (CTU) for patients with high-risk disease.

Predicting recurrence and progression in Ta/T1 TCC

A validated scoring system based on the following factors has been developed (by the EORTC):[2]

- Number of tumours (e.g. 1 = 0 points; 2–7 = 3 points; ≥8 = 6 points).
- Tumour diameter (<3cm vs >3cm).
- Prior recurrence <1 vs >1 per year).
- T stage (Ta vs T1).
- Tumour grade (G1 vs G2 vs G3).
- Presence of concomitant CIS.

This system divides superficial tumours into those at low risk (50%), intermediate risk (35%), or high risk (15%) of recurrence and progression at 1y or 5y. The scoring tables and risk calculators are available at: http://www.eortc.be/tools/bladdercalculator/.

See Table 7.10 for a summary of the management of bladder cancer by grade and stage.

Table 7.10 A summary of the management of bladder cancer

Histology	Risk of recurrence post-TURBT	Risk of stage progression	Further treatment	Urological follow-up
G1/2, Ta/1, TCC	30%	10–15%	Immediate post-operative single dose intravesical chemotherapy	Review cystoscopies, commencing 3 months
Recurrent multifocal G1/2, Ta/1 TCC	70%+	10–15%	Intravesical chemotherapy x 6 weekly doses	Review cystoscopies, commencing 3 months
G3, Ta/T1 TCC	80%	40%	Second resection; intravesical BCG x 6 weekly doses; consider cystectomy for recurrence	Review cystoscopies, commencing 6–12 weeks
CIS (carcinoma *in situ*, severe intraepithelial dysplasia)	80%	40%	Intravesical BCG x 6 weekly doses 9 maintenance; consider cystectomy for recurrence	Cystoscopies + biopsy and cytology commencing 3 months
pT2/3, N0, M0 TCC, SCC or adenocarcinoma	Usually TUR is incomplete	N/a	Cystectomy or radiotherapy 9 neoadjuvant chemotherapy or palliative TURBT (unfit)	Cystoscopies if bladder is preserved. Urethral washings for cytology.
T4 or metastatic TCC, SCC, or adenocarcinoma	Usually TUR is incomplete	N/a	Systemic chemotherapy; multidisciplinary team symptom palliation	Palliative treatment for local bladder symptoms

1 European Association of Urology Guidelines on Non–Muscle-Invasive Urothelial Carcinoma of the Bladder, the 2011 update. *Eur Urol* **59**: 997–1008.

2 Sylvester RJ, van der Meijden AP, Oosterlinck W, *et al.* (2006) Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* **49**: 466–77.

Bladder cancer (non-muscle invasive TCC): adjuvant treatment

Intravesical chemotherapy (e.g. mitomycin C (MMC) 40mg in 50mL saline) is used for G1-2, Ta or T1 tumours, and recurrent multifocal TCC. MMC is an antibiotic chemotherapeutic agent that inhibits DNA synthesis. In experimental studies, it may cause regression of small papillary TCC so it should be cytotoxic for microscopic residual disease post-TURBT. A meta-analysis of seven randomized trials[1] demonstrated that a single dose given within 24h of first TURBT significantly (24%) reduces the likelihood of tumour recurrence compared to TURBT alone, from 48% to 37%. This is now standard treatment for all new papillary bladder tumours post-TURBT.

For many patients at low risk of recurrence, the risk reduction seen with single-dose chemotherapy is equivalent to that seen using weekly instillations for 6 weeks, commencing up to 2 weeks post-TURBT. Such longer courses are still recommended for patients at higher risk of recurrence or who have multifocal recurrences, excluding those with high-grade Ta/1 TCC or CIS.

Intravesical chemotherapy has never been shown to prevent progression to muscle invasion and has no impact upon survival. It is administered via a urethral catheter, is held in the bladder for 1h, and should not be used if there is ongoing haematuria or if bladder perforation is suspected.

Toxicity of MMC: 15% patients report transient filling-type LUTS; occasionally a rash develops on the genitals or palms of the hands so treatment must be stopped. Systemic toxicity is rare with MMC.

Other effective intravesical chemotherapy agents include doxorubicin and epirubicin, but not gemcitabine.

Intravesical BCG: is an attenuated strain of *Mycobacterium bovis*. Commercially available strains include Pasteur, Connaught, and Tice. It acts as an immune stimulant, upregulating cytokines such as IL-6 and IL-8 in the bladder wall, activating immune effector cells.

BCG produces complete responses in 60–70% of patients. It is as effective as chemotherapy for adjuvant treatment of low- and intermediate-risk G1/2, Ta/1 TCC, therefore, is not often used (except as second-line) because of the additional toxicity. *In high-risk patients, with multiple G2T1, high-grade G2 or G3Ta/T1, or* CIS, *the benefit of* BCG *over chemotherapy in reducing risk of recurrence is clear* and it is standard care. BCG is given as a 6-week induction course, starting at least 2 weeks post-TURBT. It is administered via a urethral catheter, 80mg in 50mL saline and retained in the bladder for 1h.

A meta-analysis of 24 trials has demonstrated that *BCG reduces risk of stage progression* (to muscle invasion) by 27%, based on a median follow-up of 2.5y.[2] This effect was only seen in patients who received *maintenance BCG* (e.g. 30 treatments over 3y after the initial 6-week induction), which is now the standard recommendation for high-grade Ta/T1 or CIS initial responders, though the optimal dose and schedule remain unclear. For recurrent high-grade Ta/T1 or CIS, a second course of BCG may

be offered if maintenance was not given, as 50% will respond. A total of 66% of BCG non-responders and 10–20% of initial responders will eventually progress to muscle-invasive TCC. Hence, if no response is seen or relapse diagnosed despite BCG maintenance or a second course, proceed without delay to *radical cystectomy*; the cure rate is 90%.

Though less expensive and more effective, BCG is more toxic than intravesical chemotherapy, causing cystitis symptoms in >90% patients and low-grade fever with myalgia in 25%. Up to 6% of patients develop a high persistent fever, requiring antituberculous therapy for 6 months with isoniazid and pyridoxine or standard triple therapy (rifampicin, isoniazid, and ethambutol) in critically ill patients. Death due to BCG sepsis, granulomatous prostatitis, and epididymo-orchitis are rare complications.

Contraindications to intravesical BCG include:

- Immunosuppressed patients.
- Pregnant or lactating women.
- Patients with haematological malignancy.
- Following traumatic catheterization.

The appearances at cystoscopy performed too soon after BCG can appear alarming due to a generalized inflammatory response. Cystoscopy and biopsy 3 months after BCG may still reveal chronic granulomatous inflammation.

1 Sylvester RJ, Oosterlinck W, van der Meijden AP (2004) A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage TaT1 bladder cancer: a meta-analysis. *J Urol* **171**:2186–90.

2 Sylvester RJ, van der Meijden AP, Lamm DL (2002) Intravesical BCG reduces the risk of progression in patients with superficial baldder cancer: a combined analysis of results of published clinical trials. *J Urol* **168**:1964–70.

Bladder cancer (muscle-invasive): staging and surgical management of localized (pT2/3a) disease

This is a dangerous disease; the untreated 5y survival is just 3%. Management of patients with invasive bladder cancer requires a *multidisciplinary team* approach, involving case-by-case discussion between the urological surgeon, radiotherapist, and medical oncologist, with support from the pathologist, radiologist, and cancer specialist nurse.

Staging investigations

- **Pelvic CT or MRI**: may demonstrate extravesical tumour extension, upper tract obstruction, or iliac lymphadenopathy reported if >8mm in maximal diameter. T stage correlation with pathological findings at cystectomy is 65–80%. Both modalities will miss microscopic nodal disease in 70% of cases.
- **Chest CT or plain X-ray**.
- **Isotope bone scan** (positive in 5–15% of patients with muscle-invasive TCC): is obtained in cases being considered for radical treatment.
- **Ultrasound scanning**: is used for detection of liver metastases if the *serum liver function* is abnormal; albumin indicates the nutritional status of the patients; alkaline phosphatase is not a reliable marker for bone disease in bladder cancer patients.

In the absence of prospective randomized trials comparing the surgical and non-surgical treatments, the options for a patient with newly diagnosed confined muscle-invasive bladder cancer are:

- Bladder preserving.
  - Radical TURBT plus systemic chemotherapy: little data, not mainstream.
  - Palliative TURBT ± palliative radiotherapy (RT): for elderly/unfit patients.
  - Partial cystectomy ± neoadjuvant systemic chemotherapy.
  - TURBT plus definitive RT (see 📖 p. 286): poor options for squamous and adenocarcinoma as they are seldom radiosensitive.
- Radical cystectomy with:
  - Ileal conduit urinary diversion.
  - Ureterosigmoidostomy urinary diversion.
  - Continent urinary diversion.
  - ± Neoadjuvant chemotherapy: some evidence of benefit (see 📖 p. 286).
  - ± Neoadjuvant RT: no evidence of benefit (see 📖 p. 288).

Partial cystectomy is a good option for well selected patients with small solitary disease located near the dome and for urachal carcinoma. Morbidity is less than with radical cystectomy and diversion is not required. The surgical specimen should be covered with perivesical fat, with a 1.5cm margin of macroscopically normal bladder around the tumour. There should be no biopsy evidence of CIS elsewhere in the bladder.

The bladder must be closed without tension and catheterized for 7–10 days to allow healing. Subsequent review cystoscopies are mandatory to ensure no tumour recurrence.

Radical cystectomy with urinary diversion

This is the most effective primary treatment for muscle-invasive TCC, SCC, and adenocarcinoma and can be performed as salvage treatment if RT has failed. It is also a treatment for G3T1 TCC and CIS, refractory to BCG. Any ureteric obstruction caused by the primary tumour will be relieved by the concomitant urinary diversion. However, this is a major undertaking for the patient and surgeon, requiring support from the cancer specialist nurse, stomatherapist, or continence advisor. Preoperative bowel preparation is discouraged by 'enhanced recovery' specialists since it is considered to cause unnecessary dehydration without any evidence of benefit.

The procedure: through a midline transperitoneal or extraperitoneal approach, a bilateral pelvic lymphadenectomy is undertaken. The extent of lymphadenectomy ranges from limiting dissection to the obturator fossa to extending the dissection up to the aortic bifurcation. Studies have suggested a survival advantage to the extended approach, provided the primary cancer is stage T2 or less. The findings of frozen section histology may influence the decision to proceed in some cases. The entire bladder is then excised along with perivesical fat, vascular pedicles, and urachus, plus the prostate/seminal vesicles or anterior vaginal wall. The anterior urethra is not excised unless there is prior biopsy evidence of tumour at the female bladder neck or prostatic urethra (when recurrence occurs in 37%). The ureters are divided close to the bladder, ensuring their disease-free status by frozen section histology, if necessary, and anastomosed into the chosen urinary diversion (see 📖 p. 290).

Some centres are pioneering *laparoscopic and robot-assisted cystectomy*. Advantages include less blood loss, less post-operative analgesia requirement, and reduced hospital stay. However, long operating times, high cost, and technical considerations may limit widespread adoption of this approach. Oncological outcomes are still under evaluation.

Major complications affect 25% of cystectomy patients. These include perioperative death (1.2%), reoperation (10%), bleeding, thromboembolism, sepsis, wound infection/dehiscence (10%), intestinal obstruction or prolonged ileus (10%), cardiopulmonary morbidity, and rectal injury (4%). Erectile dysfunction is likely after cystectomy due to cavernosal nerve injury.

The complications of urinary diversion are discussed on 📖 p. 290.

Post-operative care

- Many patients will spend the first 24h in the high dependency unit or ITU.
- Daily clinical evaluations, including inspection of the wound (and stoma, if present), fluid balance, urine and drain outputs, blood count, creatinine/electrolytes, and albumin.
- Broad-spectrum antimicrobial prophylaxis.

- Venous thromboembolism prophylaxis with TED stockings, pneumatic calf compression, and subcutaneous LMWH (unfractionated heparin for patients with renal impairment); NICE (2010) recommends continuing heparin for 28 post-operative days.
- Early mobilization within 24h, if possible.
- Chest physiotherapy and adequate analgesia is especially important in smokers and patients with chest comorbidity.
- Oral intake is commenced early, an integral part of the Enhanced Recovery concept; however, patients may require parenteral nutrition in the presence of GI complications or prolonged ileus.
- Drains are usually sited in the pelvis and near the ureterodiversion anastamosis; ureteric catheters pass from the renal pelves through the diversion and exit percutaneously; a catheter drains the diversion (except in the case of ileal conduit), exiting urethrally or suprapubically.
- Most patients stay in hospital for 10–14 days.

Salvage radical cystectomy is technically a more difficult and slightly more morbid procedure. Relatively few patients who have failed primary RT are suitable for this second chance of a cure; these are fit patients with mobile clinically localized disease.

Efficacy of radical cystectomy

Failure to cure may result from inadequate excision of the primary tumour or presence of metastases (Table 7.11). Treatment delay should be avoided if possible; cystectomy performed within 3 months of diagnosis (T2 TCC) results in significantly improved survival compared with >3 months.[1] Pathological upstaging of the primary can occur in up to 40% of cases. Lymph node metastases occur in 10% of T1 and up to 33% of T3–4 cancers. The use of neoadjuvant chemotherapy in muscle-invasive disease is discussed on 📖 p. 288.

Table 7.11 5y survival rates for cystectomy alone

Stage T1/CIS	90%+
Stages T2,T3a	55–63%
Stage T3b	31–40%
Stage T4a (into prostate)	10–25%
Stage TxN1–2	30%
Salvage T0	70%
Salvage T1	50%
Salvage T2, 3a	25%

1 Lee CT, Madii R, Daignault S, *et al.* (2006) Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. *J Urol* **175**:1262–7.

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Bladder cancer (muscle-invasive): radical radiotherapy and palliative treatment

Management of patients with invasive bladder cancer requires a *multidisciplinary team* approach, involving case-by-case discussion between the urological surgeon, radiotherapist, and medical oncologist, supported by the pathologist, radiologist, and cancer nurse specialist.

Radical external beam RT is a good option for pT2–4 TCC in patients who are unfit or unwilling to undergo cystectomy, but who still wish to have the chance of cure. Typically, a total dose of 66 Gray is administered in 30 fractions over 6 weeks. The target field comprises the bladder only, with a 1.5cm safety margin to allow for movement.

The 5y survival rates at 40–60%, are inferior to those of cystectomy, but the bladder is preserved and the complications are less significant (Table 7.12). Higher-grade tumours tend to do less well, perhaps because of the undetected presence of disease outside the field of irradiation. Beyond this, prediction of RT response remains difficult, relying on follow-up cystoscopy, and biopsy. Local recurrence occurs in approximately 30% of patients. There may be a small benefit in the use of *neoadjuvant or adjuvant cisplatin-based combination chemotherapy* with RT in locally advanced (pT3b/4) disease (see 🕮 p. 288).

Interstitial brachytherapy using caesium or iridium sources can be used to treat small T2 TCC in combination with RT and bladder-preserving surgery. Use of this technique is not widespread.

CIS, SCC, and adenocarcinoma are poorly sensitive to RT. There is no advantage in giving precystectomy RT for invasive TCC.

Complications occur in 70% of patients, self-limiting in 95% of cases. These include radiation cystitis (filling LUTS and dysuria) and proctitis (diarrhoea and rectal bleeding), usually lasting only a few months. Refractory radiation cystitis and haematuria may rarely require desperate measures such as intravesical alum, formalin, hyperbaric oxygen, iliac artery embolization, or even palliative cystectomy.

Table 7.12 Efficacy of RT: 5y survival

Stage T1	70% (with adjuvant chemotherapy)
Stages T2	40%
Stage T3a	35%
Stage T3b,T4	10–20%
Stage TxN1–2	7%

If disease persists or recurs, salvage cystectomy may still be successful in appropriately selected patients, 5y survival rates 30–50% (see 📖 p. 284). Otherwise, cytotoxic chemotherapy (see 📖 p. 289) and palliative measures may be considered.

Palliative treatment

RT (30 Gray) is effective for *metastatic bone pain* or to palliate symptomatic (bleeding) local tumour (40–50 Gray).

Intractable haematuria may be controlled by intravesical formalin or aAlum, hyperbaric oxygen, bilateral internal iliac artery embolization or ligation, or palliative cystectomy/diversion.

Ureteric obstruction may be relieved by percutaneous nephrostomy and antegrade stenting (see 📖 pp. 363 and 546).

Involvement of the palliative care team can be very helpful to the patient and family.

Bladder cancer: management of locally advanced and metastatic disease

Management of patients with invasive bladder cancer requires a *multidisciplinary team* approach, involving case-by-case discussion between the urological surgeon, radiotherapist and medical oncologist, with support from the pathologist, radiologist, and cancer specialist nurse.

Locally advanced bladder cancer (pT3b/4)

Many patients treated with primary cystectomy or RT with curative intent succumb to metastatic disease due to incomplete tumour excision or micrometastases. Up to 50% of patients develop metastases, mostly at distant sites. At this stage, the 5y survival is only 25%. There is interest in augmenting primary treatment in an effort to improve outcomes.

Neoadjuvant and adjuvant RT

Randomized studies have suggested improvements in local control (pathological downstaging) using RT (45–50 Gray in 25 fractions) 4–6 weeks prior to cystectomy, but no survival benefit has been demonstrated. The rationale for post-cystectomy RT is that patients with proven residual or nodal disease may benefit from locoregional treatment. However, it leads to unacceptably high morbidity and has no demonstrable advantages. Post-treatment bowel obstruction occurs 4.5 times more commonly in RT patients.

Adjuvant cystectomy

Two studies have demonstrated an improvement in local control and a survival advantage when treating locally advanced disease with cystectomy after RT compared to RT alone. However, this treatment strategy does not happen in current UK practice, probably due to the increased morbidity of surgery in this setting.

Neoadjuvant chemotherapy with cystectomy

Preoperative chemotherapy is increasingly given to operable patients with non-metastatic T2–T4a disease. It may downstage the disease and treat micrometastases before the patient is debilitated by surgery. A meta-analysis of 10 trials[1] has suggested a 5–7% 5y survival advantage with the use of cisplatin-based combination chemotherapy prior to cystectomy compared with cystectomy alone. The absolute gain was the same regardless of stage; from 55 to 60% for T2, 40–45% for T3, and 25–30% for T4 patients. The relative gain was, therefore, greater for higher stage patients. One randomized trial demonstrated a median survival of advantage of 31 months in the group treated with neoadjuvant combination chemotherapy compared to the group receiving cystectomy alone.[2] Eligible patients must have a good performance status (<2—ambulatory and able to carry out light work) and renal function (GFR >60mL/min). *This treatment should be discussed with suitable patients suspected of having locally advanced or micrometastatic disease prior to cystectomy.*

Adjuvant chemotherapy

The rationale for post-cystectomy chemotherapy is that patients with proven residual or nodal disease may benefit from systemic treatment. Trials have been hampered by protocol problems, small numbers,

surgical complications interfering with treatment, and difficulty in assessing response in the absence of measurable disease. However, two of four studies have shown a survival benefit of almost 2y in the treated groups, using cisplatin-based regimes.

Neoadjuvant or adjuvant chemotherapy with RT

While controversial, neoadjuvant cisplatin-based combination chemotherapy with bladder preservation has been demonstrated to produce 5y survival rates of 42–72% when RT was used as definitive treatment. *This may be offered to patients suspected of having locally advanced disease after clinical examination and staging imaging.*

Metastatic bladder cancer

Five percent of patients have metastatic disease at the time of diagnosis.

Systemic chemotherapy

TCC is a chemosensitive cancer; it is recommended for patients with unresectable, diffusely metastatic measurable disease. Combination is more effective than single-agent treatment. A complete response is seen in 15% of patients given methotrexate, vinblastine, adriamycin, and cisplatin (MVAC), though 20% of patients develop neutropenia and 3% die of sepsis. Median survival is 14 months. Most UK centres are using gemcitobine, an antimetabolite agent, alone or in combination with cisplatin. Complete responses are reported in 25–40% of patients and it is better tolerated than MVAC, with 1% toxic death rate. Carboplatin may be used if cisplatin is contraindicated (i.e. performance status ≥2 of GFR <60mL/min). Taxanes (paclitaxel and docetaxel) are microtubule disassembly inhibitors; responses range from 25 to 80%, using these agents alone or in combination.

Prognostic factors predicting response to chemotherapy include alkaline phosphatase, age >60y, performance status, and visceral metastases. Depending on the number of factors, median survival varies from 9 to 30 months.[3] In future, molecular markers such as tumour p53 status may be shown to predict chemosensitivity. Unfortunately, no biomarker is currently available to predict outcome, drive treatment decisions, or monitor response to treatment.

Radiotherapy

Roles for RT include palliation of metastatic pain, haematuria, and spinal cord compression.

Surgery

There is no surgical role in treatment of extravesical metastatic disease. Palliative cystectomy or urinary diversion is justified for severe local symptoms.

1 Advanced bladder cancer meta-analysis collaboration (2003) Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* **361**:1927–34.

2 Grossman HB, Natale RB, Tangen CM, *et al.* (2003) Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* **349**:859–66.

3 Bajorin DF, Dodd PM, Mazumbar M, *et al.* (1999) Long-term survival in metastatic transitional cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol* **17**:3173–81.

Bladder cancer: urinary diversion after cystectomy

The choice of urinary diversion requires consideration of both *clinical and quality of life (QoL) issues*. Patients planned for cystectomy should be informed of the possible options. Contraindications to the continent reconstructive procedures include debilitating neurological and psychiatric illness, short life expectancy, and impaired renal or liver function. These patients must be motivated and able to perform ISC. Contraindications to orthotopic neobladder include tumour in the prostatic urethra, widespread CIS, and urethral stricture disease.

The majority of patients report good overall QoL following urinary diversion. The reconstructive procedures were expected to be better for social functioning compared to the ileal conduit; most QoL studies have not shown significant differences, although patients with continent diversions generally score more favourably in terms of body image, social activity, and physical function.

Ureterosigmoidostomy

Dating back to 1821, the oldest form of urinary diversion, whereby the ureters drain into the sigmoid colon, either in its native form or following detubularization and reconstruction into a pouch (Mainz II). This diversion requires no appliance (stoma bag, catheter) so remains popular in developing countries. In recreating a 'cloaca', the patient may be prone to upper UTI with the risk of long-term renal deterioration, metabolic hyperchloraemic acidosis, and loose frequent stools. The low-pressure and capacious Mainz II pouch reduces, but does not abolish, these complications.

Ileal conduit

This was developed during the 1940's by Eugene Bricker of St. Louis; it remains the most popular form of urinary diversion in the UK. Fifteen cm of subterminal ileum is isolated on its mesentery and the ureters are anastomosed to the proximal end. The distal end is brought out in the right iliac fossa as a stoma. The native ileum is anastomosed to gain enteral continuity.

Complications of ileal conduit are:

- Prolonged ileus.
- Urinary leak.
- Enteral leak.
- Pyelonephriris.
- Uretero-ileal stricture.
- Stoma problems (20%—skin irritation, stenosis, and parastomal hernia).
- Upper tract dilatation (30%).

Patients require stomatherapy support and some find difficulty in adjusting their lifestyle to cope with a stoma bag. Metabolic complications are uncommon.

In post-RT salvage patients, a jejunal or colonic conduit is used because of concerns about the healing of radiation-damaged ileum. The conduit

may be brought out in the upper abdomen and patients require careful electrolyte monitoring due to sodium loss and hyperkalaemia.

Continent diversion

The advantage is the absence of an external collection device. There are two types of continent diversion.

- A *continent pouch* is fashioned from 60cm of detubularized ileum or right hemicolon. The ureters drain into this low-pressure balloon-shaped reservoir, usually through an antireflux submucosal tunnel. This is drained by the patient via a continent *catheterizable stoma*, such as the appendix or uterine tube (the *Mitrofanoff* principle) brought out in the right iliac fossa.
- A similarly constructed pouch may be anastomosed to the patient's urethra to act as an *orthotopic neobladder* so that natural voiding can be established and no stoma is necessary. Patients void by relaxing their external sphincter and performing a Valsalva. This neobladder should require no catheter, unless the pouch is too large and fails to empty adequately. In this case, the patient must be prepared to perform ISC.

Popular ileal pouches include those of Studer (see Fig. 7.4), Camey II, and Kock. Ileocaecal pouches include the Indiana and Mainz I. Which one is chosen often comes down to the surgeon's preference; they carry similar complication risks. Previously irradiated bowel can safely be used to form pouches though complications are more likely.

Complications relating to pouches and neobladders are divided into early (12%) and late (37%). They include:

- Urinary leakage and peritonitis.
- Pelvic abscess.
- Stone formation.
- Catheterizing difficulties and stomal stenosis.
- Urinary incontinence and nocturnal enuresis (particularly with neobladders).
- Pouch ureteric reflux and UTI.
- Ureteropouch anastomotic stricture.
- Late neobladder rupture.

Metabolic abnormalities include early fluid and electrolyte imbalances; later, urinary electrolyte absorption may cause hyperchloraemic acidosis and loss of small bowel may result in vitamin B12 deficiency. Metabolic acidosis is less likely in patients with normal renal function; treatment is with sodium bicarbonate and potassium citrate. Annual B12 monitoring should be undertaken with supplementation if necessary.

Adenocarcinoma may develop (5%) in intestinal conduit, neobladder, or sigmoid colon mucosa in the long term due to the carcinogenic bacterial metabolism of urinary nitrosamines. This tends to occur near to the inflow of urine. It is, therefore, advisable to perform annual visual surveillance of urinary diversions after 10y. If the urethra is *in situ*, annual urethroscopy and cytology is important.

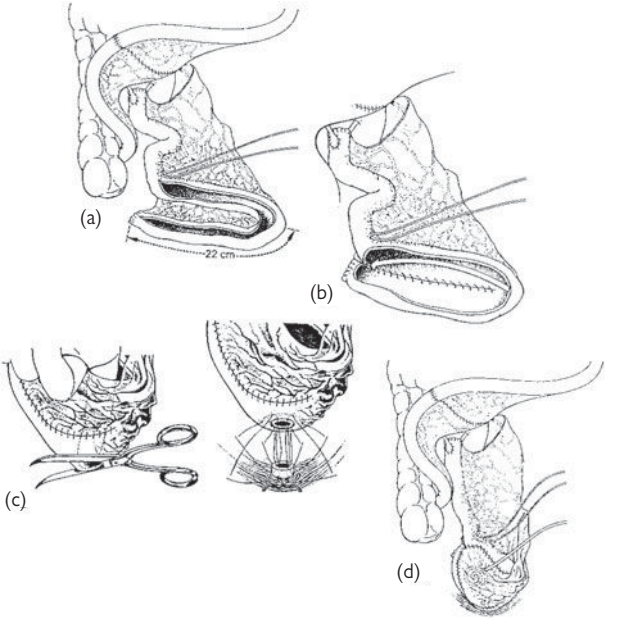

Fig. 7.4 (a) The distal 40–44 cm of resected ileum opened along the antimesenteric border with scissors. Spatulated ureters are anastomosed end to side with 4-0 running suture on either side of proximal end of afferent tubular ileal limb. Ureters are stented. (b) The two medial borders of the U-shaped, opened distal ileal segment are oversewn with a single layer seromuscular continous suture. The bottom of the U is folded between the two ends of the U. (c) Before complete closure of the reservoir, a 8–10 mm hole is cut into the most caudal part of the reservoir (left). Six sutures are placed between the seromuscular layer of the anastomotic area of the reservoir and the membraneous urethra (right). An 18F urethral catheter is inserted. (d) Before complete closure of the pouch, a cystostomy tube is inserted and brought out suprapubically adjacent to the wound. (Reproduced with permission from Studer et al. 1996).[1]

1 Studer UE, Danuser H, Hochreiter W, *et al.* (1996) Summary of 10 years experience with an ileal low-pressure substitute combined with an afferent tubular isoperistaltic segment. *World J Urol* **14**:29–39.

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Prostate cancer: epidemiology and aetiology

Hormonal and growth factors and diet

Growth of prostate cancer (PC), like benign prostatic epithelium, is largely under the promotional influence of *testosterone* and its potent metabolite, DHT. Androgen ablation by orchidectomy results in programmed epithelial cell death (apoptosis) and involution of the prostate. PC is not seen in eunuchs or people with congenital deficiency of 5α-reductase. Response to castration therapy in the treatment of patients with PC may be suboptimal if the serum testosterone is not fully suppressed (<50nmol/L).

Oestrogens, including phyto-oestrogen isoflavones (genistein, daidzein) found in foodstuffs used in Asian and Oriental cuisine, have a similar negative growth effect on PC. This may explain why these races rarely develop (or die of) PC. Other possible *dietary inhibitors* of PC growth include vitamin D, the antioxidants lycopene (present in cooked or processed tomatoes) and polyphenols (pomegranate, blueberry, green tea, red wine), isothiocyanates in cruciferous vegetables (sprouts, broccoli), and omega-3 unsaturated fatty acids present, for example, in mackerel and other oily fish. Conversely, arachidonic and linolenic acids and omega-6 polyunsaturated fatty acids (present in high-fat red meat) promote PC cell growth *in vivo* and increases risk of advanced PC in prospective cohort studies. Obesity does not confer increased risk of PC diagnosis, but appears to be associated with more aggressive disease.

Vegan and dairy-free diets are associated with lower circulating IGF-1; this is of interest because high serum IGF-1 levels have been associated with increased risk of developing PC. A pan-European study involving 142 000 men followed up for 8y showed high intake of dairy protein/calcium increased risk of PC (see also 📖 p. 298).

Other risk factors

Age is an important risk factor for development of histological PC, the disease being rare below 40 and becoming increasingly common with rising age, according to post-mortem studies. Prevalence of PC rises from 29% in the fiftfh decade to 67% in the ninth decade. This is paralleled 20y earlier by the presence of prostatic intraepithelial neoplasia (PIN), the accepted premalignant lesion. However, most prostate cancer does not become clinically recognized or life-threatening. Seventy-five percent of prostate cancers are diagnosed in men >65y, the peak incidence is 70–74y. The incidence amongst men aged 50–59 has trebled since the 1970's.

Geographic variation, the disease is more common in western nations, particularly Scandinavian countries (where low sunlight and vitamin D synthesis may be implicated) and North America. The disease is rare in Asia and the Far East, but US migrants from Asia and Japan have a 20-fold increased risk. This suggests an environmental aetiology, such as the western diet, may be important.

Ethnicity: black men are at greatest risk, then Caucasians; Asians and Oriental races develop PC uncommonly unless they migrate to the West.

The world's highest incidence is among African Americans and Jamaican; there are scant data available regarding native African men. A recent British study suggests that African Europeans are at 3 times risk of developing PC compared to white men, although the risk of PC death is similar.

Family history: 5% of PC are believed to be inherited. Hereditary PC tends to occur in younger (<60y) men who have a family history; genetic abnormalities on chromosomes 1q (HPC1 locus), 8p (MSR-1 locus), Xp and Y; mutations of the BRCA2 gene on 13q are also reported. The risk of a man developing PC is doubled if there is one affected first-degree relative and is 4-fold if there are two. Men without sons are at greater risk than those that have fathered sons. Recently there has been an interest in a rare recurrent mutation in HOXB13, a homeobox transcription factor gene that is important in prostate development, located on chromosome 17q.

Exercise appears to confer protection against PC. It is known to reduce serum IGF-1, insulin, leptin, and testosterone while stimulating antioxidant protection pathways and immune function, thereby reducing harmful reactive oxygen species. Serum from exercised men on low-fat diet slows growth of LNCaP cells *in vitro*. Several case control studies have significantly associated exercise with reduced PC risk: in the largest of these, 47 000 men >65y were followed for 14y; 3h/week of vigourous exercise was associated with reduced risk of high-grade, metastatic, and fatal PC. In another study of 190 subjects undergoing biopsy, men taking the equivalent of 1h of strenuous exercise per week were less likely to be diagnosed with PC, adjusting for PSA and other variables, and >1h of mild/moderate exercise reduced risk of high-grade diagnosis.

Some controversy surrounds the possible increased risk of developing PC conferred by *sexual activity*, infectious agents, and vasectomy. The balance of data and opinion go against these putative risk factors at present. Exposure to cadmium has been suggested to raise the risk of PC, but no new data have been forthcoming since the 1960's. High *alcohol* intake appears to be associated with increased risk while smoking does not. However, *smoking* appears to increase the risk of fatal PC.

Prostate cancer: incidence, prevalence, mortality, and survival

Incidence

The diagnosis of PC is on the increase, probably as a result of increasing use of serum PSA testing for both symptomatic and asymptomatic men, and the use of more extensive prostatic biopsy protocols. PC is the most commonly diagnosed male cancer (excluding skin) in the UK and USA. In 1999, 24 714 men were diagnosed with PC in the UK, mean age 72y; by 2008, this had increased to 37 051. The lifetime risk of a man being diagnosed with PC is estimated to be 1 in 9. Risk factors and aetiology are discussed on 📖 p. 294.

Prevalence

While the incidence of PC continues to rise (now approximately 8% of all men), the true prevalence of the disease is highlighted by post-mortem studies carried out on men who died of unrelated causes. These have demonstrated histological evidence of PC in 10% of men in their third decade, 34% in the fifth decade, and rising to 67% in the ninth decade. It is feared that much of this 'latent' or clinically insignificant PC could be detected by PSA screening and treated unnecessarily at the older end of the age spectrum. As the incidence of PC is high and 5y survival rates are around 70–80%, an estimated 215 000 men are alive in the UK who are diagnosed with PC.

Mortality

It is estimated that 3% of men die of PC. In 2008, 10 168 deaths were attributed to prostate cancer in the UK, the second most common (13% of all) form of male cancer death. This compares with 8524 deaths due to colorectal cancer and 20 384 due to lung cancer. Because most deaths occur in men over 75y, however, the number of years of life lost per PC death is very low compared to less common cancers. Worldwide, PC claimed 258 000 lives in 2008, the areas with greatest mortality were southern Africa and northern Europe.

Mortality increased slowly in the UK and USA during the 1970's and 80s, peaking in 1990 at 3% per year. However, in 1991, mortality started to decrease in the USA by 2% per year. In the UK too, there was a small reduction in mortality which stabilized at the turn of the century. This could have been due to changes in the way death certificates were written or treatment, perhaps earlier use of hormone therapy for advanced disease, or increased treatment of localized disease carried out in the 1990's.

Survival

Survival rates for PC have been improving for the past 30y. The detection of a greater proportion of latent, earlier, slow-growing tumours has had a beneficial effect on survival rates. The relative 5y survival rate for men diagnosed in England in 2001–2006 was 77% compared with only 31% for men diagnosed in 1971–75. The relative 10y survival rate for men

diagnosed in England in 2001–2006 was 60% compared with only 21% for men diagnosed in 1971–75 (Source: Cancer Research UK website: http://info.cancerresearchuk.org/cancerstats/types/prostate/). Indeed, it has been suggested that PC patients have an overall improved life expectancy due to more intensive overall health care received.

Prostate cancer: prevention

The fact that as many as 32% of men in their fifth decade have histological PC, even though the disease is rarely detected clinically below the age of 50y, suggests the opportunity for preventative strategies.

Dietary and lifestyle intervention

There are growing epidemiological and laboratory data supporting dietary and lifestyle interventions, though randomized prospective trials are few and mostly small.

High fat consumption results in increased production of insulin and IGFs. Diets rich in saturated fat such as arachidonic, linolenic, and omega-6 fatty acids promotes PC cell growth *in vivo* and increases the risk of advanced PC in prospective cohort studies. Obese men generally have lower PSA, but higher risk for high-grade or extracapsular disease at presentation, recurrence post-treatment, metastasis, and death.

Soy products contain phyto-oestrogens, including the isoflavone, genistein. Genistein is a natural inhibitor of tyrosine kinase receptors and inhibits PC cell lines. Chinese Americans have a 24-fold risk of developing PC compared to native Chinese, perhaps due to a difference in their respective diets.

Lycopene, present in cooked tomatoes and tomato products, is considered to reduce risk of PC progression and inhibits cell lines.

Selenium supplementation (0.2mg/day = 2 brazil nuts) was shown to reduce the risk of developing PC in a melanoma prevention trial. Selenium is a trace element required as an antioxidant. It is found in relatively low concentration in European soil and can be assayed using toenail clippings. ***Vitamin E*** supplementation was shown to reduce the incidence of PC in Finnish smokers. It is an antioxidant. However, a large prospective randomized North American trial (SELECT) recently showed no risk reduction using either of these agents alone or in combination.

Vitamins A (retinoids) and D both inhibit growth of PC cell lines and vitamin D receptor polymorphisms appear to predispose to certain individuals to PC.

Pomegranite juice appears to reduce PSA doubling time during relapse following radical prostatectomy for high-risk disease.

Green tea contains polyphenol catechin and antioxidant compounds. A cohort study of >65 000 unscreened Japanese men followed up for 14y observed that the risk of developing PC was reduced proportional to the volume of green tea consumed; a randomized trial of men with PIN suggested less subsequent cancer diagnosed in men randomized to 600mg green tea catechin daily.

A large pan-European (EPIC) study of diet demonstrated consumers of ***vegetables*** (including vegetarians) did not exhibit a reduced incidence of PC; conversely, consumers of meat did not exhibit greater risk of PC diagnosis. The same study did show that consumption of one portion of cruciferous vegetables per week (e.g. ***broccoli***) reduces the incidence of PC by 40%. Other beneficial dietary ingredients include ***turmeric*** and ***black pepper***.

Studies from UK, Europe, and USA have shown that 25–40% of PC patients are taking some form of complementary therapy, most without informing their doctor. These can occasionally be harmful: for example, a 'Chinese herb' mixture called PC-SPES, now withdrawn, frequently caused thromboembolism.

Smoking has been shown in population studies to be associated not with diagnosis, but with fatal PC. No definite link exists between ***vasectomy*** or ***sexual activity*** and PC. Studies have suggested an increased risk associated with ***early sexual activity*** and a reduced risk associated with frequent ***masturbation***, but these require substantiation. Similarly, a protective effect of ***regular physical exercise*** on PC has been suggested by laboratory and prospective cohort studies.

Chemoprevention

Antiandrogens

Given that most PC is initially an androgen-dependent disease, interest in its prevention has focussed on antiandrogens. While non-steroidal antiandrogens would have unacceptable side effects, the 5α-reductase inhibitors (5ARI) could be feasible chemoprevention agents. The Prostate Cancer Prevention Trial recruited 18 000 men who had no clinical or biochemical evidence of PC and PSA <3ng/mL.[1] They were randomized to placebo or finasteride 5mg daily for up to 7y. The men were offered biopsy if they developed a rising PSA, an abnormality on DRE, or at the end of study. PC was detected in 24% and 18% of participants in placebo and finasteride arms, respectively, suggesting that finasteride reduces the risk of developing PC by 25%. However, Gleason 7+ cancers were significantly more frequent in the finasteride arm. While this could be due to the effect of the 5ARI on tissue architecture or a selection artefact due to gland shrinkage, there is as yet no licence for prescribing 5ARI for PC prevention. The REDUCE study to assess the chemopreventative effects of dutasteride has yielded similar results in a population of men with PSA 3–10ng/mL and a history of previous negative biopsy.[2] Table 7.13 compares these two studies. Careful interpretation of these data suggest 5ARI do not reduce the risk of clinically significant PC developing.

Statins

Statins are HMG-CoA reductase inhibitors, a commonly prescribed class of medications that reduce cholesterol levels and prevent cardiovascular events. Statins can induce apoptosis and growth arrest in PC cell lines by suppressing IGF-1 receptor expression; they also reduce inflammation in PC tissue. In a population-based cohort of men aged 40–79y followed for 17y, 38 of 634 statin users (6%) were diagnosed with PC, compared with 186 (10%) of 1813 non-statin users. In other studies, statin use significantly reduced risk of elevated PSA, needle biopsy and high-grade PC, and correlated to duration of statin use. In a cohort study of 7042 treated PC patients followed up for 4y, any statin or NSAID use reduced the risk of all-cause mortality.

Table 7.13 A comparison of PCPT and REDUCE studies

	PCPT (2003): finasteride vs placebo	REDUCE (2010): dutasteride vs placebo
Number; age recruited	18 882; >55y	8231; 50–75y
Patient characteristics	Normal DRE; PSA <3ng/mL	PSA 2.5/3.0–10ng/mL; 6 month, 1 previous negative biopsy
Duration of study/time of protocol-driven biopsy	7y/7y	4y/2y and 4y
Number of cancers (%)	803 (18) vs 1147 (24); p<0.001	659 (20) vs 858 (25); p<0.001
Gleason 7–10 cancer (% of all cancers detected) at biopsy	280 (37) vs 237 (22); p<0.001	220 (33) vs 233 (27); p=0.81
Gleason 7–10 cancer, % detected at subsequent RP (correctly predicted at biopsy)	31 (70) vs 19 (50)	N/A

1 Thompson IM, Goodman PJ, Tangen CM, *et al.* (2003) The influence of finasteride on the development of prostate cancer. *N Engl J Med* **349**:215–24.

2 Andriole GL, Bostwick DG, Brawley OW, *et al.* (2010) Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* **362**:1192–202.

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Prostate cancer: pathology of adenocarcinoma

PC was first described by Venetian anatomist, Nicolo Massa, in 1536, at a similar time to the first anatomical drawings of the prostate by Vesalius in Padua. In 1786, John Hunter demonstrated that castrating young male animals prevented the growth of the prostate. In 1817, the first good description of a PC was made in London by George Langstaff in a paper on cases of *Fungus Haematodes*; 1853 saw the first histological description of PC by J Adams. In those times, PC was considered a rare disease due to the shorter life expectancy of the population and poor detection methods.

By far, the most common (>95%) prostatic malignancy is *adenocarcinoma*, carcinoma of the acinar or ductal epithelium. The basal cell layer is absent and the basement membrane is breached by the malignant cells which invade into the prostatic fibromuscular stroma. Macroscopically, they tend to be hard and white, though a soft mucin-producing variety exists. The prostatic urethra, ducts, or stroma may be invaded by *transitional cell carcinoma* of the bladder (see 📖 p. 266 on Bladder cancer pathology and 📖 p. 364 on Urethral cancer). Prostatic *sarcomas,* most common of which is the rhabdomyosarcoma, are rare and mostly seen in childhood. *Secondary deposits* (metastases) from other sites are rare.

Adenocarcinoma of the prostate

Most (75%) adenocarcinomas are located in the peripheral zone and most (85%) are multifocal. The mean number of cancers in a radical prostatectomy specimen is 7. Twenty percent arise more anteriorly in the transition zones and 5% in the embryologically distinct central zone. The tumour spreads locally through the flimsy prostatic capsule (this is absent at the apex and base of the gland) into surrounding tissue, at which time it is termed *'locally advanced'*. The disease may involve the urethral sphincter, corpora of the penis, seminal vesicles, or trigone of the bladder, including the distal ureters, but rarely invades through Denonvilliers fascia to involve the rectum. Local spread is often along the course of autonomic nerves, so-called perineural invasion. The most frequent sites of *metastasis* are bone and lymph nodes of the obturator fossae, internal, external and common iliac arteries, and presacral regions. Soft tissue metastases in lung, liver, testis, and brain are less common. Bone metastases are characteristically sclerotic, rarely lytic. The axial skeleton (spine, ribs, and pelvis) are most commonly affected, followed by the proximal long bones, clavicles, and skull.

PC is a complex disease, exhibiting *genetic* as well as morphological heterogeneity, increasing with stage and grade. Epigenetic changes such as inactivating hypermethylation of the detoxifying enzyme, GSTP1 gene, are observed in 90% of PC and 70% of PIN lesions, suggesting this may be an early event in carcinogenesis. Up to 50% of PC carry a rearrangement of chromosome 21, whereby a translocation results in the fusion of an androgen-dependent protease, *TMPRSS2* and the *ERG* transcription factor (which then itself becomes androgen-dependent). It is postulated that this 'gene fusion' rearrangement could be an early step in

prostate tumourigenesis. Frequent changes include somatic loss of alleles on chromosomes 16 and 18, inactivation of tumour suppressor genes, pTEN (chromosome 10q) and MSR-1 (chromosome 8p), p53 (chromosome 17p) and activation of c-myc and bcl-2 protooncogenes. Evidence is also gathering on the potential tumourigenic role of a subset of prostatic basal epithelial cells that are thought to be immortal, undifferentiated stem cells.

Prostate cancer: grading

Adenocarcinoma of the prostate is graded by the Gleason system (Fig. 7.5), developed in 1966 by Minneapolis pathologist, Dr Donald Gleason. Using low power microscopy, adenocarcinoma is graded 1 to 5 according to its gland-forming differentiation. Since most PCs are multifocal and heterogeneous, allowance is made by adding the two dominant grades to give a score between 2 and 10. If only one pattern is observed, that grade is doubled to give the score. This system is used to grade needle biopsies, TURP, and radical prostatectomy specimens.

Gleason scores 2–6 are considered well differentiated, 7 is moderately differentiated, and 8–10 are poorly differentiated. In practice, 75% of PC is graded 5, 6, or 7; less than 5% are graded 2–4; and 20% are graded 8–10. Gleason 8–10 PC is usually referred to as *high-grade*, though sometimes even 7 is considered high-grade because of the presence of pattern 4. Among expert pathologists, there is good interobserver reproducibility with Gleason scoring. However, scores assigned to needle biopsies are rarely less than 3 + 3 = 6, since grades 1 and 2 are rarely if ever observed. In 30–40% of cases, needle biopsy scores are lower than those assigned to the subsequent radical prostatectomy specimen while overgrading by needle biopsy is uncommon (5%). If a minority pattern 5 is seen, pathologists will mention this as a *tertiary* grade in their report since it carries a worse prognosis than the same Gleason score without it.

The importance of the Gleason score is that it correlates well with prognosis, stage for stage, however the patient is managed. Indeed, it remains the most important prognostic indicator, following radical curative treatment. Cancers of the same Gleason score have a worse prognosis if the predominant grade is higher (for example, 4 + 3 = 7 is worse than 3 + 4 = 7). Some men with low-grade tumours develop high-grade tumours after several years. This is probably due to clonal expansion of high-grade cells rather than dedifferentiation of tumour cells. In general, large volume tumours (for example, the 'index' tumour in a multifocal primary PC) are more likely to be of high-grade than smaller tumours, but occasionally, exceptions are seen.

Finally, caution must be taken when Gleason-scoring tissue that has been subject to certain interventions, including RT and androgen deprivation therapy. It is recognized that PCs treated with androgen ablation exhibit changes similar to those seen in cancers of Gleason score 8–10. It is possible that treatment of BPH with 5ARIS could adversely affect the Gleason score of cancer present in the gland. Pathologists are, therefore, keen to know relevant clinical details and are reluctant to provide Gleason scores for such patients.

Although cytological features play no part in this grading system, the diagnosis requires absence of acinar basal cells, including absence of immunohistochemical staining for basal cell markers p63 (a homologue of tumour suppressor gene, p53) and cytokeratin 34βE12. In addition, positive staining for the α-methylacyl CoA racemase (AMACR or racemase) enzyme, overexpressed in PC and PIN, is used routinely by pathologists to help make the diagnosis.

Other prognostic indicators

As well as Gleason score, tumour stage and PSA level are independent predictors of PC prognosis. Tissue molecular markers, such as overexpression of PCA3 and p53, have been shown to correlate with adverse outcome following radical prostatectomy.

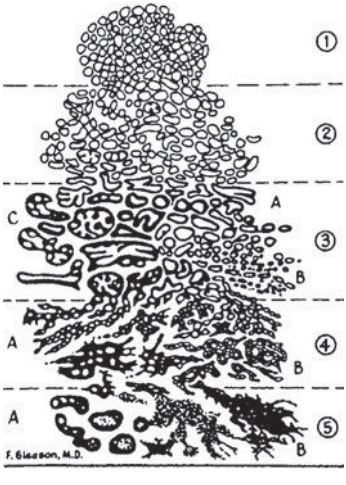


Fig. 7.5 A diagrammatic representation of the Gleason grading system for prostrate cancer. The grade depends on the structure of the prostatic glands and their relationship to the stromal smooth muscle.

Prostate cancer: staging and imaging

Tumour staging is by the TNM classification (Table 7.14). As with all cancer, PC staging may be considered clinical (prefixed with 'c') or pathological (prefixed with 'p').

T stage is assessed by DRE (Fig. 7.6), imaging (TRUS, MRI), or examination of radical prostatectomy (RP) specimens. Imaging resolution limits reliability in detection of multifocal and microscopic extraprostatic disease. Only 60% of cancers are visible on TRUS and only 40% of pT3 tumours will be detected. Seminal vesicle biopsy may be carried out in cases considered at high risk of seminal vesicle involvement.

Higher pathological stage (i.e. pT3 disease) found at radical prostatectomy may also be predicted by:

- Higher percentage (>66%) of positive biopsies.
- Cancer invading adipose in the biopsies (there is no fat in the prostate).
- Presence of perineural cancer invasion within the prostate.

Using standard MRI, prediction of extraprostatic extension and seminal vesicle involvement has 50–84% sensitivity and 22–95% specificity. Recent prostatic biopsy may confuse the interpretation of MRI images, particularly the issue of haemorrhage or tumour infiltration of seminal vesicles. Endorectal MRI appears more accurate for T staging than surface MRI or CT, but patients find it uncomfortable and it has not gained wide acceptance. The use of multiparametric MRI (dynamic gadolinium contrast enhancement (DCE-MRI), diffusion weighting, resonance spectroscopy) for high resolution diagnosis and T staging is currently under evaluation.

N stage is assessed by imaging (MRI) or histological examination. Pelvic lymphadenectomy is the gold standard assessment of N stage: this should be bilateral, even in cases where prostate biopsy shows unilateral cancer, since contralateral positive nodes are present in up to one-third of such cases. This has commonly involved obturator lymphadenectomy (OLND) during the performance of RP. Since low-risk patients have <10% risk of metastatic disease, current EAU guidelines recommend these patients are spared OLND. In contrast, 'extended' pelvic lymphadenectomy (EPLND) is becoming standard practice for intermediate- and high-risk disease; a study of high-risk cases undergoing RP has demonstrated that <40% of patients would be correctly staged by OLND. EPLND also includes the external and iliac nodes up to the common iliac bifurcation; even the presacral nodes were positive in 9%. There is ongoing debate regarding the potential therapeutic value of EPLND, with some studies associating it with improved biochemical relapse-free survival (BRFS) and suggesting the number of positive nodes removed correlates with cancer-specific survival (CSS), while others have failed to show such benefits.

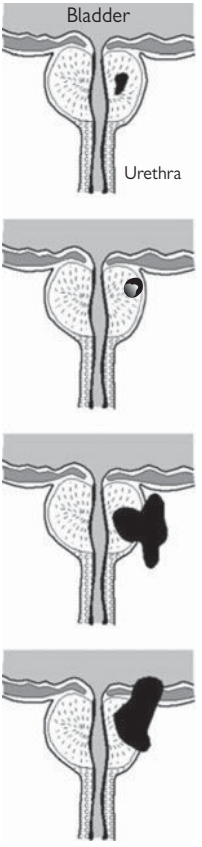
MRI or CT scanning can image enlarged nodes; radiologists report nodes of >8mm in maximal diameter. However, nodes larger than this often contain no cancer, while micrometastases may be present in normal-sized nodes. Sensitivity ranges from 0–70%, with a positive predictive value of only 50%. In practice, MRI pelvic imaging is restricted to intermediate- and high-risk patients (cT3 or PSA >10 or Gleason ≥7).

Table 7.14 UICC (2009) TNM staging of adenocarcinoma of the prostate

T0	No tumour (pT0 if no cancer found by histological examination)
Tx	T stage uncertain
T1a	Cancer non-palpable or visible by imaging, incidental finding in ≤5% of TURP specimen (found in up to 18% of TURPs);
T1b	Cancer non-palpable or visible by imaging, incidental finding in >5% of TURP specimen
T1c	Cancer non-palpable or visible by imaging, present in needle biopsy taken because of elevated PSA
T2a	Palpable tumour, feels confined, in ≤ half of one 'lobe'
T2b	Palpable tumour, feels confined, in > half of one 'lobe'
T2c	Palpable tumour, feels confined, in both 'lobes'
T3a	Palpable tumour, locally advanced, through prostatic capsule into periprostatic fat, uni- or bilaterally, and mobile
T3b	Palpable tumour, locally advanced, growing into seminal vesicle(s)
T4a	Palpable tumour, feels locally advanced, and fixed onto adjacent structures or pelvic side wall
Nx	Regional lymph not assessed
N0	No regional lymph node metastasis
N1	Tumour involves regional (pelvic) lymph nodes (i.e below bifurcation of common iliac arteries)
Mx	Distant metastases not assessed
M0	No distant metastasis
M1a	Tumour involves non-regional lymph nodes
M1b	Tumour metastasis in bone
M1c	Tumour metastasis in other sites

There is interest in ^{11}C-choline PET/CT and lymphotropic nanoparticle-enhanced MRI for improving imaging N staging. A nomogram predicting the risk of lymph node invasion at extended pelvic lymphadenectomy is published.[1]

M stage is assessed by physical examination, imaging (MRI 'marrow screen' or isotope bone scan, chest radiology) and biochemical investigations (including creatinine and alkaline phosphatase—elevated in 70% of patients with bone metastases). MRI marrow is more sensitive than isotope bone scintigraphy. In practice, bone imaging is not carried out unless there is biopsy Gleason score ≥ 4 + 3 = 7, PSA >20ng/mL or a clinical indication. In these circumstances, the chance of detecting M+ disease is >5%. PSA >100ng/mL predicts metastatic disease in almost 100%.



T1

Early (non-palpable) prostate cancer only detectable under the microscope; found at TURP or by needle biopsy

T2

Early (palpable) prostate cancer—still confined to the capsule

T3

Locally advanced prostate cancer—into peri prostate fat or seminal vesicles

T4

Locally advanced prostate cancer—invading the bladder, rectum, penile urethra, or pelvic side wall

Fig. 7.6 The T stages of prostate cancer.

Partin's nomograms, based on >5000 radical prostatectomies, are widely used to help predict pathological T and N stage by combining clinical T stage, PSA, and biopsy Gleason score (Table 7.15).[2] However, it is recognized that N staging is underestimated because lymphadenectomies were confined to the obturator fossa.

There is no provision in the T staging for suspected *local recurrence following RP* since the primary tumour has been removed. A nodule is occasionally palpable by DRE; imaging is usually unhelpful and not recommended unless there is a clinical indication or PSA is >7ng/mL. ^{11}C-choline PET/CT imaging has been reported to detect local and lymph node recurrence even when PSA <2.5ng/mL.

1 Briganti A, Larcher A, Abdollah F, *et al.* (2012) Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. *Eur Urol* **61**:480–7

2 Studer UE, Danuser H, Hochreiter W, *et al.* (1996) Summary of 10 years experience with an ileal low-pressure substitute combined with an afferent tubular isoperistaltic segment. *World J Urol* **14**:29–39.

Table 7.15 Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. (Adapted with permission from Elsevier.[1])

PSA range (ng/mt)	Pathologic stage	Gleason score				
		2–4	5–6	3+4=7	4+3=7	8–10
		Clinical stage T1c (nonpalpable, PSA elevated)				
0–25	Organ confined	95 (89–99)	90 (88–93)	79 (74–85)	71 (62–79)	66 (54–76)
	Extraprostatic extension	5(1–11)	9(7–12)	17(13–23)	25 (18–23)	28 (20–38)
	Seminal vesicle (+)	–	0 (0–1)	2 (1–5)	2 (1–5)	4(1–10)
	Lymph node (+)	–	–	1 (0–2)	1 (0–4)	1(0–4)
2.6–4.0	Organ confined	92 (82–98)	84 (81–86)	68 (62–74)	58 (48–67)	52 (41–63)
	Extraprostatic extension	8(2–18)	15 (13–18)	27 (22–33)	37 (29–46)	40 (31–50)
	Seminal vesicle (+)	–	1 (0–1)	4(2–7)	4(1–7)	6(3–12)
	Lymph node (+)	–	–	1 (0–2)	1 (0–3)	1(0–4)
4.1–6.0	Organ confined	90 (78–98)	80 (78–83)	63 (58–83)	52 (43–60)	46 (36–56)
	Extraprostatic extension	10(2–22)	19(16–21)	32 (27–36)	42 (35–50)	45 (36–54)
	Seminal vesicle (+)	–	1 (0–1)	3 (2–5)	3 (1–6)	5 (3–9)
	Lymph node (+)	–	0 (0–1)	2 (1–3)	3 (1–5)	3 (1–6)

6.1–10.0	Organ confined	87 (73–97)	75 (72–77)	54 (49–59)	43 (35–51)	37 (28–46)
	Extraprostatic extension	13(3–27)	23 (21–2 5)	36 (32–40)	47(40–54)'	48 (39–57)
	Seminal vesicle (+)	–	2 (2–3)	8(6–11)	8 (4–12)	13 (8–19)
	Lymph node (+)	–	0 (0–1)	2 (1–3)	2(1–4)	3 (1–5)
>10.0	Organ confined	80 (61–95)	62 (58–64)	37 (32–42)	27 (21–34)	22 (16–30)
	Extraprostatic extension	20 (5–39)	33 (30–36)	43 (38–48)	51 (44–59)	50 (42–59)
	Seminal vesicle (+)	–	4 (3–5)	12(9–17)	11 (6–17)	17(10–25)
	Lymph node (+)	–	2 (1–3)	8(5–11)	10(5–17)	11 (5–18)
	Clinical stage T2a (palpable <1/2 of one lobe)					
0–2.5	Organ confined	91 (79–98)	81 (77–85)	64 (56–71)	53 (43–63)	47 (35–59)
	Extraprostatic extension	9 (2–21)	17(13–21)	29 (23–36)	40 (30–49)	42 (32–53)
	Seminal vesicle (+)	–	1 (0–2)	5 (1–9)	4 (1–9)	7(2–16)
	Lymph node (+)	–	0 (0–1)	2 (0–5)	3 (0–8)	3 (0–9)
2.6–4.0	Organ confined	85 (69–96)	71 (66–75)	50 (43–57)	39 (30–48)	33 (24–44)
	Extraprostatic extension	15 (4–31)	27(23–31)	41 (35–48)	52 (43–61)	53 (44–63)
	Seminal vesicle (+)	–	2 (1–3)	7 (3–12)	6 (2–12)	10(4–18)
	Lymph node (+)	–	0 (0–1)	2(0–4)	2 (0–6)	3 (0–8)
4.1–6.0	Organ confined	81 (63–95)	66 (62–70)	44 (39–50)	33 (25–41)	28 (20–37)
	Extraprostatic extension	19(5–37)	32 (28–36)	46 (40–52)	56 (48–64)	58 (49–66)
	Seminal vesicle (+)	–	1 (1–2)	5 (3–8)	5 (2–8)	8(4–13)
	Lymph node (+)	–	1 (0–2)	4(2–7)	6(3–11)	6(2–12)

(*Continued*)

Table 7.15 Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. (*Continued*)

PSA range (ng/mt)	Pathologic stage	Gleason score				
		2–4	5–6	3+4=7	4+3=7	8–10
6.1–10.0	Organ confined	76 (56–94)	58 (54–61)	35 (30–40)	25 (19–32)	21 (15–28)
	Extraprostatic extension	24 (6–44)	37 (34–41)	49 (43–54)	58 (51–66)	57 (48–65)
	Seminal vesicle (+)	–	4 (3–5)	13 (9–18)	11 (6–17)	17(11–26)
	Lymph node (+)	–	1 (0–2)	3 (2–6)	5 (2–8)	5 (2–10)
>10.0	Organ confined	65 (43–89)	42 (38–46)	20(17–24)	14 (10–8)	11 (7–15)
	Extraprostatic extension	35 (11–57)	47 (43–52)	49 (43–55)	55 (46–64)	52 (41–62)
	Seminal vesicle (+)	–	6 (4–8)	16(11–22)	13 (7–20)	19(12–29)
	Lymph node (+)	–	4(3–7)	14 (9–21)	18 (10–27)	17(9–29)
Clinical stage T2b (palpable >½ of one lobe, not both lobes)						
0–2.5	Organ confined	88 (73–97)	75 (69–81)	54 (46–63)	43 (33–54)	37 (26–49)
	Extraprostatic extension	12(3–27)	22(17–28)	35 (28–43)	45 (35–56)	46 (35–58)
	Seminal vesicle (+)	–	2 (0–3)	6 (2–12)	5(1–11)	9 (2–20)
	Lymph node (+)	–	1 (0–2)	4 (0–10)	6 (0–14)	6(0–16)

2.6–4.0	Organ confined	80 (61–95)	63 (57–69)	41 (33–48)	30 (22–39)	25 (17–34)
	Extraprostatic extension	20 (5–39)	34 (28–40)	47 (40–55)	57 (47–67)	57 (46–68)
	Seminal vesicle (+)	–	2(1–4)	9(4–15)	7 (3–14)	12(5–22)
	Lymph node (+)	–	1 (0–2)	3 (0–8)	4(0–12)	5 (0–14)
4.1–6.0	Organ confined	75 (55–93)	57 (52–63)	35 (29–40)	25 (18–32)	21 (14–29)
	Extraprostatic extension	25 (7–45)	39 (33–44)	51 (44–57)	60 (50–68)	59 (49–69)
	Seminal vesicle (+)	–	2 (1–3)	7(4–11)	5 (3–9)	9(4–16)
	Lymph node (+)	–	2 (1–3)	7 (4–13)	10(5–18)	10(4–20)
6.1–10.0	Organ confined	69 (47–91)	49 (43–54)	26 (22–31)	19(14–25)	15 (10–21)
	Extraprostatic extension	31 (9–53)	44 (39–49)	52 (46–58)	60 (52–68)	57 (48–67)
	Seminal vesicle (+)	–	5 (3–8)	16(10–22)	13 (7–20)	19(11–29)
	Lymph node (+)	–	2 (1–3)	6 (4–10)	8 (5–14)	8(4–16)
>10.0	Organ confined	57 (35–86)	33 (28–38)	14 (11–17)	9 (6–13)	7 (4–10)
	Extraprostatic extension	43 (14–65)	52 (46–56)	47 (40–53)	50 (40–60)	46 (36–59)
	Seminal vesicle (+)	–	8(5–11)	17(12–24)	13 (8–21)	19 (12–29)
	Lymph node (+)	–	8 (5–12)	22(15–30)	27 (16–39)	27 (14–40)
	Clinical stage T2c (palpable on both lobes)					
0–2.5	Organ confined	86 (71–97)	73 (63–81)	51 (38–63)	39 (26–54)	34 (21–48)
	Extraprostatic extension	14 (3–29)	24(17–33)	36 (26–48)	45 (32–59)	47 (33–61)
	Seminal vesicle (+)	–	1(0–4)	5 (1–13)	5 (1–12)	8(2–19)
	Lymph node (+)	–	1(0–4)	6 (0–18)	9 (0–26)	10(0–27)

(*Continued*)

Table 7.15 Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. (*Continued*)

PSA range (ng/mt)	Pathologic stage	Gleason score				
		2–4	5–6	3+4=7	4+3=7	8–10
2.6–4.0	Organ confined	78 (58–94)	61 (50–70)	38 (27–50)	27(18–40)	23 (14–34)
	Extraprostatic extension	22 (6–42)	36 (27–45)	48 (37–59)	57 (44–70)	57 (44–70)
	Seminal vesicle (+)	–	2 (1–5)	8 (2–17)	6 (2–16)	10(3–22)
	Lymph node (+)	–	1(0–4)	5 (0–15)	7 (0–21)	8 (0–22)
4.1–6.0	Organ confined	73 (52–93)	55 (44–64)	31 (23–4)	21 (14–31)	18(11–28)
	Extraprostatic extension	27 (7–48)	40 (32–50)	50 (40–60)	57 (43–68)	57 (43–70)
	Seminal vesicle (+)	–	2(1–4)	6(2–11)	4 (1–10)	7(2–15)
	Lymph node (+)	–	3(1–7)	12(5–23)	16 (6–32)	16(5–33)
6.1–10.0	Organ confined	67 (45–91)	46 (36–56)	24(17–32)	16(10–24)	13 (8–20)
	Extraprostatic extension	33 (9–55)	46 (37–55)	52 (42–61)	58 (46–69)	56 (43–69)
	Seminal vesicle (+)	–	5 (2–9)	13 (6–23)	11 (4–21)	16 (6–29)
	Lymph node (+)	–	3 (1–6)	10(5–18)	13 (6–25)	13 (5–26)
>10.0	Organ confined	54 (32–85)	30 (21–38)	11(7–17)	7(4–12)	6(3–10)
	Extraprostatic extension	46(15–68)	51 (42–60)	42 (30–55)	43 (29–59)	41 (27–57)
	Seminal vesicle (+)	–	6 (2–12)	13 (6–24)	10 (3–20)	15 (5–28)
	Lymph node (+)	–	13 (6–22)	33 (18–49)	38 (20–58)	38 (20–59)

Key PSA = prostate-specific antigen.

Prostate cancer: clinical presentation

Since the introduction of serum PSA testing in the late 1980's, the majority of new patients have non-metastatic disease at presentation. Shown here are possible presentations, grouped by disease stage.

Localized prostate cancer (T1–2)

- Asymptomatic; detected in association with elevated or rising serum PSA or incidental abnormal DRE.
- LUTS (in most cases due to coexisting benign hyperplasia causing BOO).
- Haematospermia.
- Haematuria (probably in most cases due to coexisting benign hyperplasia).
- Perineal or voiding discomfort (probably due to coexisting prostatitis).

Locally advanced cancer, non-metastatic (T3–4 NOMO)

- Asymptomatic; detected in association with elevated or rising serum PSA or incidental abnormal digital rectal examination (DRE).
- LUTS.
- Haematospermia.
- Haematuria.
- Perineal or voiding discomfort.
- Symptoms of renal failure/anuria due to ureteric obstruction.
- Malignant priapism (rare).
- Rectal obstruction (rare).

Metastatic disease (N+, M+)

- Asymptomatic ('occult disease'); detected in association with elevated or rising serum PSA or incidental abnormal DRE.
- Swelling of lower limb(s) due to lymphatic obstruction.
- Anorexia, weight loss.
- Bone pain, pathological fracture.
- Neurological symptoms/signs in lower limbs (spinal cord compression).
- Anaemia.
- Dyspnoea, jaundice, bleeding tendency (coagulopathy).

A note about DRE

Since most prostate cancers arise in the peripheral, posterior part of the prostate, they should be palpable on DRE. An abnormal DRE is defined by asymmetry, a nodule, or a fixed craggy mass. Approximately 50% of abnormal DREs are associated with PC, the remainder being caused by benign hyperplasia, prostatic calculi, chronic prostatitis, or post-RT change. Only 40% of cancers diagnosed by DRE will be organ-confined. The fact that an abnormal DRE in the presence of a 'normal' PSA (<4.0ng/mL) carries a 30% chance of predicting PC underlines its important role in clinical practice.

Prostate cancer: screening

Screening is defined as 'The systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder' (UK National Screening Committee, 2001).

The obvious candidate test to be applied to PC screening is PSA.

By early detection and treatment, population screening of men aged 50 to 70–75y using PSA ± DRE may reduce the significant mortality and morbidity caused by PC. Proponents of screening say these acceptable and relatively inexpensive evaluations will detect clinically significant, but curable (localized) disease. The *lead time*, estimated at 9–12y, between the screened diagnosis and the clinical diagnosis due to symptoms should enable more organ-confined cancers to be diagnosed and cured. However, because of the low specificity of PSA (40%) and the high prevalence of latent PC, those against screening argue that many men would suffer unnecessary anxiety, biopsy, overdiagnosis, and overtreatment. Added to this, the treatments have morbidity and add cost to the already overburdened health care systems of most developed countries. Mathematical models suggest fewer men screened in their sixth decade would be overdiagnosed compared to those in their seventh or eighth decade; younger men have potentially more to gain in terms of life expectancy.

From an academic point of view, PC fails to fulfil many of the 10 screening criteria set out by Wilson and Jungner, including the possession of a highly sensitive and specific test and a clear understanding of the disease's natural history.

UK population screening studies have diagnosed PC in 2–3% of men tested, the vast majority diagnosed with localized disease. A large non-randomized study over a 6y period from Tyrol, Austria, demonstrated an 80% reduction in the diagnosis of metastatic disease and a 30% reduction in the expected mortality due to PC.

The results of pivotal European and North American randomized trials were published in 2009: the European Randomized trial of Screening for Prostate Cancer (ERSPC) and the US PLCO trial.[1,2] Cancer-specific survival (CSS) was the key outcome measure in both trials. While the ERSPC, mean follow-up 8y, showed a 20% CSS advantage in the screened group over the control group, no difference between groups was observed in the PLCO. Even with the CSS advantage, ERSPC concluded that the number (of men) needed to treat to save one life (NNT) was 48 men so highlighting concerns regarding overtreatment. Interestingly, the Swedish subset of the ERSPC, with 14y mean follow-up, reported a 40% CSS advantage to the screened group, the NNT reduced to 12.[2] *This suggests that the benefits of screening continue to accrue in the longer term.* Despite this, a 2011 Cochrane meta-analysis of randomized trials concluded that there is no CSS advantage to PSA screening. The ERSPC was updated with mean follow-up of 11y; adjusting for non-compliance, CSS is reduced by 29% in the screened arm and the number (of cancers) needed to detect to save one life (NND) had fallen to 33.[3] ERSPC also reported a 30% reduction of metastasis in the screened group at 11y follow-up.

A large UK multicentre study, ProTECT, aims to address both the screening question and randomizes treatment of screen-detected disease. Starting in 2001 and with 260 000 men now recruited, results are not expected until 2013. Currently, there is little support for a PC screening programme in the UK; unchanged since 2002, the Department of Health recommends that asymptomatic men requesting screening should be counselled prior to being offered a PSA test (see 🕮 p. 322).

1 Schröder FH, Hugosson J, Roobol MJ, *et al.* (2009) Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* **360**:1320–8.

2 Andriole GL, Grubb RL 3rd, Buys SS, *et al.* (2009) Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* **360**:1310–9.

3 Hugosson J *et al.* (2010) Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* **11**: 725–732.

4 Schröder FH, Hugosson J, Roobol MJ, *et al.* (2012) Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* **366**:981–90.

Prostate cancer: prostate-specific antigen (PSA)

See 📖 p. 43 for an introduction to the serum PSA test. Until the development of commercial serum PSA assays in the late 1980s, the only serum marker for PC was acid phosphatase. This was highly specific for PC metastatic to bone, but lacked sensitivity in detecting less advanced disease and was normal in >20% patients with bone metastases. Prior to the PSA era, most men with newly diagnosed PC had advanced incurable disease. PSA has revolutionized the diagnosis and management of PC, although its use in screening remains controversial. The predictive values of PSA and DRE for diagnosing PC in biopsies are shown in Table 7.16. Two sophisticated PC predictors, which also consider family history, LUTS, race, and previous negative biopsy, are available online at:
🖱 http://www.compass.fhcrc.org/edrnnci/bin/calculator/main.asp?t=prostateandsub=disclaimerandv=prostateandm=andx=Prostate%20Cancer
and 🖱 http://www.prostatecancer-riskcalculator.com/via.html

Table 7.16 The predictive value of PSA and DRE for TRUS-biopsy diagnosis of prostate cancer

PSA (ng/mL)	0.1–1.0	1.1–2.5	2.6–4.0	4–10	>10
DRE normal	10%	17%	23%	26%	>50%
DRE abnormal	15%	30%	40%	50%	>75%

In addition to its use as a serum marker for the diagnosis of PC, PSA elevations may help in staging, counselling, and monitoring PC patients. PSA is used, along with clinical (DRE) T stage and Gleason score, to predict pathological tumour staging and outcome after radical treatments using statistically derived nomograms and artificial neural networks. Here are some examples:

- PSA generally increases with advancing stage and tumour volume, although a small proportion of poorly differentiated tumours fail to express PSA.
- A single PSA ≤1.0ng/mL at age 60 carries 0.2% risk of PC death or 0.5% risk of metastatic disease by age 85.
- Any PSA rise from its nadir when on 5ARI treatment for BPH should prompt concern regarding the presence of PC and consideration of biopsy.
- Over 50% of patients have extraprostatic disease if PSA >10ng/mL.
- Less than 5% of patients have obturator lymph node metastases and only 1% have bone metastases shown by isotope scintigraphy if PSA <20ng/mL.
- Sixty-six percent of patients have lymphatic involvement and 90% have seminal vesicle involvement if PSA >50ng/mL.
- PSA should be undetectable (<0.1ng/mL in many laboratories) following radical prostatectomy for gland-confined disease.

- PSA rise after radical prostatectomy precedes the development of metastatic disease by a mean time of 8y.
- PSA falls to within the normal range in 80% of patients with metastatic disease within 4 months of starting androgen ablation therapy; the PSA rises in a mean time of 18 months after starting hormone therapy, signalling progressing disease.

PSA is prostate-specific, but not prostate cancer-specific. Other causes of elevated serum PSA are shown in Table 7.17, the most common of which is BPH.

Table 7.17 Conditions, excluding prostate cancer, which cause elevated PSA

Cause of elevated PSA	Minor elevation <1.0ng/mL	Intermediate elevation 1.0–20ng/mL	Major Elevation 20–100ng/mL
Benign hyperplasia	√	√	
Urinary tract infection		√	√
Acute prostatitis		√	√
Chronic prostatitis	√	√	
Retention/catheterization		√	
Biopsy, TURP		√	√
Ejaculation, DRE	√		

In the presence of infection or instrumentation, PSA should be requested at least 28 days after the event to avoid a false-positive result, which may cause unnecessary anxiety. Ideally, PSA should not be requested within 2 days of ejaculation or DRE, but in practice, it causes little difference (<1ng/mL) to the result.

Prostate cancer—PSA derivatives and kinetics: free-to-total, density, velocity, and doubling time

Measurement of the *free-to-total (F:T) PSA ratio* increases the specificity of total PSA because the ratio is lower in men with PC than in men with benign hyperplasia. This may be helpful in deciding whether to rebiopsy a patient with previous benign biopsies. While overall a man with a normal DRE and a PSA of 4–10ng/mL has a 25% risk of PC (Table 7.15), this risk rises to 60% if the F:T ratio is 10% and falls to 10% if his ratio is >25%. The F:T ratio may also be useful in the total PSA range 2.5–4ng/mL. Chronic prostatitis may also cause a reduced F:T ratio. An important limitation of this investigation is the instability of free PSA. The serum must be assayed within 3h or frozen at –20°C, otherwise the free component reduces and a low ratio will be reported, perhaps leading to unnecessary biopsy.

Assays measuring the more stable *complexed PSA* concentration and the '*Prostate Health Index*' ([phi=[–2]proPSA/fPSA)x√tPSA] Beckmann Coulter combined assay) are developed, but their place in clinical practice has not been defined, despite studies claiming greater accuracy than total PSA.

Consideration may be given to the prostate volume, since large benign prostates are the most common cause of mildly elevated PSA. Serum PSA/prostate volume = *PSA density*. Various cut-off densities have been proposed to raise the specificity of total PSA in the prediction of PC diagnosis by biopsy, e.g. >0.15. If the diagnosis of PC is made, PSAD >0.19 predicts pT3 and high-grade disease in 50% of cases.

Short-term variations in serum PSA occur, the cause of which may be technical or physiological. Over longer term, the PSA tends to rise slowly (<0.3ng/mL/y) due to BPH, faster due to PC. The rate of rise per year is the *PSA velocity*. Despite current controversy over its use in untreated men, a landmark study introduced the concept of PSA velocity in 1992. It demonstrated 95% of PSA increases >0.75ng/mL/y in PSA range 4–10ng/mL (over a minimum of three measurements 6 months apart) were associated with a diagnosis of PC several years later. Only 5% of men without cancer exhibited such a velocity.[1] A PSA velocity >20% per year should also prompt the recommendation of a biopsy, although a slower velocity does not exclude the presence of cancer. It has been suggested that a PSA velocity of >2ng/mL/y in the year prior to radical curative treatment of PC is associated with a poorer cancer outcome.

PSA doubling time (PSADT): is the time it takes for the PSA to double. It is calculated with the formula: PSADT = log2 × dT/(logB – logA), A and B are the initial (A) and final (B) PSA measurements and dT is the time difference between the calendar dates of the two PSA measurements. PSADT may be the best indicator of the likely presence of PC or the rate of disease progression. Several serial measurements reduce confounding physiological variability. Not always easy to calculate, PSADT can be obtained online at: www.pcngcincinnati.org/psa/index.htm.

PSADT is used to drive clinical management following treatment of PC. Reports from Johns Hopkins confirm that PSADT correlates with cancer-specific survival (CSS) following RP: 379 patients experiencing BCR where followed up for a median of 10y. Significant risk factors included PSADT ≤3 months, GS >7, and time to BCR ≤3y. For example, patients with a PSADT <3 months had a median survival of 6y; this reduced to only 3y if their GS was >7. Conversely, patients with none of these risk factors had a 100% CSS.[2] When 21% of these patients had died of PC and 6% had died other causes, it was appreciated that only 15% of the PC deaths were associated with PSADT ≤3 month while the majority (60%) of deaths were associated with PSADT of 3–9 months. PSADT >15 months had greater risk of death from competing causes.[3] Other examples of PSADT in clinical practice include: <5y raises suspicion of the presence of PC; <3y often drives recommendation to treat a patient on active surveillance; ≤6 months should drive recommendation of hormone therapy following radical treatment.

1 Carter HB, Pearson JD, Metter EF, *et al.* (1992) Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* **267**:2215–20.

2 Freedland S, Humphreys EB, Mangold LA, *et al.* (2005) Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* **294**:433–9.

3 Freedland S, Humphreys EB, Mangold LA, *et al.* (2007) Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. *J Clin Oncol* **25**:1765–71.

Prostate cancer: counselling before PSA testing

Counselling is mandatory before offering a PSA and DRE to *asymptomatic* men, particularly to highlight the potential disadvantages of having an abnormal result. These must be weighed up against the potential benefit of having clinically significant PC diagnosed at an earlier stage than it would have been without these evaluations. There is currently no clear evidence of benefit by screening for PC (see 📖 p. 316). This forms the basis of the UK Department of Health *NHS Prostate Cancer Risk Management Programme (2002)*, whereby only men requesting the investigations and who have been appropriately counselled should be tested. Such counselling is less fundamental when investigating a *symptomatic* patient because the diagnosis of PC could alter his clinical management. However, all patients should be informed when PSA testing is being considered.

The following points should be used in counselling *asymptomatic* men:

- Cancer will be identified in <5% of men screened.
- The benefits of PC screening remain controversial.
- Sensitivity is 80%: a false-negative result is possible; there is no level of detectable PSA at which PC can be excluded.
- Specificity is 40–50%: a fals-positive result is possible; age-related benign hyperplasia and UTI are the most common causes.
- Prostatic biopsy is uncomfortable (despite local anaesthetic) and carries a risk of septicaemia or significant bleeding, each 0.5%.
- Prostatic biopsy may miss a cancer.
- Repeat biopsy may be recommended (presence of PIN, ASAP, persisting clinical suspicion or rising PSA).
- Treatment may not be necessary.
- Treatment may not be curative.
- Treatment-related morbidity could lead to a diminished quality of life.

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Prostate cancer: other diagnostic markers

Given the limitations of PSA discussed on 📖 pp. 318–321, there is considerable ongoing effort to identify better diagnostic markers in both serum and first-voided urine following a DRE. These are mostly the RNA or protein products of genes commonly over- or underexpressed in PC tissue.

Prostate cancer antigen 3 (PCA3)

The first of these, already commercially available, is the PCA3 test. This gene is overexpressed in 95% of PC, though its function is unclear. RNA transcripts are amplified and detected from urine sediment. Specificity for PC diagnosis is improved compared with serum PSA alone (around 70%) in men who have already undergone one negative biopsy, though sensitivity of 50–60% (i.e. at least 40% false-negative results) remains an issue when advising patients whether or not to undergo repeat biopsy regardless of PSA changes. Studies exploring potential improved sensitivity by combining detection of PCA3 with other molecular markers, e.g. the *TMPRSS2-ERG fusion* transcript (see 📖 p. 302) are ongoing.

Engrailed 2 (EN2) protein

EN2 is a transcription factor expressed in PC cell lines and secreted into the urine by PC in men. First pass urine DRE is collected and EN2 protein measured by ELISA. A study of 82 men with PC and 102 controls demonstrated the presence of EN2 in urine was highly predictive of PC, sensitivity of 66% and specificity 88.2%. There was no correlation with PSA levels. A large multicenter study to further evaluate the diagnostic potential of EN2 is justified.[1]

Microseminoprotein-beta (MSMB)

MSMB regulates apoptosis; using genome-wide association studies, the rs10993994 single nucleotide polymorphism in the *MSMB* promoter has been linked to an increased risk of developing PC. MSMB expression in benign and malignant prostate tissue was examined using immunohistochemistry. Urinary MSMB concentrations were determined by ELISA and correlated with urinary PSA, the presence or absence of PC, rs10993994 genotype, and age of onset. MSMB levels in prostate tissue and urine were greatly reduced with PC. Urinary MSMB was better than urinary PSA at differentiating men with PC at all Gleason grades.[2] Further studies are ongoing.

α-methylacyl CoA racemase (AMACR) immunohistochemical overexpression is 97% sensitive and 100% specific for PC diagnosis in needle biopsies. It is used routinely by histopathologists. Efforts are ongoing to develop AMACR assay for testing on body fluids.

Promotor hypermethylation of reducing enzyme **glutathione-S-transferase P1** (GSTP1) is the commonest epigenetic abnormality in PC, inactivating its transcription in 90% PCs and 70% of PIN lesions. Methylated GSTP1 DNA is detectable in both urine and serum.

Finally, **human kallikrein 2** (hK2) is a member of the same protease family as PSA (which is also known as hK3), bearing 78% sequence homology. hK2 is expressed almost exclusively by prostatic epithelium, in lesser quantity than PSA. It is relatively overexpressed in PIN and higher Gleason score cancers. The ratio of hK2:PSA mRNA in urinary sediments may help to distinguish aggressive or advanced cancers.

1 Morgan R, Boxall A, Bhatt A, *et al.* (2011) Engrailed-2 (EN2): a tumor specific urinary biomarker for the early diagnosis of prostate cancer. *Clin Cancer Res* **17**:1090–8.

2 Whittaker H. *et al.* (2010) The rs10993994 Risk Allele for Prostate Cancer Results in Clinically Relevant Changes in Microseminoprotein-Beta Expression in Tissue and Urine. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0013363 www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0013363.

Prostate cancer: transrectal ultrasonography and biopsy

The most common diagnostic modality for PC is transrectal ultrasonography (TRUS) with guided biopsies (Fig. 7.7). TRUS provides imaging of the prostate and seminal vesicles using a 7.5mHz biplane rectal probe measuring approximately 1.5cm in diameter. The peripheral/transition zones, cysts, and calcifications within the prostate can be seen. Hypoechoic and hyperechoic lesions in the peripheral zone may be due to PC or inflammatory conditions, although most PCs are isoechoic and are not identified. Seminal vesicles may be compared for asymmetry.

Patients usually find the biopsy procedure uncomfortable, some painful. It takes about 5min and is undertaken on an outpatient basis with local anaesthetic. Ultrasound-guided periprostatic injection of 1–2% lignocaine is the gold standard; perianal GTN paste or inhalation of nitrous oxide/air (Entonox) are less effective alternatives. A DRE precedes insertion of the probe. Antiseptic rectal wall cleansing using aqueous iodine on a sponge stick may reduce risk of sepsis if transrectal biopsies are planned. Broad-spectrum antimicrobial prophylaxis (usually oral quinolone ± metronidazole) are given at least 30min prior and typically for 48h after the procedure. It is not safe to biopsy a warfarinized patient; the INR should be <1.5. However, biopsying patients on low-dose aspirin is not considered unsafe. Other antiplatelet drugs (e.g. clopidogrel) are usually stopped for 10 days prior.

Indications for TRUS alone

- Estimation of prostate volume (cm^3) = anteroposterior distance (cm) × width (cm) × sagittal length (cm) × 0.52.
- Male infertility with azoospermia to look for seminal vesicle and ejaculatory duct obstruction due to calculus or Müllerian cyst.
- Suspected prostatic abscess.
- Investigation of chronic pelvic pain, looking for prostatic cyst, abscess, or calculi.

Indications for TRUS with biopsies

The 2008 UK NICE guidelines stress the importance of discussing the risks and benefits of biopsy, individual risk factors, the use of nomograms to predict results (see 📖 pp. 310–314), and allowing time for decision-making before proceeding.

- An abnormal DRE and/or an elevated PSA*.
- Previous biopsies showing multifocal PIN or ASAP.
- Previous biopsies normal, but PSA rising or DRE abnormal.
- Previous biopsies showing low-risk localized PC**.
- As part of active surveillance protocol for low-risk localized PC.
- To confirm viable PC following treatment if a salvage treatment is being considered.

Biopsy protocol

Systematic 18g trucut needle biopsies are taken, including any palpable or sonographic target lesion. The traditional sextant protocol (a parasagittal base, midgland, and apex from each side) has been superseded by 8, 10, or

12 biopsies, adding samples from the far lateral peripheral zones (Fig. 7.8). Studies have demonstrated these extra biopsies detect up to 15% more cancers. Relating the number of biopsies to the prostatic volume seems logical; attempts have been made to optimise this concept, e.g. the Vienna nomogram (Table 7.18).[1]

Table 7.17 The Vienna nomogram: optimal number of cores on TRUS-guided prostate biopsy

Prostate volume on TRUS (mL)	Patient age (y)			
	<50	50–60	60–70	>70
20–29	8	8	8	6
30–39	12	10	8	6
40–49	14	12	10	8
50–59	16	14	12	10
60–69	–	16	14	12
≥70	–	18	16	14

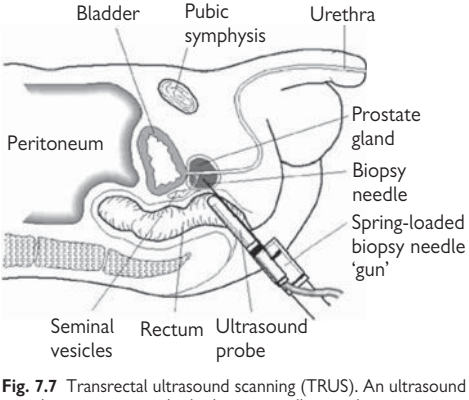


Fig. 7.7 Transrectal ultrasound scanning (TRUS). An ultrasound probe is inserted into the rectum to guide the biopsy needle into the correct position so that several core biopsies can be taken from different areas of the prostate.

* Prostate cancer may also be diagnosed clinically (without histology) or by TURP histology. For example, it may be unnecessary to biopsy a frail elderly men with a craggy hard prostate and PSA >100ng/mL prior to commencing palliative hormone therapy or those in whom a TURP is indicated for BOO with severe LUTS/retention.

** Some centres are performing 'mapping' transperineal template biopsies under GA for patients considering active surveillance or focal therapy to exclude the presence of significant anteriorly placed cancers. NICE guidance (2010) did not find evidence to support these indications.

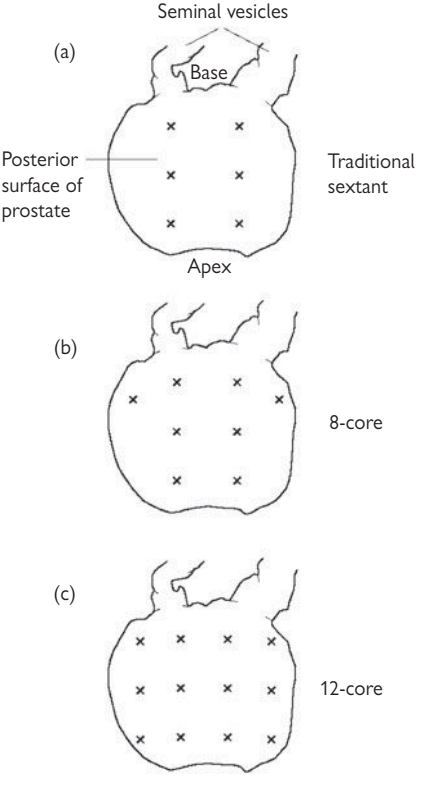


Fig. 7.8 Biopsy protocols.

Additional biopsies of each transition zone may be taken when a patient is undergoing repeat biopsies due to a rising PSA. If repeat biopsies fail to diagnose cancer in the setting of a persistently rising PSA, *saturation needle biopsies* (between 20 and 40) may be taken transrectally or transperineally using a template under general anaesthesia. This enables the anterior gland and apices to be properly sampled. Alternatively, some advocate resorting to *transurethral resection biopsies*, especially if the patient has a degree of BOO. Seminal vesicle biopsies occasionally add staging information and may influence treatment options if they are positive. A basal nodule or PSA >15ng/mL increases the likelihood of seminal vesicle (SV) invasion.

In future, TRUS and systematic biopsy may be replaced by multiparametric MRI-guided biopsy. T2-weighted MRI, supplemented by diffusion weighting and/or T1-dynamic contrast enhancement (gadolinium), is currently undergoing validation studies following reports that it can detect cancers >0.5cm^3 with 90% sensitivity and 88% specificity.[2]

Complications of prostatic biopsy

- Occasional vasovagal 'fainting' immediately after the procedure.
- 0.5% risk of septicaemia or prostatic abscess which may be life-threatening (TRUS and biopsy).
- 0.5% risk of significant rectal bleeding (TRUS and biopsy); treated by DRE using a swab soaked in 1:10000 adrenaline or rectal balloon catheter.
- 2–11% acute or clot urinary retention (after saturation/transperineal biopsy).
- Likely mild haemospermia (for up to 3 weeks) and haematuria; 0.1% risk of clot urinary retention (TRUS).

It is important that the patient understands that negative biopsies do not rule out PC and occasionally, repeat biopsies may be recommended (e.g. ASAP).

1 Remzi M, Fong YK, Dobrovits M, *et al.* (2005) The Vienna nomogram: validation of a novel biopsy strategy defining the optimal number of cores based on patient age and total prostate volume. *J Urol* **174**:1256–60.

2 Villers A, Puech P, Mouton D, *et al.* (2006) Dynamic contrast enhanced, pelvic phased array magnetic resonance imaging of localized prostate cancer for predicting tumor volume: correlation with radical prostatectomy findings. *J Urol* **176**:2432–7.

Prostate cancer: suspicious lesions

Two histological lesions are currently regarded as either pre- or peri-malignant. They are prostatic intraepithelial neoplasia and atypical small acinar proliferation.

Prostatic intraepithelial neoplasia (PIN)

PIN consists of architecturally benign prostatic acini and ducts lined by cytologically atypical cells. The basal cell layer is present, although the basement membrane may be fragmented. PIN was formerly known as ductal dysplasia or reported by pathologists as 'suspicious for cancer'. PIN was classified into low-grade (mild) and high-grade (moderate to severe) forms, based on the presence of prominent nucleoli. Subsequently pathologists have agreed to report only high-grade PIN since low-grade PIN reporting is very subjective and has no prognostic value. On the other hand, high-grade PIN is believed to be a precursor for intermediate or high-grade PC. PIN is reported in 5–10% of prostate needle biopsies. It does not appear to affect the serum PSA value. The site of the PIN is not indicative of the site of subsequently diagnosed cancer nor is PIN always present in a prostate-containing cancer. When found in sextant prostate biopsies carries a 30–40% prediction of PC at subsequent biopsy. However, with the widespread use of more extensive biopsy protocols, the significance of isolated PIN has become less clear, with some studies reporting a positive repeat biopsy rate that is equal or lower than the original cancer detection risk.

Atypical small acinar proliferation (ASAP)

This histopathological lesion reported by pathologists on needle biopsies as 'suspicious for cancer' must be taken seriously. The focus containing small acini is typically small, averaging 0.4mm in diameter. Acini are lined with cytologically abnormal epithelial cells and may exhibit atrophic features. The columnar cells have prominent nuclei containing nucleoli, while the basal layer is focally absent, according to high molecular weight cytokeratin immunostaining. PIN may be present in the same sample. Studies have shown ASAP in needle biopsies predict cancer at subsequent biopsy in over 40% of cases.

Currently it is recommended that repeat systematic biopsies should be performed if any isolated ASAP or multifocal PIN is reported on needle biopsy or TURP specimens. Most favour further PSA surveillance without repeat biopsy if a single focus of PIN is reported. The timing of repeat biopsy varies, although concern regarding antibiotic-resistant bowel flora following the first biopsy has led to some authorities recommending a gap of 6–12 weeks between procedures.

Prostate cancer: general considerations before treatment (modified from the 2008 UK NICE Guidance)

Once a diagnosis of PC has been made, it is essential to discuss the implications and management options with the patient and any relative or friend he wishes to involve.

Treatment may or may not be appropriate; it may be given with curative or palliative intent.

If treatment is not recommended, explain the advantage and disadvantages to help the patient understand why he is not being treated.

Before starting treatment, inform the patient that it *may* result in:

- Altered physical appearance.
- Altered sexual experience.
- Loss of sexual function, ejaculation, and fertility.
- Changes in urinary or bowel function.
- Other common side effects or complications.

Offer the patient:

- Support in decision-making, access to written material, and specialist nurse services.
- Ongoing access to erectile dysfunction services, if necessary.
- Ongoing access to specialist psychosexual services, if necessary.
- A urological assessment if LUTS are present.
- Sperm storage (if appropriate).

Assess the risk category[1] applicable to men with clinically-localised prostate cancer (Table 7.19).

Table 7.19 Assessing the risk category applicable to men with clinically localized prostate cancer*[1]

Risk	PSA (ng/mL)		Gleason score		Clinical stage by DRE
Low	<10	and	≤6	and	T1–T2a
Intermediate	10–20	or	7	or	T2b–T2c
High	>20	or	8–10	or	T3–4

* 'Risk' relates to the chance of failure of local treatment: low <25%; intermediate = 25–50%; high >50%.

1 D'Amico AV, Whittington R, Malkowicz SB, *et al.* (1998) Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* **280**:969–74.

Prostate cancer: watchful waiting and active surveillance

It can be understood from incidence, mortality, and survival data that the oft quoted statement '*more men die with prostate cancer than because of it*' is correct. This is because most PCs are slow-growing and the majority of men diagnosed are >70y, often with competing morbidities. This forms the basis for watchful waiting (WW) by deferring hormone therapy until the development of metastatic disease for some men diagnosed with non-metastatic PC.

The risks of developing metastatic disease and of death due to PC after 10–15y of WW can be considered using published data, according to biopsy grade. Table 7.20 summarizes these data. For survival and cumulative mortality from PC and other causes up to 20y after diagnosis, stratified by age at diagnosis and Gleason.

Table 7.20 Natural history of localized prostate cancer managed with no initial treatment

Biopsy grade	% risk of metastasis (10y)	% risk of prostate cancer death (15y)	Estimated lost years of life
2–4	19	4–7	<1y
5	42	6–11	4
6	42	18–30	4
7	42	42–70	5
8–10	74	56–87	6–8

Selection of patients for watchful waiting

WW is the best option for patients with localized PC and:

- Gleason score 2–4 disease at any age.
- Gleason score 5 and 6 disease in elderly or unfit men, with life expectancy considered to be <10y, for whom radical curative treatment would not be contemplated.
- Stage T1a disease with normal PSA (only 17% T1a patients will progress compared to 68% with T1b).

Watchful waiting protocols

Most men with localized PC on WW are seen every 6 months for clinical history, examination, including a DRE and a serum PSA test (before or after DRE). If the disease progresses during follow-up, palliative treatment (for example, androgen ablation therapy) is recommended. The threshold for treatment was traditionally when symptoms and signs of advanced disease appeared, for example, back pain and metastases on bone scan. However, the use of PSA kinetics (e.g. doubling time <12 months), the evidence of benefit with earlier use of hormone therapy, and involve-

ment of patient choice have driven earlier thresholds for treatment. Hence, an asymptomatic patient with a rising PSA may choose whether to treat his disease and accept the side effects or whether to maintain his current quality of life while leaving the disease untreated.

Active surveillance (AS)

With increasing numbers of low-risk cancers being diagnosed, there is concern that we are overtreating clinically insignificant disease, leading to unnecessary loss of quality of life for patients and consumption of health care resources. This issue will be amplified by possible future introduction of PSA screening. AS has a different goal from WW, which is to identify and treat localized cancers that are demonstrably progressing with curative intent whilst avoiding overtreatment for the majority.

The 2008 UK NICE Guidelines recommend AS as the 'preferred' option for men with low-risk (stage T1c–T2a and Gleason score ≤6 and PSA <10ng/mL) disease who might be considered for curative treatment. These men undergo more intensive evaluations than WW: PSA testing every 3 months (for velocity or doubling time calculation), DRE 6-monthly, and 2-yearly repeat biopsy to assess for upgrading. PSA velocity >1ng/mL/y and doubling times <3y are currently considered evidence of progression, which prompts the recommendation of curative treatment.

The largest published series of AS comes from Toronto. Of 450 patients, median age 70y with median follow-up 6.8y, 60% remained alive and on AS long-term. About one-third of patients were treated for progression, of whom 50% subsequently relapsed. The majority of deaths were due to non-PC causes.[2] Other studies are ongoing in the UK and Europe.

The risk with AS, suggested by the Toronto series, is that the disease may progress beyond the possibility of cure or that the disease is initially understaged. This has prompted some centres to perform template mapping biopsies prior to enrolling patients for AS. Randomized trials of AS vs immediate treatment are needed to identify subgroups of patients with localized PC who could most benefit from AS, rather than undergoing immediate treatment.

1 Albertsen PC, Hanley JA, Fine J (2005) 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* **293**:2095–101.

2 Klotz L, Zhang L, Lam A, *et al.* (2010) Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* **28**:126–31.

Prostate cancer: radical prostatectomy and pelvic lymphadenectomy

Radical (total) prostatectomy (RP) is excision of the entire prostate, including the prostatic urethra, with the seminal vesicles. In 1867, Vienna's Billroth performed the first perineal prostatectomy for PC, later propagated by Young (Johns Hopkins) in 1904. The retropubic approach was first undertaken by Millin (London) in 1945, though refinements in the 1980's led by Patrick Walsh gained its acceptance as the gold standard curative treatment for localized PC. Following excision of the prostate, reconstruction of the bladder neck and vesicourethral anastomosis completes the procedure.

RP may be performed by open retropubic, open perineal, manual laparoscopic, or robot-assisted laparoscopic approaches. The perineal approach does not allow a simultaneous pelvic lymph node dissection.

RP is indicated for the treatment (with curative intent) of fit men with localized PC whose life expectancy exceeds 10y. Patients with Gleason score 2–4 disease appear to do as well in the long term with surveillance as with treatment. The 2008 UK NICE Guidelines recommend RP for high-risk disease (PSA ≥20 *or* Gleason score ≥8 *or* cT3) only if there is a 'realistic prospect of long-term disease control', and for low-risk disease (PSA <10 *and* Gleason score ≤6 *and* cT1–2) if active surveillance is offered and declined. The surgeon should take part in multidisciplinary team discussion of each case. The patient should consider all available treatment options and the complications of RP before proceeding.

Steps in open RP

- The patient is under anaesthetic, catheterized, and positioned supine with the middle of the table 'broken' to open up the entry to the pelvis.
- Through an 8cm lower midline incision, staying extraperitoneal, the retropubic space is opened.
- Bilateral obturator lymphadenectomy is undertaken if the PSA >10 or the Gleason score is 7 or higher; extended lymphadenectomy should be carried out in high-risk patients; frozen section histology is rarely requested.
- Incisions in the endopelvic fascia on either side allow access to the prostatic apex and membranous urethra.
- Division and haemostatic control of the dorsal vein complex passing under the pubic arch allows access to the membranous urethra which is divided at the prostatic apex.
- The prostate is mobilized retrogradely from apex to base, taking Denonvilliers fascia on its posterior surface.
- If nerve sparing is undertaken, the apical and posterior dissection is modified, as described below.
- Denonvilliers fascia is incised at the prostatic base, allowing access to the vasa (divided) and seminal vesicles (excised).
- The bladder neck is divided, thereby freeing the prostate; the ureteric orifices are identified.

- The bladder neck is reconstructed to the approximate diameter of the membranous urethra.
- A vesicourethral anastomosis with six interrupted sutures is stented by a 16 Ch urethral catheter, typically for 10–14 days.
- The wound is closed leaving a pelvic drain, typically for 24h.

The 'interfascial' *nerve-sparing modification* aims to reduce the risk of post-operative erectile dysfunction, minimizing cavernosal nerve injury as they pass from the autonomic pelvic plexus on either side in the groove between prostate and rectum during mobilization of the prostate. The outer layer of prostatic fascia is incised to allow these nerves to fall away from the prostatic fascia and capsule. This should not be attempted in the presence of palpable disease as it may compromise cancer control. Non-nerve sparing is, therefore, 'extrafascial' (Fig. 7.9). The tips of the seminal vesicles may also be spared in cases with low risk of cancer involvement, potentially reducing bleeding and cavernosal nerve injury.

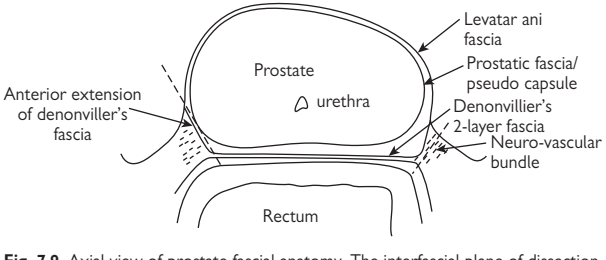


Fig. 7.9 Axial view of prostate fascial anatomy. The interfascial plane of dissection is shown on the left, while the extrafascial plane is shown on the right.

Laparoscopic radical prostatectomy (LRP): was pioneered in the late 1990's in a number of European centres. It is carried out transperitoneally or extraperitoneally, the latter having much in common with the open retropubic technique. Via five ports, with a 20–25° head-down tilt, extraperitoneal LRP is carried out in 12 steps shown below, with varying levels of difficulty (I–V).[1]

1. Trocar placement and dissection of the preperitoneal space: I.
2. Pelvic lymphadenectomy: II.
3. Incision of the endopelvic fascia and dissection of the puboprostatic ligaments: I.
4. Santorini plexus ligation: III.
5. Anterior and lateral bladder neck dissection: II ***and*** dorsal bladder neck dissection: III.
6. Dissection and division of vasa deferentia: III.
7. Dissection of the seminal vesicles: III.
8. Incision of the posterior Denonvillier's fascia—mobilization of the dorsal surface of the prostate from the rectum: III.
9. Dissection of the prostatic pedicles: III.
10. Nerve-sparing procedure: V.

11. Apical dissection, urethral division: IV.
12. Urethrovesical anastomosis;
    dorsal circumference (4, 5, 6, 7, 8 o'clock stitches): IV.
    3 and 9 o'clock stitches: II.
    Bladder neck closure and 11 and 1 o'clock stitches: III.

The improved view has allowed a more precise 'intrafascial' nerve-sparing modification during mobilization of the gland, with dissection between the prostatic capsule and the inner layer of covering fascia (Fig. 7.9). In highly experienced hands, LRP operating times are comparable to those of open RP.

Robot-assisted RP: has gained popularity in the USA (where >80% RPs are now done this way) and increasingly in Europe since its introduction in 2000. As with laparoscopic/endoscopic prostatectomy, it is minimally invasive with advantages of reduced bleeding, pain, and recovery time. Beyond this, the benefits remain uncertain in the absence of randomized trials. The training 'learning curve' is thought to be steeper than that of manual laparoscopy because of the intuitive 'wristed' instrumentation of the da Vinci® surgical system. The patient is positioned in a steep reverse Trendelenberg so great care must be taken to avoid lower limb circulatory complications, e.g. compartment syndrome. It is carried out via six transperitoneal ports (one camera, three robot arms, two assistants). Steps followed are similar to those of LRP, except the vesicourethral anastomosis is completed with a double-ended continuous suture rather than interrupted sutures. The surgeon sits at a remote console, while the assistant stands with the robot 'cart' at the patient side. The major disadvantage to robot-assisted RP is cost, currently approximately £1M plus £100K annual maintenance. Operating times also tend to be longer than open RP.

Bilateral pelvic lymphadenectomy (BPLND)

There is no longer a place for frozen section analysis of lymph nodes, with a view to aborting RP if they are positive; aside from the technical issues concerning the pathological evaluation of frozen sections, at least two studies have demonstrated improved CSS in patients with lymph node invasion (LNI) who still underwent RP compared to those who did not. The EAU 2012 Guidelines recommend no BPLND for low-risk cases (because the risk of LNI <5%). High-risk localized disease and cT3 are associated with 15–40% and 45% risk of LNI, respectively. Limited (obturator fossae) BPLND inadequate for intermediate and high-risk cases, missing up to 60% of LNI compared with extended BPLND, which includes removal of internal and external iliac nodes.

Extended BPLND should yield >20 nodes. It, therefore, gives more accurate pN staging and guides further management options. However, it increases operative time and complications (lymphoedema, DVT, PE). Therapeutic benefit is controversial; no randomized trial exists, demonstrating improved outcome following extended BPLND; number of nodes (regardless of status) removed is reported to correlate with BRFS and CSS; the greater number of positive nodes removed correlates with CSS in one report.

1 Stolzenberg JU, Schwaibold H, Bhanot SM, *et al.* (2005) Modular surgical training for endoscopic extraperitoneal radical prostatectomy. *BJU Int* **96**:1022–7.

Prostate cancer—radical prostatectomy: post-operative care and complications

Post-operative routine course after RP

- Day 1: mobilize, check FBC, CandE; free fluids.
- Day 2: diet, drains removed, catheter care, encourage bowels.
- Day 3: home.

Some surgeons discharge their patients on day 2, even if bowels have not moved.

Catheter time varies between 7 and 21 days; cystography is carried out if early removal (<7 days) is planned or if there has been a urine leak or persistent haematuria.

Complications of RP

General complications

- Those of any major surgery (all rare 1–2%): bleeding requiring reoperation and/or transfusion (especially after open RP), infection, VTE, and lower limb compartment syndrome (possible after RARP). Risks are minimized by attention to haemostasis, prophylactic antimicrobials, careful positioning, and early mobilization. VTE prophylaxis consists of TED stockings, pneumatic calf compression, and SC LMWH (unfractionated heparin for patients with renal impairment); NICE (2010) recommends continuing heparin for 28 post-operative days. Chest infection may be prevented by physiotherapy and encouragement of deep breathing, especially in smokers. Post-operative death is estimated to occur <1 in 500 cases.

Specific complications (early)

- Perioperative ureteric or rectal injury (both rare, <0.5%): these should be managed immediately, if recognized; ureteric re-implantation, primary rectal closure with or without a loop colostomy.
- Post-operative catheter displacement (rare): managed with careful replacement if within 48h; if >48h, urethrography may reveal no anastomotic leak.
- Post-operative urine or lymphatic leak (distinguished by dipstick glycosuria or creatinine concentration) through drains (occasional, 5%); managed by prolonged catheter and wound drainage; lymphatic leaks may require sclerotherapy with tetracycline.

Specific complications (late)

- Erectile dysfunction (ED): affects 60–90% of patients; spontaneous erections can return up to 3y post-operatively. Men >65y or with pre-existing ED are more likely to suffer long-term. Nerve-sparing techniques imporve outcomes. 40–70% respond to oral PDE5 inhibitors at 6 months while others require intraurethral or intracavernosal prostaglandin E1 treatments, a vacuum device, or rarely a prosthesis.

- Incontinence (stress type): requiring >1 pad/day affects 5% of patients beyond 6 months; this is due to injury of the external urethral sphincter during division and haemostatic control of the dorsal vein complex. Predisposing factors include age >65y and excessive bleeding. Preoperative teaching of pelvic floor exercises helps to regain continence; periurethral bulking injections, a urethral sling, or implantation of an artificial urinary sphincter are occasionally necessary. Incontinence may also develop secondary to bladder neck stenosis or detrusor instability; flow rates, post-void residual measurement, urodynamics, and cystoscopy may help.
- Bladder neck stenosis: affects 5% of patients. It typically presents 3–9 months post-operatively, patients complaining of poor flow and frequency/urgency of micturition. Predisposing factors include heavy bleeding, post-operative urinary leak, and previous TURP. It is treated by endoscopic bladder neck incision and rarely becomes a recurrent problem.

In experienced hands, the *complications of laparoscopic/endoscopic/robot-assisted RP* are comparable to those of open RP. Blood loss is significantly less. Earlier full recovery time (30 vs 47 days) has been reported. ED is reduced to 49% at 48 months by the robot-assisted nerve-sparing technique.[1]

1 Menon M. *et al.* (2007) Vattikuti Institute prostatectomy: contemporary technique and analysis of results. Eur Urology: **51**, 648-58.

Prostate cancer: oncological outcomes of radical prostatectomy

While no randomized studies have compared RP outcomes to those of radiotherapy or brachytherapy, the Swedish SPCG-4 study randomized 695 men aged <75 with low and intermediate risk to RP or WW.[1] After a median follow-up of 12.8y, a 48% risk reduction in CSS (20.4% WW vs 14.6% RP, p=0.01) and a 26% risk reduction in OS (53% WW vs 46% RP, p=0.007) was demonstrated. The number of RP required to save one life was 15 overall, but only 7 for men <65y. In addition, 40% and 66% reductions in metastatic and local progression in favour of the RP group were reported. High-grade cancers were excluded from this trial.

A retrospective analysis of >400 000 patients with localized PC treated by RP, radiotherapy, or observation showed CSS was best in patients up to the age of 80 treated surgically, although patients with high-risk PC aged 70–79 survived equally well when treated either way.[2]

The long-awaited US-based PIVOT (RP vs observation RCT) study has been reported. A total of 731 patients with low- and intermediate-risk PC were randomized and followed up for a median of 10y. No significant CSS difference was found between the two groups (5.8% in RP group vs 8.4%, p=0.09), though RP was associated with improved overall survival in men with PSA >10 (p=0.04) and possibly men with intermediate-risk disease (p=0.07).[3]

Excellent long-term results are seen in well selected patients following RP, particularly those with organ-confined disease and prior lower urinary tract symptoms due to bladder outflow obstruction. Serum PSA is measured a few days after RP, then 6-monthly; it should fall to <0.1ng/mL. The 5y outcomes LRP and RARP are similar to those of open RP. The 10y PSA progression rate following open RP for clinically localized PC, usually defined as a serum PSA >0.2ng/mL, is about 30%. Of these, 80% will fail within 3y of RP and 5% will occur beyond 10y. Without additional treatment, the time to development of clinical disease after PSA progression averages 8y.[4] A 20y clinical disease-free survival of 60% is reported.[5] Outcome correlates with Gleason score, preoperative PSA, pathological T stage, and surgical margin status. Certain tissue markers, yet to be used routinely, may also predict PSA progression, e.g. aberrant p53 expression in biopsy or RP specimen.[6]

Progression-free probabilities in four prognostic groups are shown in Table 7.21.[7] Probability of biochemical recurrence-free survival following radical prostatectomy can be predicted for individual patients using preoperative or post-operative factors (PSA, PSA doubling time, pT stage, and Gleason score) using various tables,[8] nomograms,[9,10] (Fig. 7.10) or estimated online, at: http://www.mskcc.org/mskcc/applications/nomograms/PostRad Prostatectomy.aspx.

Neoadjuvant hormone therapy (hormone therapy given 3 months prior to RP) does not alter the biochemical recurrence-free survival, despite apparently reducing the incidence of positive surgical margins.

Management of biochemical relapse post-RP

The definition of rising PSA is controversial, though most agree >0.2ng/mL. Biopsy of the vesicourethral anastomosis is not recommended unless there is a palpable abnormality. Studies have shown that CT and bone scans are rarely helpful in searching for metastatic disease unless the PSA is >7ng/mL. ^{11}C-choline PET/CT is reported be helpful even when PSA <1.0.

Current management options include observation, pelvic radiotherapy (66Gy), or hormone therapy. A good response to pelvic radiotherapy is likely if:

- PSA rise is delayed > 1y post-RP.
- PSA doubling time >12 months.
- PSA is <1ng/mL.
- Low-grade and low-stage disease.

If the PSA never falls below 0.2 or it rises in the first year with a doubling time of less than 10 months, the response to pelvic radiotherapy is usually disappointing. It is likely in these circumstances that metastatic disease is present; hormone therapy, either non-steroidal antiandrogen monotherapy (e.g. bicalutamide 150mg daily) or androgen deprivation, may be recommended. There are no comparative outcomes data in this clinical setting so discussion focuses on the side effects.

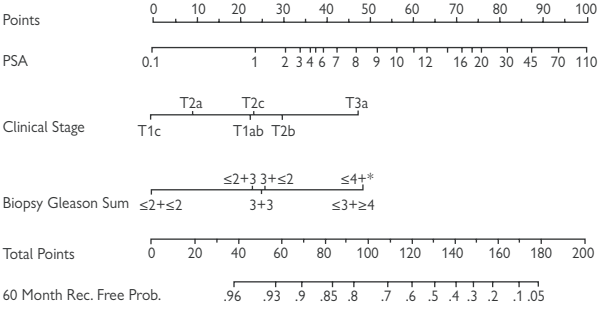
Adjuvant vs salvage RT

Standard care in the UK has been to refer for salvage radiotherapy if the PSA rises consecutively above 0.2ng/mL following RP. It is unclear whether patients considered at risk of relapse benefit in terms of overall survival from immediate (adjuvant) RT. However, three randomized trials (EORTC 22911, German intergroup, and SWOG 8794) have shown significant improvements in biochemical disease-free survival and SWOG 8794 demonstrated improved metastasis-free survival following adjuvant RT (compared with salvage RT) for pT3 and margin-positive patients. In UK, the RADICALS trial is ongoing. The effect of adjuvant RT on continence recovery following RP also merits investigation.

Table 7.21 Progression-free probabilities in four prognostic groups by PSA and by margin status, following RP

Pathological stage	Progression-free 5y (%)	Progression-free 10y (%)
Gleason 2–6, T1–3, margin –ve	97	95
Gleason 2–6, T1–3, margin +ve OR Gleason 7, T1–3, margin –ve	86	72
Gleason 8–10, T1–2, margin +/–ve, OR Gleason 8–10, T3, margin –ve OR Gleason 7–10, T3, margin +ve	62	41
Any LN +ve	37	13
PSA <4	91	
PSA 4–9.9	87	
PSA 10–19.9	70	
PSA 20–50	50	
Margin clear		81
Margin positive		36*

* Only 40–50% of patients with a positive surgical margin after RP develop a rising PSA.



Instructions for Physician: Locate the patient's PSA on the PSA axis. Draw a line straight upwards to the Points axis to determine how many points towards recurrence the patient receives for his PSA. Rapeat this process for the Clinical Stage and Biopsy Gleason Sum axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a line straight down to find the patient's probability of remaining recurrence free for 60 months assuming he does not die of another cause first.

Note: This nomogram is not applicable to a man who is not otherwise a candidate for radical prostatctomy, You can use this only on a man who has already selected radical prostatectomy as treatment for his prostate cancer.

Instruction to Patient: "Mr. X, if we had 100 man exactly like you, we would expect between <predicated percentage from nomogram – 10%> and <predicated percentage + 10%> to remain free of their disease at 5 years following radical prostatectomy, and recurrence after 5 years is very rare."

Fig. 7.10 A pre-operative nomogram per prostate cancer recurrence. Reproduced from Kattan.[11]

1 Bill-Axelson A, Holmberg L, Ruutu M, *et al.* (2011) Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* **364**:1708–17.

2 Abdollah F, Sun M, Thuret R, *et al.* (2011) A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. *Eur Urol* **59**:88–95.

3 Wilt T *et al.* (2012) Radical prostatectomy versus observation for localized prostate cancer. *NEJM* **367**: 203–213.

4 Pound CR, Partin AW, Eisenberger MA, *et al.* (1999) Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* **281**:1591–7.

5 Swanson GP, Riggs MW, Earle JD, *et al.* (2002) Long-term follow-up of radical retropubic prostatectomy for prostate cancer. *Eur Urol* **42**:212–6.

6 Brewster SF, Oxley JD, Trivella M, *et al.* (1999) Preoperative p53, bcl-2, CD44 and E-cadherin immunohistochemistry as predictors of biochemical relapse after radical prostatectomy. *J Urol* **161**:1238–43.

7 Khan MA, Partin AW, Mangold LA, *et al.* (2003) Probability of biochemical recurrence by analysis of pathologic stage, Gleason score, and margin status for localized prostate cancer. *Urology* **62**:866–71.

8 Freedland SJ, Humphreys EB, Mangold LA, *et al.* (2007) Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. *J Clin Oncol* **25**:1765–71.

9 Kattan MW, Eastham JA, Stapleton AM, *et al.* (1998) A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst* **90**:766–71.

10 Katttan MW, Wheeler TM, Scardino PT (1999) Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol* **17**:1499–507.

11 Kattan MW *et al.* (1999) Postoperative nomogram per disease recurrence after radical prostatectomy. *J Clin Oncol* **17**:1499–507.

Prostate cancer: radical external beam radiotherapy (EBRT)

Since the early 1980's, advances in radiotherapy for localized prostate cancer have included the advent of linear accelerators, conformal, and intensity-modulated techniques to minimize toxicity to the rectum and bladder. Increasing the doseage, shaping the beam intensity using multileaf collimators, and more accurate treatment planning by TRUS-guided insertion of gold fiducial markers are becoming the standard of care. EBRT is administered with curative intent to men with a life expectancy >5y, accompanied by 24 months of neoadjuvant/adjuvant androgen deprivation therapy in high-risk cases. A small, randomized study has demonstrated benefit in terms of progression and survival for patients treated with 6 months (2 months each of neoadjuvant, concurrent, and adjuvant) androgen ablation in addition to radiotherapy compared with radiotherapy alone.[1]

Indication

All risk clinically localized prostate cancer, Gleason score ≥6. Patients with Gleason score 2–5 disease appear to do as well with surveillance as with any other treatment at 15y follow-up. The UK 2008 NICE Guidelines recommend low-risk cases (PSA <10 *and* Gleason score ≤6 *and* cT1–2) should first be offered active surveillance.

Contraindications

- Severe lower urinary tract symptoms.
- Inflammatory bowel disease.
- Previous pelvic irradiation.

Protocol

UK 2008 NICE Guidelines recommend conformal fractions (up to 2Gy per treatment), amounting to a minimum dose of 74Gy.

Side effects

- Transient moderate/severe filling-type LUTS (common, rarely permanent).
- Haematuria, contracted bladder 4–23%.
- Moderate to severe gastrointestinal symptoms, bloody diarrhoea, pain, rectal stenosis 3–32%.
- Erectile dysfunction gradually develops in 30–50%.
- The risk of a second solid pelvic malignancy is estimated to be 1 in 300, falling to 1 in 70 long-term survivors.

Outcomes of EBRT

Definitions of treatment failure: the 2005 Phoenix definition is the time at which the PSA rises by 2ng/mL or more above the nadir. This has succeeded the complicated and flawed 1996 ASTRO (American Society of Therapeutic Radiation Oncologists) definition which required three consecutive PSA increases above the nadir measured 4 months apart.
Pretreatment prognostic factors: PSA, Gleason score, clinical stage, percentage of positive biopsies.

10-year biochemical disease-free survival using IMRT delivered at 81Gy is:

- 81% for *low-risk disease* (T1–2a and PSA <10ng/mL and Gleason ≤6).
- 78% for *intermediate-risk disease* (T2b or PSA 10–20 or Gleason 7).
- 62% for *high-risk disease* (T2c or PSA >20ng/mL or Gleason 8–10).

Treatment of PSA relapse post-EBRT

Hormone therapy, either with antiandrogens or androgen deprivation, is currently the mainstay of treatment in this setting. However, local salvage treatments appear attractive, potentially offering another chance of cure if metastases cannot be demonstrated at repeat staging. *Salvage radical prostatectomy* is seldom undertaken because it is associated with highly morbidity and disappointing oncological outcomes. Other local salvage treatments include *brachytherapy*, *cryotherapy* and *high-intensity focused ultrasound (HIFU)* (see 🕮 p. 348). If salvage local treatment is under consideration, repeat prostatic biopsies should be taken to demonstrate viable tumour cells. This should be at least 18 months post-EBRT, because fatally damaged cells may survive a few cell divisions.

Individual predictions of 6y progression-free probability can be found online at: 🖱 http://nomograms.mskcc.org/Prostate/SalvageRadiationTherapy.aspx.

1 D'Amico AV *et al.* (2004) 6-month androgen suppression plus radiotherapy vs. radiation alone for patients with clinically-localized prostate cancer: a randomised drug trial. *JAMA* **292**:821–7.

Prostate cancer: brachytherapy (BT)

The commonly used low-dose rate (LDR) BT is ultrasound-guided transperineal implantation of radioactive seeds, usually I^{125}, into the prostate. It is currently popular, having failed in the 1970's, prior to transrectal ultrasonography. BT is minimally invasive, requires general anaesthesia, and is completed in one or two stages. Either way, approximately 150Gy is delivered and this may be augmented by an EBRT boost in high-risk cases. Another approach, high-dose rate (HDR) BT is to use iridium^{192} wires, left for several hours *in situ* in a series of applications, either before or after EBRT. The treatment is expensive due to the cost of the consumables.

Indications for BT: low- and intermediate-risk localized prostate cancer, cT1–2, and Gleason ≤7 and PSA <20; life expectancy >5y. The 2008 UK NICE Guidance suggests patients with low-risk disease (PSA <10 and Gleason score ≤6 and cT1–2) should first be offered active surveillance and for those with intermediate-risk disease, radical prostatectomy or conformal radiotherapy are preferred treatments.

Indications for BT with EBRT: T1–3, Gleason 7–8, PSA <20, prostate cancer.

Contraindications to BT: previous TURP (increases risk of incontinence); large volume prostate (>60mL) causes difficulty with seed placement due to pubic arch interference unless cytoreductive hormone therapy is used; moderate to severe lower urinary tract symptoms, IPSS >12 (increases risk of retention).

Complications of LDR BT

- Perineal haematoma (occasional).
- Lower urinary tract symptoms (common) due to prostatic oedema post-implant.
- Urinary retention (5–20%); α-blockers are often used to treat LUTS and to improve the chance of successful trial without catheter in patients with urinary retention.
- Incontinence (5%), usually if TURP is required to treat urinary retention.
- ED affects up to 50% of patients, gradual onset.
- Seed migration; second primary cancer (rare).

Outcomes of BT

PSA rises in the first 3 months post-implant ('PSA bounce'), then subsequently declines. As with EBRT, the ASTRO or Phoenix definitions (see 🕮 p. 344) are used to define progression. Neoadjuvant androgen ablation therapy is often used.

- 7y biochemical progression-free survival (bPFS) for low-risk disease (cT1c–2a, Gleason <7, PSA <10ng/mL) is 80–90%; 10y bPFS for low-risk disease is 60%.
- 7y bPFS for intermediate-risk disease (T2b, PSA 10–20ng/mL, Gleason 7) is 70–80%.
- 7y bPFS for high-risk disease (T2c, PSA >20ng/mL, Gleason >7) is 50–60%.

Individual predictions of 5y progression-free probability can be found online at: http://www.mskcc.org/mskcc/applications/nomograms/PreTreatment.aspx.

Outcomes of BT plus EBRT (usually with androgen ablation)

- 15y bPFS for low-risk disease is 86%.
- 15y bPFS for moderate-risk disease is 80%.
- 15y bPFS for high-risk disease is 68%.

Comparisons of BT or BT plus EBRT with RP or EBRT alone

These are confounded by treatment heterogeneity. There are no randomized studies.

In non-randomized comparisons, an age and tumour-matched radical prostatectomy series at 8y yielded a progression-free survival of 98%, compared to 79% with BT alone. Outcome of BT alone appears inferior to EBRT and RP in men with PSA >10 and Gleason score 7–10.

Rising PSA post-BT

Salvage radical prostatetcomy, EBRT, cryotherapy, or HIFU are options if local recurrence is suspected; calculation of PSA doubling time, repeat biopsy, and staging are necessary to select suitable cases. Whilst offering a further chance of cure, morbidity is higher with all, compared to their use in primary treatment (e.g. prostate–rectal fistula rates are ≥5% vs 1% for primary cases). If metastatic disease is suspected or proven, further local treatment is unjustified.

Salvage brachytherapy following EBRT treatment failure is gaining popularity in some centres. Biochemical 5y disease-free rates of 34–53% are reported, with moderate toxicity.

Prostate cancer (minimally invasive management of localized and radio-recurrent prostate cancer): cryotherapy, high-intensity focused ultrasound, and photodynamic therapy

Minimally invasive treatments for localized prostate cancer currently evolving are attractive to patients and their doctors. Proponents claim them to be alternatives to radical surgery or radiotherapy with shorter hospital stay and less morbidity; they are also the only potentially curative options for 'salvage' treatment of organ-confined recurrent disease following radical radiotherapy since most surgeons will not offer salvage prostatectomy.

Careful patient selection and mentored training is important to achieve good results. No randomized outcomes data exist. The 2008 UK NICE guidance recommended that these technologies should be used only in the setting of a controlled clinical trial.

Cryotherapy

This involves transperineal ultrasound-guided placement of cryoprobes delivering argon or liquid nitrogen at temperature –20°C to –40°C. When applied in two cycles of freeze thaw, cellular necrosis occurs. The diameter of the ice ball is monitored using ultrasound; precautions are taken to protect the urethra, external sphincter, and rectal wall such as warming devices. An anaesthetic is required although this is a day case procedure which can be repeated.

Results: PSA nadir is usually achieved within 3 months; 25–48% of men with localized disease achieve a PSA nadir of <0.1ng/mL in 3 months and 96% of men achieved PSA <0.2ng/mL within 6 months. Positive biopsies are observed in 8–25% of patients after cryotherapy.

Complications

Erectile dysfunction (40–80%); incontinence (4–27%); lower urinary tract symptoms due to urethral sloughing; pelvic pain; transient penile numbness; rectourethral fistula (rare).

In the **salvage** setting, good short-term PSA responses are reported in 66% of men at the expense of significant morbidity, including incontinence and urinary retention (70% each). In a contemporary UK series, 5y freedom from PSA progression (ASTRO definition) was 73%, 45%, and 11% in low-, medium-, and high-risk patients, respectively. Careful disease staging with prostate biopsy and MRI is important; the best results are seen when the PSA is <4ng/mL. Persistent incontinence developed in 13% of patients while 1% developed rectourethral fistula.

HIFU

HIFU allows the selective destruction of tissues at up to 4cm depth without damaging intervening structures, most importantly the rectal wall. Tissue is heated to the point of coagulative necrosis (over 85°C) by high energy ultrasound transmitted to the prostate using a transrectal device. Numerous 6 × 2 × 2mm cigar-shaped lesions are produced side by side to create a continuous volume in which the tissue is ablated. An anaesthetic is required although this is a day case procedure which can be repeated.

Results: from a large (n=463) French series, PSA nadir is usually achieved within 4 months; 77% patients achieve PSA nadir 0.5ng/mL or less. At 2y median follow-up, 64% remained disease-free by the Phoenix definition. In a Japanese series of 181 patients, half of whom received neoadjuvant androgen ablation, the 3y BDFS (ASTRO definition) for low-, intermediate-, and high-risk PC was 94%, 75% and 35%, respectively.

Complications: erectile dysfunction (50%), urinary retention 8%, urethral stricture (10–25%), stress incontinence (2%), and rectourethral fistula (1%).

Data for HIFU in the **salvage** setting are scarce. Good PSA responses are reported in 61% of men, with 38% remaining disease-free in a mixed group of patients. Morbidity is increased in the salvage treatment setting, rectourethral fistula or osteomyelitis are seen in ≥5%.

Another technology, **photodynamic therapy (PDT)**, is also under investigation in the salvage setting. This involves parenteral administration of a chlorophyll-derived photosensitizing drug (Tookad®) followed by light activation using transperineal template-guided interstitial laser. The free radicals generated cause thrombosis of nearby vasculature and ischaemic tissue necrosis. Phase I studies have yielded promising results and multicentre phase II PDT studies are in progress.

Focal therapy

Whilst currently treating the whole prostate, these technologies are potentially suitable for *focal ablation* of localized PC; such a strategy could reduce morbidity, treatment time, and cost; currently under investigation in the UK and USA.

Prostate cancer: management of locally advanced non-metastatic disease (T3–4 N0M0)

Radical prostatectomy (RP)

RP has traditionally been discouraged for men with cT3 disease in the UK. However, younger men with apparently non-metastatic mobile disease may benefit from surgery as part of a multimodality treatment plan. Proponents accept that 50–80% will require additional treatment, but argue that 27% of cT3 cases are pathologically organ-confined. Cyto-reductive surgery for pT3 disease could reduce morbidity from local progression and improve oncological outcome while concurrent extended BPLND (lymphadenectomy) provides additional staging and possible therapeutic value. A 10y cancer-specific survival following RP plus BPLND for cT3 PC is 73% for low-grade, dropping to 30% for high-grade disease. Outcomes are better for patients with PSA <10ng/mL. Lymph node metastases will be found in around 40% of patients with cT3 PC. There are survival data suggesting that RP should not be abandoned if lymph node metastases are identified at time of surgery (frozen section of nodes should not be done) and that removal of the prostate may reduce risk of development of metastases compared with radiotherapy treatment.[1] EAU 2012 Guidelines state that RP is an option for selected, well-informed, fit patients with cT3a PC, PSA <20ng/mL, and Gleason score ≤8. Clinical trials in this area are urgently required.

EBRT in combination with androgen ablation therapy (AAT) is currently the gold standard treatment for cT3–4 PC in fit men. The combination consistently demonstrated better outcomes compared to EBRT alone, which is associated with a 15–30% 10y survival. In a European randomized study,[2] the ADT group received LHRH analogues for 3y starting at time of EBRT. The 5y overall survival was 79% compared to 62% in the group treated with EBRT alone; the 5y cancer-specific survival was 85% compared to 48%. A randomized trial (MRC PR07) of hormone therapy alone vs EBRT plus hormone therapy of 1200 patients with cT3N0M0 PC reported recently cancer-specific survival at 7y follow-up was significantly (8%) better in the combination arm. The optimal timing and duration of AAT remains unclear; the 2008 UK NICE Guidance recommends neoadjuvant and concomitant AAT for 3–6 months, increasing to a minimum of 2y if the Gleason score ≥8; the EAU 2011 Guidelines recommend EBRT dose of ≥74Gy with 3y of concomitant and adjuvant AAT.

Pelvic EBRT may be considered if risk of N+ disease >15%, according to the Roach formula: 2/3 PSA + (10 × [Gleason score – 6]). However, the historic evidence of benefit for whole pelvic EBRT in locally advanced PC is unconvincing; randomized trials involving contemporary patients are ongoing.

Minimally-invasive treatments such as *LDR brachytherapy*, *HIFU*, and *cryotherapy* are not recommended outside clinical trials. *High-dose rate brachytherapy* in combination with AAT is becoming popular, though long-term trial outcomes are awaited.

Bisphosphonates are not currently recommended to prevent PC bone metastases.

Hormone therapy alone is an option for symptomatic elderly patients or those unwilling to undergo EBRT, especially if the disease is bulky, the PSA is >25ng/mL, or the PSA doubling time is <1y. In this setting, a non-steroidal antiandrogen, such as bicalutamide 150mg daily, has equivalent efficacy to androgen ablation by orchidectomy or LHRH analogue, with reduced side effects. Patient counselling should include the explanation that hormone therapy is not a curative treatment.

Watchful waiting is an option for non-metastatic T3 disease in an elderly asymptomatic patient who may prefer to avoid side effects of treatment.

Palliative treatment of locally advanced disease

See also 🕮 p. 362. Palliative TURP or medical therapy for LUTS or urinary retention may be necessary. Incontinence can be a problem due to sphincter involvement, though bladder outflow obstruction and instability should be considered. A urinary convene sheath or catheter may be required. Patients may present in renal failure; percutaneous nephrostomy or ureteric stenting are occasionally necessary for bypassing ureteric obstruction. ADT in this setting may relieve this tumour compression of the distal ureters. Very rarely, a colostomy is necessary to bypass a rectal stenosis. Palliative EBRT may be useful for treatment of persistent prostatic haematuria or perineal pain.

1 Zelefsky MJ *et al.*, (2010) Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. *J Clin Oncol* **28**: 1508–13.

2 Bolla M, Gonzalez D, Warde P, *et al.* (1997) Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* **337**:295–300.

Prostate cancer: management of advanced disease—hormone therapy I

Metastatic disease is the cause of nearly all prostate cancer-related death. Currently incurable, the 5y survival is about 35%; 10% survive <6 months, while <10% survive >10y. The gold standard treatment is hormone therapy (usually androgen ablation), with cytotoxic chemotherapy for progression and novel treatments (such as growth factor inhibitors, angiogenesis inhibitors, immunotherapy) in development. The concept of hormone therapy was realised in 1941 when Chicago physicians, Charles Huggins and Clarence Hodges, reported favourable symptomatic and biochemical (acid and alkaline phosphatase) responses in metastatic PC patients when castrated or given oestrogens.[1]

Hormone dependence of prostate cancer

All prostate epithelial cells, with the exception of rare undifferentiated stem cells, are dependent on androgens and fail to grow or undergo programmed cell death (apoptosis) in their absence. Similarly, most previously untreated prostate cancer cells are dependent on androgens. In men, 95% of circulating androgen, mainly testosterone, is produced by the testicular Leydig cells under the influence of luteinising hormone (LH). The anterior pituitary synthesises LH, stimulated by hypothalamic LH-releasing hormone (LHRH). The remaining 5% of circulating androgen (mainly dehydoepiandrosterone) is synthesized by the adrenal cortex from cholesterol, under the influence of pituitary ACTH. Testosterone is metabolized to the more 5-fold more potent dihydrotestosterone (DHT), by 5α-reductase (5AR) enzymes types 1 and 2. DHT binds cytoplasmic androgen receptor which translocates to the nucleus, there activating transcription of androgen-responsive genes which drive the cell cycle or inhibit apoptosis.

Androgen deprivation results in a reduction in PSA and clinical improvements in >70% of patients. However, most patients with metastatic disease will still die within 5y due to the emergence of **castrate-resistant growth**. This may be due to selection of androgen-independent cell clones or intracellular androgen biosynthesis. The mean time to disease progression after androgen deprivation is 14 months in men with metastatic disease.

Prognostic factors

Predictors of poor hormone therapy response include:

- ≥5 metastatic lesions at presentation.
- Elevated alkaline phosphatase at presentation.
- Anaemia at presentation.
- Poor performance status (level of activity) at presentation.
- Low serum testosterone at presentation.

- Failure of bone pain to improve within 3 months of treatment.
- Failure of PSA to normalize (to <4ng/mL) within 6 months of treatment; (conversely a PSA nadir (= lowest value) of <0.1ng/mL predicts a long-term response).

1 Huggins C, Hodges CV (1941) Studies on prostate cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* **1:** 293–7.

Prostate cancer: management of advanced disease—hormone therapy II

Methods of androgen ablation therapy

- Surgical castration: *bilateral orchidectomy*.
- Medical castration:
  - LHRH agonists.
  - LHRH antagonists.
  - Oestrogens.
- Maximal androgen blockade (MAB): medical or surgical castration plus antiandrogen.

Both forms of castration have equivalent efficacy so patients can be given the choice. Oestrogens are no longer used first-line due to the significant cardiovascular morbidity observed when they were the only alternative to orchidectomy. MAB has a theoretical advantage over castration in blocking the effects of the adrenal androgens; significant clinical advantages (>5% improved 5y survival) have not been demonstrated by trial meta-analyses.

Bilateral orchidectomy (subcapsular technique)

A simple procedure, usually carried out under general anaesthesia. Through a midline scrotal incision, both testes may be accessed. The tunica albuginea of each testis is incised and the seminiferous tubules removed, after which the capsule is closed. The epididymes and testicular appendages are preserved. Post-operative complications include scrotal haematoma or infection (both rare). Serum testosterone falls within 8h to <50ng/dL.

LHRH agonists

LHRH agonists (or analogues) were developed in the 1980's, giving patients an alternative to bilateral orchidectomy, with which they are considered clinically equivalent. They are given by subcutaneous or intramuscular injection, as monthly or 3-monthly depots. Examples include goserelin, triptorelin, and leuprorelin acetates. A 6-monthly triptorelin formulation is recently available.

When the anterior pituitary is overstimulated by an agonist of LHRH, it switches off LH synthesis, although serum testosterone rises in the first 14 days due to a surge of LH. This can result in *'tumour flare'*, manifest in a small number of patients by increased symptoms, including catastrophic spinal cord compression. To prevent this, cover with antiandrogen is recommended for a week before and two weeks after the first dose of LHRH agonist. There is awareness that on occasions, the serum testosterone level may not be suppressed to castrate levels by all LHRH agonists.

One **LHRH antagonist**, *degarelix*, is currently licensed in Europe. Given by monthly subcutaneous injection, it rapidly reduces serum testosterone to castrate, abolishing the issue of tumour flare and antiandrogen cover. To date there are no published clinical trials comparing immediate or long-term outcomes of LHRH agonists and antagonists.

Side effects of bilateral orchidectomy and LHRH agonists/antagonists

- Loss of sexual interest and ED.
- Hot flushes and sweats can be frequent and troublesome during work or social activity.
- Weight gain.
- Lethargy, fatigue.
- Gynaecomastia.
- Anaemia.
- Cognitive changes, depression, and memory loss.
- Osteoporosis and pathological fracture (particularly of the hip): secondary to osteoporosis may occur in patients on long-term (>5y) treatment. A single yearly dose of the bisphosphonate, zoledronic acid, appears to maintain bone mineral density, though the clinical advantage this may confer remains uncertain.

Antiandrogens

These are orally bioavailable blockers of the androgen receptor. Examples include bicalutamide (monotherapy dose is 150mg daily or 50mg daily for flare cover or MAB in combination with androgen ablation therapy), flutamide, and cyproterone acetate (CPA). The first two raise the serum testosterone slightly so sexual interest and performance should be maintained although many such patients have pre-existing ED due to the advancing age and disease. Bone demineralization, lethargy, and cognitive changes are not seen with antiandrogens.

Antiandrogen monotherapy with bicalutamide 150mg daily is less effective than ADT in treating metastatic disease, but equivalent for non-metastatic locally advanced disease. It could be offered to such patients who were unsuitable or refusing radiotherapy. Side effects include frequent gynaecomastia, breast tenderness, and occasional liver dysfunction. The troublesome breast toxicity may be reduced or prevented by tamoxifen 20mg twice weekly. Flutamide not uncommonly causes diarrhoea and is now rarely used. Similarly, CPA is rarely used as monotherapy at its full dose of 100mg tds because it is less effective than androgen ablation; it can also cause unpleasant, but reversible, dyspnoea. At 50mg bd, CPA may be helpful for prevention of castration-induced hot flushes.

A new, highly potent antiandrogen, MDV3100, is presently undergoing clinical trials in patients with castration-resistant PC.

Prostate cancer: management of advanced disease—hormone therapy III

Monitoring treatment during ADT

Typically, patients will have baseline PSA, full blood count, renal and liver function tests, a renal ultrasound, and a bone scan. The PSA is repeated after 3 months, 6 months, and 6-monthly thereafter until it rises. Liver function is checked 3-monthly if antiandrogen monotherapy is used. Physical examination including DRE and serum renal function is checked on disease progression; imaging if clinically indicated. While PSA is very useful as a marker for response and progression, 5% of patients show clinical progression without PSA rise. This may occur in anaplastic tumours that fail to express PSA.

Advice on exercise, diet, and treatment of erectile dysfunction is often sought by patients during treatment. Exercise and vitamin D supplements should be encouraged to minimize risk of osteoporotic complications. Patients with bone metastases should be advised to react to symptoms and signs of possible spinal cord compression. If there is a history of bone fractures or osteoporosis, bisphosphonates should be prescribed and bone mineral densitomtry carried out. Specialist nursing and counselling support is much needed by many of these patients.

Immediate vs delayed hormone therapy

Traditionally hormone therapy was reserved for patients with symptomatic metastatic disease. Arguments against immediate use of hormone therapy focused on its side effects and cost. However, studies of patients with locally advanced and metastatic PC have demonstrated slower disease progression and reduced morbidity when treated with androgen ablation early (i.e. before the onset of symptoms). Improved survival has also been reported in patients without bone metastases (but including node-positive disease) when treated immediately. Subgroups of patients <70y old, those with PSA doubling times <12 months and patients with baseline PSA >50ng/mL appear to benefit most.

Trials have demonstrated slower disease progression in patients given bicalutamide 150mg daily (compared with placebo) for 2y after treatment of high-risk locally advanced prostate cancer with RP or RT. This benefit is not seen in patients managed by watchful waiting. The survival advantage for high-risk patients undergoing EBRT combined with ADT provides further evidence of benefit in immediate hormone therapy.

Intermittent hormone therapy

The potential advantages of stopping hormone therapy when the disease has remitted (PSA <4ng/mL), then restarting it when the PSA has risen again (to perhaps 10 or 20 ng/mL) are the reduced side effects, improved quality of life during the 'off treatment' periods, and cost. These have been demonstrated in phase II trials. Of several ongoing phase III studies comparing long-term outcomes of intermittent vs continuous ADT or MAB, only one has so far reported equivalent survival at 5y in men with locally advanced or metastatic disease. Recently another randomized trial of similar design conducted on patients with biochemical failure following radiotherapy has shown no differences in overall survival or CSS after a median follow-up of 7y.[1] None of the LHRH agonists/antagonist or antiandrogens are currently licensed for intermittent therapy, though it is already an option for patients enjoying disease remission who are intolerent of side effects.

1 Crook JM et al. (2012) Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy. *N Engl J Med* 367: 895–903.

Prostate cancer: management of advanced disease—castrate-resistant prostate cancer (CRPC)

CRPC is defined by two consecutive PSA rises from its nadir or symptomatic progression despite a favourable biochemical response, following androgen ablation therapy in the presence of a castrate serum testosterone level (<50ng/dL). Biologically, this state may be due to proliferation of androgen-independent clones, androgen receptor amplification, aberrant stimulation of androgen-dependent transcription pathways, or a block to apoptosis induced by androgen withdrawal. It is recently recognized that intracellular androgen synthesis occurs in cancer cells, which has provided a new therapeutic target. Clinically, CRPC is an incurable, debilitating condition requiring multidisciplinary management, often of frail elderly patients.

Treatment of CRPC, especially with a rapid (<12 months) PSA doubling time, is initially with **second-line hormone therapy.** Up to 25% of patients respond by adding an antiandrogen, e.g. *bicalutamide 50mg daily*, to establish MAB. If MAB was used from initiation of hormone therapy, withdrawal of the antiandrogen paradoxically elicits a favourable response in 25% of patients.

A further rise in PSA may require **third-line hormonal therapy**, such as the addition of oestrogens or corticosteroids. For example, *diethylstilboestrol 1mg daily* with 75mg aspirin for thromboembolic prophylaxis elicits a response in up to 60% of these patients. The mean duration of response is 4 months.

The **prognostic factors** for survival with CRPC are identical to the factors predicting response to hormone therapy (see 📖 p. 352 Hormone therapy I); also time from initiation of hormone therapy to initiation of chemotherapy and visceral metastasis status.

The mean survival at this point ranges from 9 months, in the presence of extensive metastatic disease, to 27 months in asymptomatic patients without demonstrable metastases.

Cytotoxic chemotherapy

Systemic chemotherapy is offered to appropriate patients with CRPC by the medical oncologist. Men with low-volume disease who have failed radical local treatment and hormone therapy are also candidates for chemotherapy. Frail and infirm patients with renal impairment or haematological abnormalities are unsuitable. Correction of renal and bone marrow dysfunction is necessary prior to treatment.

Symptom palliation

This is discussed in further detail on 📖 p. 362. Symptomatic improvements may be achieved with cytotoxic chemotherapy. In a randomized trial of mitoxantrone plus prednisolone vs prednisolone alone, 29% in the combination group experienced a reduction in pain and analgesic use compared with 12% in the 'prednisolone alone' group. PSA response did not predict palliative response. In another study, docetaxel plus prednisolone

produced a pain reduction in 35% compared to 22% of patients given mitoxantrone and prednisolone, resulting in improved quality of life scores.

Bisphosphonates (in particular zoledronic acid) have been shown to reduce skeletal-related events (SRE), such as pathological fractures, in CRPC. Denosumab, an antiosteolytic fully human monoclonal anti-RANKL antibody, is even more effective at preventing SREs and reducing bone pain. Neither agent is currently approved for CRPC by NICE. These agents should be discussed with patients, although side effects can include hypocalcaemia and (rarely) osteonecrosis of the jaw.

Other palliative treatments may include opiate analgesics, external beam radiotherapy to symptomatic primary or metastatic bone lesions, systemic radionuclides (e.g strontium) for widespread bone pain, surgery or drainage procedures for urinary obstruction, and neurosurgery for spinal cord compression (see also 📖 p. 548).

Cancer control

Most single agent cytotoxic chemotherapy trials define response as >50% decrease in PSA. Responses are reported in 20–40% of patients, with haematological toxicity (especially neutropenia), using most agents. Better responses (up to 75%) are reported with combination regimes (for example, estramustine phosphate plus docetaxel), but with greater toxicity. The median survival following chemotherapy ranges from 24 to 44 weeks. Results of two randomized studies comparing docetaxel 3-weekly cycles with mitoxantrone plus prednisolone have shown a 2.4–3 month median survival advantage in favour of docetaxel. This is now the standard care of established CRPC. Toxicity includes neutopenic sepsis in ~5%. While there is interest is evaluating its use in earlier stage disease (for example, in the UK STAMPEDE RCT), docetaxel maintenance and salvage regimens using cabazitaxel (confering a 2.5 month survival advantage compared with mitoxantrone) are already in clinical use.

Novel therapies

While clinical trials of tyrosine kinase and endothelin-1 receptor antagonists have so far yielded disappointing results, promising results are reported for several effective and relatively well tolerated new treatment options for CRPC, including the following agents:

- **Abiraterone**: a CYP450c17 enzyme inhibitor which blocks androgen biosynthesis within cancer cells (Fig. 7.11). Administered orally with prednisolone, it prolongs overall survival in men who have failed docetaxel by 3.6 months compared with prednisolone alone. Mineralocorticoid side effects (hypokalaemia, hypertension, cardiac failure) occur in 8% (3% serious). FDA and European licensing approval is granted; NICE has approved the use of Abiraterone in 2012 for patients with CRPC who are progressing after docetaxel.
- **Enzalutamide:** an orally bioavailable androgen receptor antagonist, 5-fold more potent than bicalutamide, which also inhibits the process by which the receptor–hormone complex is transported to the cell nucleus. Trials in men with chemorefractory and chemonaive CRPC have shown median times to PSA progression of 21 and 41 weeks, respectively. A placebo-controlled RCT has demonstrated a 4.8 month

median overall survival advantage in patients with docetaxel-refractory disease when treated with oral Enzalutamide.[1]

- **Provenge®** (sipuleucel-T) vaccine: this is the first patient-derived FDA-approved CRPC immunotherapy against prostatic acid phosphatase. A 4-month survival advantage has been demonstrated over placebo in trials of men suffering minimally symptomatic CRPC. Serious infusion-related adverse events occur in 3% of patients. It is estimated to cost around £60 000 for three doses.
- **Radium-223 (alpharadin)**: reduced bone SREs and prolonged survival by 3 months in a UK placebo-controlled RCT of 922 CRPC patients.

The future challenge in treating patients with advanced CRPC will be the *sequencing and/or combination of agents* in order to obtain the best results in terms of survival, quality of life, and cost-effectiveness.

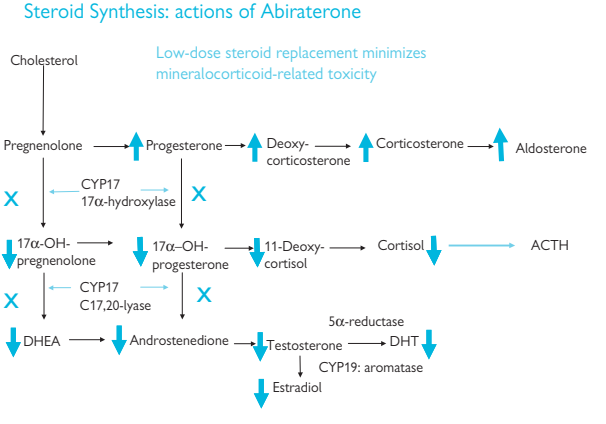


Fig. 7.11 A diagram showing testicular, adrenal, and prostatic metabolism of cholesterol, with inhibition of CYP17 17-alpha hydroxylase, C17,20 lyase by abiraterone.

1 Scher HI, *et al.* (2012) Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. *N Engl J Med* DOI: 10.1056/NEJMoa1207506.

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Prostate cancer: management of advanced disease—palliative care

Multidisciplinary involvement of the oncologist, urologist, cancer nurse specialist, palliative care, and acute pain teams is often necessary in the terminal phase of the illness to optimize the patients comfort and quality of life.

Pain is undoubtedly the most debilitating symptom of advanced prostate cancer. The pathogenesis of this pain is poorly understood, but there is known to be increased osteoclastic and osteoblastic activity. Table 7.22 categorizes the pain syndromes and their management. *Androgen ablation therapy* is effective in newly presenting disease. In castrate-resistant disease, *bisphosphonates* (especially zolendronic acid) can reduce bone pain in up to 80% patients and the risk of skeletal complications such as pathological fracture. Chemotherapy also has a palliative role.

Table 7.22 Pain syndromes and their management

Pain type	Initial management	Other options
Focal bone pain	Medical: simple, NSAIDs, opiates Single-shot radiotherapy, 800cGy (75% respond up to 6 months)	Surgical fixation of pathological fracture or extensive lytic metastasis
Diffuse bone pain	Medical: NSAIDs, opiates Multi-shot radiotherapy or radiopharmaceutical (e.g. strontium[89])	Steroids; bisphosphonates (eg. zolendronic acid); denosumab; chemotherapy
Epidural metastasis and cord compression	📖 See p. 548	
Plexopathies (rare—caused by direct tumour extension)	Medical: NSAIDs, opiates Radiotherapy; nerve blocks	Tricyclics; anticonvulsants
Other pain syndromes: skull/cranial nerve, liver, rectum/perineum	Radiotherapy Medical: NSAIDs, opiates, steroids	Intrathecal chemotherapy for meningeal involvement

Spinal cord compression

See 📖 p. 548.

Lower urinary tract symptoms/urinary retention

A TURP may be required for bladder outflow obstruction (BOO) or retention. Instrumentation can be difficult if there is a bulky fixed prostate cancer. The prostate may be friable and bleed spontaneously, causing intractable haematuria; this may temporarily settle following bladder washouts and TURP, but palliative radiotherapy can be helpful for longer-term control; some advocate the use of tranexamic acid with appropriate thromboprophylaxis. The bladder may be contracted due to disease involvement, causing misery even after relief of BOO. This may perhaps respond to anticholinergic therapy or a long-term urethral or suprapubic catheter may be required for persistent voiding symptoms or recurrent retention.

Ureteric obstruction

This is a uro-oncological emergency (see 📖 p. 546). Locally advanced PC and bladder cancer may cause bilateral ureteric obstruction. The patient presents either with symptoms and signs of renal failure, anuric without a palpable bladder, occasionally with signs of sepsis. Renal ultrasound will demonstrate bilateral hydronephrosis and an empty bladder. After treating any life-threatening hyperkalaemia, treatment options include bilateral percutaneous nephrostomies or ureteric stents. A clotting screen is required prior to nephrostomy insertion. Antegrade ureteric stenting following placement of nephrostomies is usually successful. Insertion of retrograde ureteric stents in this scenario is usually unsuccessful because tumour affecting the trigone obscures the ureteric orifices. Hormone therapy should be commenced if not previously used.

Unilateral ureteric obstruction is occasionally observed at presentation or on progression. Usually asymptomatic, this may be managed conservatively provided there is a normal contralateral kidney. Preservation of renal function becomes important if cytotoxic chemotherapy is being considered.

Anaemia, thrombocytopenia, and coagulopathy

Some patients with extensive bone marrow replacement by tumour rapidly and regularly become symptomatic with anaemia. This tends to be normochromic and normocytic, often occurring without other symptoms and with normal renal function. They require regular blood transfusions. Platelet transfusions are rarely required for bleeding/thrombocytopenia. Terminal patients may develop a clinical picture similar to disseminated intravascular coagulation, also leading to problematic haematuria.

Urethral cancer

Primary urethral cancer is very rare, occurring in elderly patients, four times more commonly in women.

Risk factors include urethral stricture and sexually transmitted disease are implicated. Direct spread from tumour in the bladder or prostate is more common.

Pathology and staging

Seventy-five percent are squamous cell carcinomas occurring in the anterior urethra, 15% are TCC occurring in the posterior/prostatic urethra, 10% are adenocarcinomas, and the remainder include sarcoma and melanoma.

Urethral cancer metastasises to the pelvic lymph nodes from the posterior urethra and to the inguinal nodes from the anterior urethra in 50% of patients. Staging is by the TNM system (Table 7.23).

Presentation

- Often late; many patients have metastatic disease at presentation.
- *Painless haematuria*, initial, terminal or a *bloody urethral discharge*.
- *Voiding-type LUTS* (less common).
- *Perineal pain* (less common).
- Periurethral abscess or urethrocutaneous fistula (rare).
- Past history of sexually transmitted or stricture disease.

Examination may reveal a *hard palpable mass* at the female urethral meatus or along the course of the male anterior urethra. *Inguinal lymphadenopathy*, chest signs, and hepatomegaly may suggest metastatic disease.

The differential diagnosis in men is:

- Urethral stricture.
- Perineal abscess.
- Metastatic disease involving the corpora cavernosa.
- Urethrocutaneous fistula.

The differential diagnosis in women is:

- Urethral caruncle.
- Urethral cyst.
- Urethral diverticulum.
- Urethral wart (*Condylomata acuminata*).
- Urethral prolapse.
- Periurethral abscess.

Investigations

Cystourethroscopy, biopsy, and bimanual examination under anaesthesia will obtain a diagnosis and local clinical staging. Chest radiography and abdominopelvic CT scan will enable distant staging.

Treatment

For localized anterior urethral cancer, radical surgery or radiotherapy are the options. Results are better with anterior urethral disease. Male patients would require perineal urethrostomy. Post-operative incontinence due to disruption of the external sphincter mechanism is minimal unless the bladder neck is involved, but the patient would need to sit to void. For posterior/prostatic urethral cancer, cystoprostatourethrectomy should be considered for fit men while anterior pelvic exenteration (excision of the pelvic lymph nodes, bladder, urethra, uterus, ovaries, and part of the vagina) should be considered for women. In the absence of distant metastases, inguinal lymphadenectomy is performed if nodes are palpable since 80% contain metastatic tumour.

For locally advanced disease, a combination of preoperative radiotherapy and surgery is recommended.

For metastatic disease, cytotoxic chemotherapy is the only option.

Table 7.23 5y survival

Surgery: anterior urethra	50%
Surgery: posterior urethra	15%
Radiotherapy	34%
Radiotherapy and surgery	55%

Staging is by the TNM (1997) classification following histological confirmation of the diagnosis (Table 7.24). All rely upon physical examination and imaging, the pathological classification (prefixed 'p') corresponding to the TNM categories.

Table 7.24 TNM staging of urethral carcinoma

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Urethra (male and female)	
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades corpus spongiosum, prostate, or periurethral muscle
T3	Tumour invades corpus cavernosum, prostatic capsule, vagina, or bladder neck
T4	Tumour invades adjacent organs, including bladder
Transitional cell carcinoma of the prostatic urethra	
Tis	Carcinoma *in situ*, prostatic urethra (pu), or prostatic ducts (pd)
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades prostatic stroma, corpus spongiosum, or periurethral muscle
T3	Tumour invades through prostatic capsule, corpus cavernosum, or bladder neck
T4	Tumour invades adjacent organs, including bladder
Nx	Regional (deep inguinal and pelvic) lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node up to 2cm in greatest dimension
N2	Metastasis in a single lymph node >2cm in greatest dimension
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

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Penile neoplasia: benign, viral-related, and premalignant lesions

Benign cutaneous lesions

- **Pearly penile papules:** multiple, small (about 1–3mm) papules running around the circumference of the corona of the glans, occur in 15% of post-pubertal males. They may be mistaken for warts, are not infectious, and require no treatment.
- **Zoon's balanitis:** bright red shiny, erythematous plaque on glans or inner prepuce.
- **Lichen planus:** flat-topped violacious papule.
- **Lichen sclerosus:** also known as *balanitis xerotica obliterans (BXO)*, this is a common sclerosing condition of glans and prepuce. It occurs at all ages and most commonly presents as non-retractile foreskin (phimosis). The meatus and fossa navicularis may be affected, causing obstructed and spraying voiding. The histological diagnosis is usually made after circumcision, with epithelial atrophy, loss of rete pegs, and collagenization of the dermis.
- **Non-specific balanoposthitis:** inflammatory condition of glans and foreskin. Can be caused by bacterial and candidal infections.
- **Psoriasis:** appears as thickened red papules or plaques with well-defined edges and often has a scaly surface.

Benign subcutaneous lesions

- **Peyronie's plaque:** appears in response to microtrauma to small blood vessels. There is strong evidence that genetic factors and drug factors also influence the start of Peyronie's disease.
- **Retention cysts.**
- Syringomas (sweat gland tumours).
- Neurilemoma.
- Angioma, lipoma.
- Iatrogenic pseudotumour following injections.
- Pyogenic granuloma following injections.

Viral-related lesions

- **Condyloma acuminatum:** also known as genital warts, related to human papillomavirus (HPV) infection. Soft, usually multiple benign lesions on the glans, prepuce, and shaft; may occur elsewhere on genitalia or perineum. A biopsy is worthwhile prior to topical treatment with podophyllin; 5% have urethral involvement, which may require diathermy. HPV infection (particularly types 16 and 18) is potentially carcinogenic and condylomata have been associated with penile SCC.
- **Bowenoid papulosis:** a condition resembling carcinoma *in situ*, but with a benign course. Multiple papules appear on the penile skin or a flat glanular lesion. These should be biopsied. HPV is the suspected cause.

- **Kaposi's sarcoma:** first described in 1972, this reticuloendothelial tumour has become the second commonest malignant penile tumour. It presents as a raised, painful, bleeding violacious papule, or as a bluish ulcer with local oedema. It is slow-growing, solitary, or diffuse. It occurs in immunocompromised men, particularly in homosexuals with HIV-AIDS. Urethral obstruction may occur. Treatment is palliative; intralesional chemotherapy, laser or cryoablation, or radiotherapy.

Premalignant lesions

Some histologically benign lesions are recognized to have malignant potential or occur in close association with squamous cell carcinoma (SCC) of the penis. The extent to which SCC is preceded by premalignant lesions is unknown.

- **Bowenoid papulosis:** a condition resembling carcinoma *in situ*, but with a relatively benign course. Single or multiple papules appear on the penile skin. These should be biopsied. HPV is the suspected cause.
- **Bowen's disease:** this is carcinoma *in situ* of the keratinizing genital or perineal skin. Treatment is wide local excision, laser, or cryoablation.
- **Erythroplasia of Queyrat:** also known as carcinoma *in situ* or penile intraepithelial neoplasia of the glans or inner prepuce. A red velvety circumscribed painless lesion though it may ulcerate, resulting in discharge and pain. Treatment is excision biopsy if possible; radiotherapy, laser ablation, or topical 5-fluorouracil may be required.
- **Buschke–Löwenstein tumour:** also known as giant condyloma acuminatum, this is an aggressive locally invasive tumour of the glans. Metastasis is rare, but wide excision is necessary to distinguish it from SCC. Urethral erosion and fistulation may occur.
- **Extramammary Paget's disease:** is a rare slow-growing condition mainly observed in the elderly. It is an intraepithelial adenocarcinoma that involves the area rich in apocrine glands.
- **Verrucous hyperplasia:** manifests as a verrucous, exophytic, or endophytic lesion that typically develops at sites of chronic irritation and inflammation. It is a premalignant lesion that may transform into a slow-growing verrucous carcinoma or squamous cell carcinoma.
- **Cutaneous horn:** rare solid skin overgrowth; extreme hyperkeratosis, the base may be malignant; treatment is wide local excision.

A chronic red or pale lesion on the glans or prepuce is always a cause for concern. Note should be made of its colour, size, and surface features. Early review following steroid, antibacterial, or antifungal creams is recommended; if persistent, biopsy should be recommended.

Penile cancer: epidemiology, risk factors, and pathology

Squamous cell carcinoma (SCC) is the commonest primary penile cancer, accounting for 95% of penile malignancies. Others include Kaposi's sarcoma (3%); rarities include basal cell carcinoma, malignant melanoma, sarcoma, and Paget's disease. Metastases are very rarely seen from bladder, prostate, rectum, and other primary sites.

Incidence and aetiology of SCC

Penile cancer is rare, representing 1% of male cancers. The incidence appears to be decreasing, most occurring in elderly men. Approximately 400 new cases and 100 deaths are reported annually in the UK.

Risk factors for SCC

- **Age:** penile cancer incidence rises during the fifth decade and peaks in the sixth decade. It is unusual below the age of 40.
- **Premalignant lesions:** around 40% of patients with penile SCC are reported to have had a pre-existing penile lesion.
- **Phimosis:** penile cancer is rare in men circumcised neonatally. It is virtually non-existent in Israel. It is thought that chronic irritation with smegma and inflammation (balanitis) is contributory.
- **Geography:** more common in parts of Asia, Africa, and South America, where it accounts for 10–20% of male cancers. Paraguay has the highest worldwide incidence.
- **Human papilloma virus (HPV)** wart infection, especially with types 16 and 18, appear to be associated with 50% of cases.
- **Smoking.**
- **Immunocompromised patients.**
- **History of priapism.**
- **Affected first-degree relative.**

Pathology and staging of penile SCC

Believed to be preceded by *carcinoma in situ*, SCC starts as a slow-growing papillary, flat, or ulcerative lesion on the glans (48%), prepuce (21%), glans and prepuce (9%), coronal sulcus (6%), or shaft (2%). The remainder are indeterminate. It grows locally by superficial spread beneath the foreskin before entering a vertical phase growth pattern, invading the corpora cavernosa, urethra and eventually, the perineum, pelvis, and prostate. Metastasis is initially to the superficial, then deep inguinal lymph nodes and subsequently, to iliac and obturator nodes. Skin necrosis, ulceration, and infection of the inguinal lymph nodes may lead to sepsis or haemorrhage from the femoral vessels. Ten percent metastasize, most commonly to lung(s).

Histologically, SCC exhibits keratinization, epithelial pearl formation, and mitoses. There are 'classic', basaloid, verrucous, sarcomatoid, and adenosquamous histological subtypes. Grading is G1 (20%), G2 (50%), or G3 (30%); grading correlates with prognosis as does the presence of vascular invasion. Staging is by the TNM classification (Table 7.25 and Fig. 7.12).

Prognostic factors for penile SCC

The presence of metastatic node disease is the most important prognostic indicator. Risk groups for N+ disease have been defined, based on the location, size, histological grade, depth of invasion, presence of corporal invasion, and vascular or lymphatic invasion.

Table 7.25 UICC (2009) TNM clinical and pathological classification of penile cancer

T–	**Primary tumour**
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Ta	Non-invasive verrucous carcinoma, not associated with destructive invasion
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1–2)
T1b	Tumour invades subepithelial connective tissue without or with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3–4)
T2	Tumour invades corpus spongiosum/corpora cavernosa
T3	Tumour invades urethra
T4	Tumour invades other adjacent structures
N–	**Regional lymph nodes**
Nx	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph node
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or extranodal extension of regional lymph node metastasis or unilateral/bilateral pelvic lymphadenopathy
M–	**Distant metastases**
M0	No distant metastasis
M1	Distant metastasis

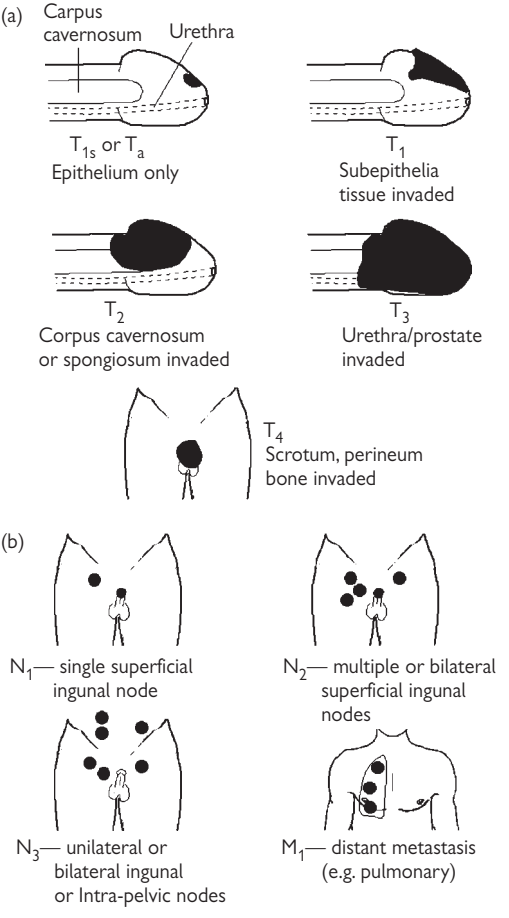

Fig. 7.12 The TNM staging of penile cancer.

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Penile cancer: clinical management

Clinical presentation

A hard painless lump on the glans penis or inner prepuce is the most common presentation. Up to 15–50% of patients delay presentation for >1y due to embarrassment, personal neglect, fear, or ignorance. A bloody discharge may be confused with haematuria. Rarely, a groin mass or urinary retention are presenting symptoms. Examination reveals a solid non-tender mass or ulcer beneath or involving the foreskin. There is usually evidence of local infection. In more advanced disease, the genitalia and even perineum are replaced by a fungating tumour.

Examination

A thorough examination of the abdomen, external genitalia, and inguinal lymph nodes is necessary.

Investigations

A biopsy is usually indicated. Chest, abdomen, and pelvic CT scan is obtained in advanced cases to assess stage and tumour depth of invasion. Penile MRI may be useful when tumour depth is difficult to assess.

Treatment

Following histological diagnosis, management of penile cancer should take place in supraregional centres that can provide multidisciplinary surgical and oncological expertise for this rare disease.

The primary tumour

The first-line treatment of penile cancer, regardless of the inguinal node status, is surgery. *Circumcision* is appropriate for preputial lesions. Penis-preserving surgery such as *glans resurfacing* and *wide excision of glanular lesions with extragenital split skin graft glanular reconstruction* is recommended for penile intraepithelial neoplasia (PIN), Ta–1 G1–2, and carefully selected small T1G3 or T2 tumours, giving safe oncological and good cosmetic and functional results. Alternatives to surgery include *topical 5-fluorouracil* (PIN only), *laser ablation, cryoablation*, *external beam radiotherapy,* or *brachytherapy.*[1]

For tumours confined to the glans and distal corpora, a *glansectomy ± corporal resection* is performed and a neoglans may be reconstructed and covered with extragenital split skin graft with good cosmetic, functional, and oncological outcomes.

Total penile amputation with formation of a perineal urethrostomy is indicated in patients with more extensive lesions. The patient must be psychologically prepared for the inability to have sexual intercourse and need to sit to void urine. Local recurrence occurs in <5% if the excision margins are clear by 1–2mm. The most common complication is urethral meatal stenosis. *Radiotherapy* or *brachytherapy* are non-surgical alternatives, though local recurrence rates of 30–50% are reported; tissue necrosis/damage leads to meatal stenosis (15–30%), urethral stricture (20–35%), fistula, and pain. The use of *neoadjuvant chemotherapy* is under investigation.

Lymphadenopathy

There is controversy regarding the management of patients with initially non-palpable nodes. While the majority overall will not harbour metastatic disease, it is argued that delayed lymphadenectomy could reduce the chance of cure. *Prophylactic inguinal lymphadenectomy* can be offered for high-risk G3 or pT2–4 tumours (risk of N+ disease is 30%), but it has a reported morbidity rate of 30–50%. *Dynamic sentinel lymph node biopsy* is currently being evaluated as an alternative with less morbidity.

For patients with persistent inguinal lymphadenopathy or positive inguinal nodes on dynamic sentinel lymph node biopsy, in the absence of demonstrable pelvic or metastatic disease, *radical inguinal lymphadenectomy* should be undertaken on the appropriate side. The boundaries of the dissection are the inguinal ligament, the adductors and sartorius, with the femoral vessels in the floor. Fine needle aspiration cytology is recommended as 20% of palpable inguinal nodes will be reactive at the time of diagnosis of penile cancer for concomitant infection. *Radiotherapy* and *chemotherapy* are alternative or adjuvant treatments for metastatic nodal disease in unfit, elderly, or inoperable patients; 5y survival 25% (Table 7.26).[2]

Pelvic lymphadenectomy should be considered when two or more positive inguinal nodes are identified at dynamic sentinel lymph node biopsy or inguinal lymphadenectomy or if CT scan has shown enlarged pelvic lymph nodes by CT criteria; here, the likelihood of pelvic node metastasis is 23–56% and cure rates of 14–54% are reported.

Fixed inguinal masses may be considered for salvage surgery following neoadjuvant chemotherapy (response rates 20–60%), ideally within a clinical trial. Rarely, lymphadenopathy ulcerates the skin, may encase the femoral vessels, and invade the deeper musculature. In these circumstances, collaboration with plastic and vascular surgeons is necessary if surgery is considered appropriate.

Distant metastatic disease is treated in a palliative setting using *systemic chemotherapy* with cisplatin-based chemotherapy. Responses are partial and short-lived. Patients with M1 disease are offered *palliative surgery* for their primary tumour as prognosis in this group of patients is extremely poor.

Follow-up

Careful follow-up, initially every 2–4 months, is essential after primary tumour surgery to detect and treat local recurrence early. Groin evaluations of patients with initially non-palpable nodes at similar intervals is necessary since late diagnosis and treatment is a negative prognostic factor. Pelvic, abdominal, and chest CT imaging is justified for those patients who have undergone inguinal lymphadenectomy for metastatic disease.

Table 7.26 5y cancer-specific survival

N0	90–100%
N1	80–95%
N2	60–80%
N3	10–20%
M1	0%

1 Solsona E, Bahl A, Brandes SB, *et al.* (2010) New developments in the treatment of localized penile cancer. *Urology* **76 Suppl 1**:S36–42.

2 Pizzocaro G, Algaba F, Horenblas S, *et al.* (2010) European Association of Urology (EAU) Guidelines Group on Penile Cancer. *Eur Urol* **57**:1002–12.

Scrotal and paratesticular tumours

Carcinoma of the scrotum

Squamous cell carcinoma was originally described in 1775 by London surgeon, Percivall Pott, as 'chimney sweepers' cancer'. Called by the unfortunate individuals 'the soot wart', it was the first cancer to be associated with an occupation. Pott wrote 'It is a disease which always makes its first attack on and its first appearance in the inferior part of the scrotum; where it produces a superficial, painful, ragged, ill-looking sore, with hard and rising edges. In no great length of time, it pervades the skin, dartos, and membranes of the scrotum, and seizes the testicle, which it inlarges, hardens, and renders truly and thoroughly distempered; from whence it makes its way up the spermatic process into the abdomen, most frequently indurating and spoiling the inguinal glands: when arrived within the abdomen, it affects some of the viscera and then very soon becomes painfully destructive'.

Nowadays, a rare disease, chronic exposure of the scrotal skin to soot, tar, or oil was the cause. It presents as a painless lump or ulcer, often purulent, on the anterior or posterior scrotal wall. If posterior, the lesion is concealed from view if the patient is lying or sitting. Inguinal lymphadenopathy may suggest metastasis or reaction to infection.

Treatment of a mass or ulcer on the scrotum is wide local excision. Antimicrobials are administered for 6 weeks if there is lymphadenopathy, after which the groins are re-evaluated. Inguinal lymphadenectomy is considered if lymphadenopathy persists, with adjuvant chemotherapy. Supraclavicular lymphadenopathy, haematogenous visceral, and bony metastasis are rare and carry a poor prognosis.

Tumours of the testicular adnexa

Epithelial tumours arising from the epididymis and paratesticular tissues are rare. They are mostly of mesenchymal origin,

Adenomatoid tumours: small solid tumours arising in the epididymis or on the surface of the tunica albuginea; usually present without change for severaly; benign vacuolated epithelial and stromal cells, origin unknown, treatment is local excision.

Cystadenoma of the epididymis: benign epithelial hyperplasia; young adults; often asymptomatic; one third bilateral and associated with VHL syndrome.

Mesothelioma: presents as a firm painless scrotal mass associated with hydrocele which gradually enlarges; any age group; 15% metastatic to inguinal nodes; treated with orchidectomy and follow-up.

Paratesticular tumours

Rhabdomyosarcoma: scrotal mass in first/second decade; in spermatic cord, compresses testis and epididymis; lymphatic spread to para-aortic nodes; treatment is multimodal radical orchidectomy with radiotherapy and chemotherapy; 5y survival, 75%.

Leiomyoma/sarcoma: scrotal mass age 40–70y; in spermatic cord; 30% are malignant, 70% are benign; haematogenous distant spread; treatment is wide excision or radical orchidectomy.

Liposarcoma: spermatic cord tumour; 70% are malignant.

Testicular cancer: incidence, mortality, epidemiology, and aetiology

Incidence and mortality

Primary testicular cancer (TC) is the most common solid cancer in men aged 20–45, rare below 15y and above 60y. Constituting 1–2% of all male cancers and 5% of all urological tumours, it is considered the most curable cancer. The incidence is increasing in most European countries (although recently it has fallen slightly in UK) while the mortality has fallen steadily since the introduction of platinum-based chemotherapy in the 1980's. Lifetime risk of developing TC is estimated at 1 in 210: 1990 new cases, but only 70 deaths occurring in the UK (2008). Public health campaigns encouraging testicular self-examination (TSE) for young men are ongoing.

Epidemiology and aetiology

- **Age:** the commonest affected age group is 20–45y, with germ cell tumours. Half of all cases occur in men <35y. Non-seminomatous germ cell tumours (NSGCT) are more common at ages 20–35, while seminoma is more common at age 35–45y. Rarely, infants and boys below 10y develop yolk sac tumours and 50% men >60y with TC have lymphoma.
- **Race:** white Caucasian people living in Europe and USA have the highest risk. Whites are three times more likely to develop TC than blacks in the USA. With the exception of the New Zealand Maoris, TC is rare in non-Caucasian races.
- **Previous TC:** confers a 12-fold increased risk of metachronous TC. Bilateral TC occurs in 1–2% of cases.
- **Cryptorchidism:** 5–10% of TC patients have a history of cryptorchidism. Ultrastructural changes are present in these testes by age 3y, although earlier orchidopexy does not completely eliminate the risk of developing TC. According to a large Swedish study, cryptorchidism is associated with a two-fold increased risk of TC in men who underwent orchiopexy <13y old, but risk is increased 5-fold in men who underwent orchiopexy >13y. A meta-analysis showed risk of contralateral TC almost doubles while ipsilateral TC risk is increased 6-fold in men with unilateral cryptorchidism.
- **Intratubular germ cell neoplasia (testicular intraepithelial neoplasia, TIN):** synonymous with carcinoma *in situ*, although the disease arises from malignant change in spermatogonia; 50% of cases develop invasive germ cell TC within 5y. The population incidence is 0.8%. Risk factors include cryptorchidism, extragonadal germ cell tumour, atrophic contralateral testis, 45XO karyotype, Klinefelter's syndrome, previous or contralateral TC (5%), and infertility.
- **Human immunodeficiency virus (HIV):** patients develop seminoma 35% more frequently than expected.

- **Genetic factors:** appear to play a role, given that first-degree relatives are at higher risk by 4–9-fold, but a defined familial inheritance pattern is not apparent.
- **Maternal oestrogen exposure:** at higher than usual levels during pregnancy appears to increase risk of cryptorchidism, urethral anomalies, and TC in male offspring.

Trauma and viral-induced atrophy have not been convincingly implicated as risk factors for TC.

Testicular cancer: pathology and staging

Ninety percent of TC are malignant germ cell tumours (GCT), split into seminomatous and non-seminomatous GCTs for clinical purposes (Table 7.27). Seminoma, the most common germ cell tumour, appears pale and homogeneous. Teratomas are heterogeneous and sometimes contain bizarre tissues such as cartilage or hair. Metastases to the testis are rare, notably from the prostate (35%), lung (19%), colon (9%), and kidney (7%).

Table 7.27 The WHO histopathological classification of testicular tumours

Germ cell tumours (90%)	Other Tumours (7%)
Seminoma (48%) Spermatocytic, classical, and anaplastic subtypes	Epidermoid cyst (benign) Adenomatoid tumour Adenocarcinoma of the rete testis Carcinoid Lymphoma (5%) Metastatic, from another site (1%)
Non-seminomatous GCT (42%) Teratoma: differentiated/mature, intermediate/immature, undifferentiated/malignant Yolk sac tumour Choriocarcinoma Mixed	
Mixed GCT (10%) Sex cord stromal tumours (3% ; 10% malignant) Leydig cell Sertoli cell Mixed or unclassified	
Mixed germ cell/sex cord tumours (rare)	

The right testis is affected slightly more commonly than the left; synchronous bilateral TC occurs in 2.5% of cases. TC spreads by local extension into the epididymis, spermatic cord, and rarely, the scrotal wall. Lymphatic spread occurs via the testicular vessels, initially to the para-aortic nodes. Involvement of the epididymis, spermatic cord, or scrotum may lead to pelvic and inguinal node metastasis. Bloodborne metastasis to the lungs, liver, and bones is more likely once the disease has breached the tunica albuginea.

TC is staged using various classifications, most recently the UICC TNM (2009) system (Table 7.28 and Fig. 7.13). Herein, T stage is pathological, N stage is clinical (physical examination, imaging with CT abdomen and chest) or pathological; M stage involves physical examination, imaging (with CT), and biochemical investigations. An additional S category is appended for serum tumour markers (see 🕮 p. 386).

Table 7.28 TNM staging of testicular germ cell tumours (UICC 2009, 7th edition)

Tx	Primary tumour has not been assessed (no radical orchidectomy)
T0	No evidence of primary tumour
Tis	Intratubular germ cell neoplasia, testicular intraepithelial neoplasia (carcinoma *in situ*)
T1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; may invade tunica albuginea, but not tunica vaginalis
T2	Tumour limited to testis and epididymis with vascular/lymphatic invasion or tumour involving tunica vaginalis
T3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
T4	Tumour invades scrotum with or without vascular/lymphatic invasion
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass ≤2cm and ≤5 lymph nodes, none >2cm
N2	Metastasis with a lymph node mass 2–5cm, or >5 lymph nodes together size 2–5cm, or evidence of extranodal extension
N3	Metastasis with a lymph node mass >5cm
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1a	Non-regional lymph node or pulmonary metastasis
M1b	Distant metastasis other than to non-regional lymph node or lungs

Intratubular germ cell neoplasia (testicular intraepithelial neoplasia, TIN)

The precursor lesion for most testicular GCTs, TIN may be observed adjacent to TC. It is present in the contralateral testis of up to 5% of TC patients. Controversy exists as to whether to biopsy the contralateral testis in all cases to diagnose TIN. At particularly high risk of TIN are patients with small (<12mL) testis, a history of cryptorchidism, and age <30y. If TIN is diagnosed, treatment is with radiotherapy. Consequently, the issues of infertility and hormone replacement need to be discussed with these patients.

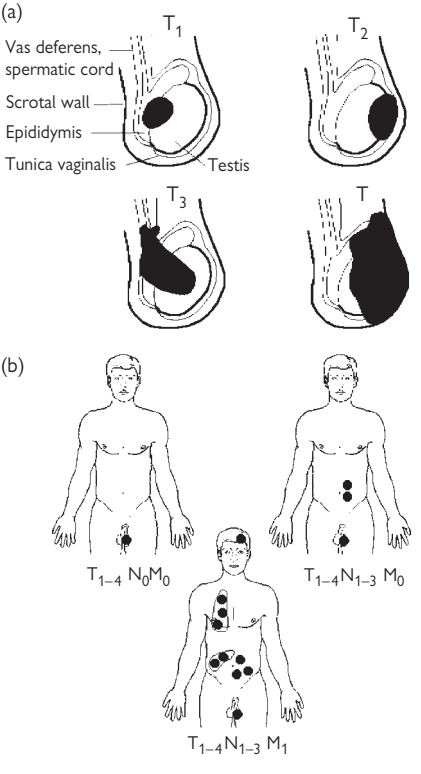

Fig. 7.13 Pathological staging of testicular cancer. (a) Primary tumours T1–4. If radical orchidectomy has not been used, Tx is used. (b) Node/metastasis: para-aortic lymphadenopathy measured in long axis on CT scan (upper fi gure); supraclavicular lymphadenopathy and/or pulmonary metastases—M1a, other distant metastases (e.g. liver, brain); M1b lower figure.

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Testicular cancer: clinical presentation, investigation, and primary treatment

Symptoms

Most patients present with a scrotal lump, usually painless. Delay in presentation is not uncommon, particularly those with metastatic disease. This may be due to patient factors (fear, self-neglect, ignorance, denial) or earlier misdiagnosis. Five percent of patients develop acute scrotal pain due to intratumoural haemorrhage, causing diagnostic confusion. The lump may have been noted by the patient, sometimes after minor trauma, or by his partner. Ten percent of patients develop symptoms suggestive of advanced disease, including weight loss, lumps in the neck, chest symptoms, or bone pain.

Signs

Examination of the genitalia should be carried out in a warm room with the patient relaxed. Observation may reveal asymmetry or slight scrotal skin discoloration. Using careful bimanual palpation, the normal side is first examined, followed by the abnormal side. This will reveal a hard, non-tender, irregular, non-transilluminable mass in the testis or replacing the testis. Care should be taken to assess the epididymis, spermatic cord, and overlying scrotal wall, which may be normal or involved in 10–15% of cases. Rarely, a secondary hydrocele may be present if the tunica albuginea has been breached. General examination may reveal cachexia, supraclavicular lymphadenopathy, chest signs, hepatomegaly, lower limb oedema, or abdominal mass, all suggestive of metastatic disease. Gynaecomastia is seen in about 5% of patients with TC due to endocrine manifestations of some tumours.

Differential diagnoses

Hydrocele, epididymal cyst (spermatocoele), indirect inguinal hernia, TB, or syphilitic gumma (both exceedingly rare nowadays in developed countries) are causes of painless scrotal swellings. Varicocele is normally apparent only when the patient is standing. Epididymal 'sperm granuloma', testicular torsion, and acute epididymo-orchitis account for most presentations of acute scrotal pain. Every patient who is concerned should be examined and if any doubt persists, further investigated.

Investigations

Ultrasound is the first-line investigation of any scrotal lump and will confirm whether the palpable lesion is within the testis, distorting its normally regular outline and internal echo pattern. The sensitivity of USS for detecting a testicular tumour is almost 100%, including impalpable lesions of 1–2mm and 'occult' primary tumours in patients presenting with systemic symptoms and signs. Any hypoechoic area within the tunica albuginea should be regarded with suspicion. USS may also distinguish a primary from a secondary hydrocele. Testicular microlithiasis is occasionally reported in association with TC. There has been uncertainty regarding the significance of this anomaly in otherwise normal testes; the few prospec-

tive studies have failed to demonstrate any increased risk of TC development. Consequently, there is no rationale for recommending serial ultrasound scans to these individuals.

Abdominal and chest CT scans are usually obtained for staging purposes if the diagnosis of TC is confirmed or considered likely. Other imaging (such as CT of brain, spine, or bone scan) is performed if clinically indicated.

Serum tumour markers (AFP, LDH, and hCG) are measured prior to any treatment of a suspected TC (see 📖 p. 386).

Treatment

Radical inguinal orchidectomy is both the definitive diagnostic investigation and primary treatment for most testicular tumours, unless tissue diagnosis has been made from biopsy of a metastasis. Radical orchidectomy is curative in approximately 75% of patients. Fertility assessment, semen analysis, and cryopreservation should be offered to patients without a normal contralateral testis. The testis, epididymis, and spermatic cord are excised en bloc through a groin incision. The cord is mobilized within the inguinal canal, clamped, transfixed, and divided 1–2cm from the internal inguinal ring before the testis is manipulated into the wound, preventing inadvertent metastasis. A silicone prosthesis may be inserted at the time or at a later date. Contralateral testis biopsy should be considered in patients at high risk for intratubular germ cell neoplasia (see 📖 p. 378 Aetiology).

Testicular cancer: serum markers

Germ cell tumours may express and secrete into the bloodstream relatively specific and readily measurable proteins. These tumour markers (with the exception of PLAP) are useful in diagnosis, staging, prognostication (see 📖 p. 388), and monitoring of response to treatment.

Oncofetal proteins

Alpha-fetoprotein (AFP): is expressed by trophoblastic elements within 50–70% of teratomas and yolk sac tumours. With respect to seminoma, the presence of elevated serum AFP strongly suggests a non-seminomatous element. Serum half-life is 3–5 days; normal <10ng/mL.

Human chorionic gonadotrophin (hCG): is expressed by syncytiotrophoblastic elements of choriocarcinomas (100%), teratomas (40%), and seminomas (10%). Serum half-life is 24–36h. Laboratory assays measure the β-subunit; normal <5mIU/mL.

When used together, 90% of patients have elevation of one or both markers; less among patients with low-stage tumours.

Cellular enzymes

Lactate dehydrogenase (LDH): is a ubiquitous enzyme, elevated in serum for various causes, therefore, less specific. It is elevated in 10–20% of seminomas, correlating with tumour burden and is most useful in monitoring treatment response in advanced seminoma.

Placental alkaline phosphatase (PLAP): is a fetal isoenzyme, elevated in up to 40% of patients with advanced germ cell tumours. It is not widely used as it is non-specific, may be elevated in smokers.

Clinical use

These markers are measured at presentation, 1–2 weeks after radical orchidectomy and during follow-up to assess response to treatment and residual disease (Table 7.29).

Normal markers prior to orchidectomy do not exclude metastatic disease; normalization of markers post-orchidectomy cannot be equated with absence of disease; and persistent elevations of markers post-orchidectomy may occur with liver dysfunction and hypogonadotrophism, but usually indicate metastatic disease.

Table 7.29 S staging (part of the UICC (2006) TNM classification)

Sx	Markers not available
S0	Markers normal
S1	LDH <1.5 times normal upper limit; hCG <5000mIU/mL; and AFP <1000ng/mL
S2	LDH 1.5–10 times normal; hCG 5000–50 000 mIU/mL; and AFP 1000–10 000ng/mL
S3	LDH >10 times normal; hCG >50 000mIU/mL; and AFP >10 000ng/mL

Testicular cancer: prognostic staging system for metastatic germ cell tumours (GCT)

The International Germ Cell Cancer Collaborative Group (IGCCCG)* devised a prognostic factor-based staging system for metastatic germ cell cancer that includes good and intermediate prognosis seminoma and good, intermediate, and poor prognosis non-seminomatous germ cell tumours (NSGCT) (Table 7.30). See 🕮 p. 386 for discussion on testicular tumour markers, including S staging.

Table 7.30 IGCCCG prognostic factor-based staging system for metastatic germ cell cancer*

Prognostic Group	Seminoma	NSGCT
Good	90% of patients	56% of patients
5y progression-free survival (%)	86	92
All factors listed present	Any primary site; **no** non-pulmonary visceral metastases; normal AFP; any hCG or LDH	Testis or retroperitoneal primary site; **no** non-pulmonary visceral metastases; AFP <1000ng/mL; HCG <5000mIU/L; and LDH <1.5 times normal upper limit (S1)
Intermediate	10% of patients	28% of patients
5y progression-free survival (%)	73	80
All factors listed present	Any primary site; non-pulmonary visceral metastases present; normal AFP; any hCG or LDH	Testis or retroperitoneal primary site; **no** non-pulmonary visceral metastases; AFP 1000–9999ng/Ml; or HCG 5000–49 999mIU/L; LDH 1.5–10 times normal upper limit (S2)
Poor		16% of patients
5y progression-free survival (%)	No patients classified as poor prognosis	48
All factors listed present		Mediastinal primary; non-pulmonary visceral metastases present; AFP >10 000ng/mL or HCG >50 000mIU/L; LDH >10 times normal upper limit (S3)

* International Germ Cell Cancer Collaborative Group (IGCCCG) (1997) International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol* **15** (2): 594–603.

Testicular cancer: management of non-seminomatous germ cell tumours (NSGCT)

Following radical orchidectomy and formal staging, the patient is normally managed by the oncologist, though the urological surgeon may perform retroperitoneal lymph node dissection (RPLND) in selected cases based on multidisciplinary team discussion. In the presence of elevated AFP, a seminoma would be managed as for teratoma. Combination chemotherapy introduced in the 1970's revolutionized the treatment of metastatic testicular teratoma which was hitherto virtually untreatable.

Treatment and follow-up varies between the UK and USA. In the UK, it depends largely on the IGCCCG prognostic staging (see 📖 p. 388), as follows.

Localized disease pT1-4N0M0S0 (often referred to as stage I)

Surveillance results in 30% relapse rate, mostly <1y post-orchidectomy. Salvage chemotherapy produces excellent responses, with disease-specific survival >99%. Hence, a *risk-adapted management* is recommended to minimize the risk of toxicity:

- Surveillance for pT1 disease without vascular invasion (only 15% relapse).
- Adjuvant chemotherapy × 2 cycles for those unwilling or unsuitable for surveillance, for pT1 disease with vascular invasion, or for pT2–4 disease.

Metastatic disease

- Good prognosis: chemotherapy (bleomycin, etoposide, cisplatin × 3 cycles); RPLND for residual or recurrent mass; salvage chemotherapy for relapse.
- Intermediate and poor prognosis: chemotherapy (bleomycin, etoposide, cisplatin × 4 cycles); RPLND for residual or recurrent mass; occasionally, salvage chemotherapy or radiotherapy if histology confirms tumour; salvage high-dose chemotherapy with autologous stem cells for relapse.

Surveillance and follow-up after treatment

Surveillance requires the following:

- **Year 1:** monthly clinic visit, serum markers and chest X-ray, abdominal CT—months 3 and 12.
- **Year 2:** 2-monthly clinic visit with serum markers and chest X-ray, abdominal CT—month 24.
- **Years 3, 4, and 5:** 3-monthly clinic visit, serum markers, and chest X-ray.
- Annual clinic visit, serum markers, and chest X-ray thereafter to 10y.

Follow-up *after treatment* is slightly less intensive, also to 10y. The risk of relapse is highest in the first 2y.

RPLND

- Retroperitoneal lymphadenopathy is usually the first and only evidence of extragonadal metastasis of NSGCT.
- In the UK, RPLND is used only to remove or debulk residual mass post-chemotherapy.
- RPLND may remove viable tumour in 10–30% of patients, taking para-aortic nodes up to the origin of the superior mesenteric artery and down to the iliac bifurcation.
- **Complications:** 1% mortality and 25% morbidity includes lymphocele, pancreatitis, ileus, and ejaculatory failure.
- Modified techniques reduce the risk of ejaculatory disturbance by taking nodes on the unaffected side only down to the inferior mesenteric artery.
- In the USA, RPLND remains the gold standard staging investigation following radical orchidectomy.

Testicular cancer: management of seminoma, IGCN, and lymphoma

Of all seminomas, 75% are confined to the testis at presentation and are cured by radical orchidectomy; 10–15% of patients harbour regional node metastasis while 5–10% have more advanced disease.

Following radical orchidectomy and formal staging, the patient is managed by the oncologist. Treatment and follow-up depends largely on disease stage according to presence of metastases and size of nodal disease as in Table 7.31.

Table 7.31 Treatment and follow-up

Non-metastatic disease	
T1N0M0S0–1	Risk of subsequent para-aortic node relapse is 20%. Adjuvant treatment reduces the risk of recurrence to <1%. Standard treatment for stage 1 disease is either surveillance or single agent carboplatin (some centres use this for those patients with tumours >4cm and/or rete testis involvement. A randomized MRC study compared one cycle of carboplatin with radiotherapy (RT; results suggested equivalence. If RT is used, 20Gy is delivered in 10 fractions, including para-aortic nodes.
	Spermatocytic subtype usually warrants surveillance.
Metastatic disease	
T1–3 N1 M0S0–1	RT
T1–3 N2 M0 S0–1	RT; chemotherapy if nodes near kidneys
T1–4 N3 M0 S0–1	Chemotherapy (either bleomycin, etoposide and cisplatin or etoposide and cisplatin); if residual node mass >3cm (rare), retroperitoneal lymph node dissection (RPLND) considered although not usually necessary or performed with pure seminomas
T1–4N0–3M1–2S0–3	Chemotherapy with etoposide and cisplatin 9 bleomycin; if residual node mass (rare), RPLND considered although not usually necessary or performed with pure seminomas

Patients should also be classified into prognostic grouping classification (IGCCCG; see 📖 p. 388) as this provides an overall prognosis for patients. These patients require careful long-term follow-up, according to national guidance.

Management of intratubular germ cell neoplasia

- Observation or orchidectomy for unilateral disease.
- Radiotherapy for unilateral disease in the presence of a contralateral tumour.
- Radiotherapy for bilateral disease to preserve Sertoli cells.
- Systemic chemotherapy (e.g. cisplatin) controversial, not currently adopted in UK.
- Sperm storage must be offered.

Management of testicular lymphoma

This may be a primary disease or a manifestation of disseminated nodal lymphoma. The median age of incidence is 60y, but has been reported in children. Twenty-five percent of patients present with systemic symptoms, 10% have bilateral testicular tumours. These patients have a poorer prognosis following radical orchidectomy and chemotherapy, while those with localized disease may enjoy long-term survival.

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Chapter 8

Miscellaneous urological diseases of the kidney

Simple and complex renal cysts

Simple renal cysts: do not communicate with any part of the nephron or the renal pelvis. They are mainly confined to the renal cortex, are filled with clear fluid, and contain a membrane composed of a single layer of flattened or cuboidal epithelium. They can be single or multiple, ranging from a few millimetres to several centimetres in diameter. They can be unilateral or bilateral and often affect the lower pole of the kidney.

Parapelvic cysts: describe simple parenchymal cysts located adjacent to the renal pelvis or hilum.

Prevalence

Increases with age, the precise prevalence depending on the method of diagnosis. On CT, 20% of adults have renal cysts by age 40y and 33% by the age of 60.[1] At post-mortem, 50% of subjects aged >50y have simple cysts. Cysts do not usually increase in size with age, but may increase in number. Males and females are affected equally.

Aetiology

Both congenital and acquired causes have been suggested. Chronic dialysis is associated with the formation of new simple cysts.

Presentation

Simple cysts are most commonly diagnosed as an incidental finding following a renal ultrasound scan (USS) or CT performed for other purposes. The majority are asymptomatic; however, very large cysts may present as an abdominal mass or cause dull flank or back pain. Acute severe loin pain may follow bleeding into a cyst (causing sudden distension of the wall). Rupture (spontaneous or following renal trauma) is rare. Rupture into the pelvicalyceal system can produce haematuria. Infected cysts (rare) present with flank pain and fever. Very occasionally, large cysts can cause obstruction and hydronephrosis.

Differential diagnosis

- Renal cell carcinoma (4–7% of RCC are cystic).
- Early autosomal dominant polycystic kidney disease (ADPKD—diffuse, multiple or bilateral cysts, associated with hepatic cysts.
- Complex renal cysts (i.e. those which contain blood, pus or calcification).

Investigation

Renal USS

Simple cysts are round or spherical, have a smooth and distinct outline, and are 'anechoic' (no echoes within the cyst, i.e. sound waves are transmitted through the cyst). USS using microbubble contrast agents can improve diagnostic accuracy. Evidence of calcification, septation, irregular margins or clusters of cysts requires further investigation (renal triphasic CT). In the absence of these features, no further investigation is required.

CT

Simple cysts are seen as round, smooth-walled lesions with homogenous fluid in the cavity (with a typical density of –10 to +20 Hounsfield units) and with no enhancement after contrast (enhancement implies that it contains vascular tissue or communicates with the collecting system, i.e. that it is not a simple cyst). Hyperdense cysts have a density of +20–90 Hounsfield units, do not enhance with contrast media, and are <3cm in diameter.

Biopsy

Image-guided cyst aspiration or biopsy can be used to help diagnose indeterminate cysts and prevent unnecessary surgery.

Treatment

A simple cyst (type I: round or spherical, smooth wall, distinct outline, and no internal echoes) requires no further investigation, no treatment, and no follow-up. In the rare situation where the cyst is thought to be the cause of symptoms (e.g. back or flank pain), treatment options include percutaneous aspiration ± injection of sclerosing agent or open or laparoscopic surgical excision of the cyst wall. In the rare event of cyst infection, percutaneous drainage and antibiotics are indicated.

Cysts with features on USS suggesting possible malignancy (calcification, septation, irregular margins) should be investigated by CT with contrast.

1 Laucks SP Jr, McLachlan MS (1981) Aging and simple cysts of the kidney. *Br J Radiol* **54**:12–4.

2 Warren KS, McFarlane J (2005) The Bosniak classification of renal cystic masses. *BJU Int* **95**: 939–42.

Table 8.1 Bosniak's classification of CT appearance of simple and complex cysts

Type	Description	Approx. % of such cysts which are malignant[2]	Treatment
I	Simple benign cyst with smooth margins, no contrast enhancement, no septation, no calcification	<2%	None; no follow-up required
II	Benign cyst with smooth margins; few thin septae; minimal calcification; no contrast enhancement; <3cm		Observation—repeat USS looking for increase in size or development of malignant features*
IIF	Increased number of thin septae; thickening and/or minimal enhancement of septae; may contain calcium, but no enhancement. Includes non-enhancing, high-attenuation >3cm cysts	19% (II and IIF combined)	Follow-up with USS (or CT). Type IIF cysts have greater malignant potential than type II cysts
III	Irregular margins; moderate calcification; thick septation (septae >1mm thick); enhancement	33%	Surgical exploration ± partial nephrectomy
IV	Cystic malignant lesion; irregular margins and/or solid enhancing elements	93%	Radical nephrectomy

*Bosniak suggested follow-up scans at 6 months and 1y. If the lesion remained stable after this time, it is considered benign.

Calyceal diverticulum

A calyceal diverticulum is a spherical outpouching of the renal collecting system (specifically from a calyx) which protrudes into the corticomedullary region of the kidney. It communicates with the renal calyx via a narrow neck or channel. It is lined by a transitional cell epithelium and is covered by a thin layer of renal cortex. They range in size from only a few millimetres to many centimetres in size.

Aetiology

The exact aetiology of calyceal diverticula is unknown. Some may be congenital. Acquired calyceal diverticula can develop after obstruction of a calyceal infundibulum or following blunt renal trauma.

Presentation

They are usually asymptomatic and are discovered incidentally on an IVU, most commonly seen in upper pole calyces. Symptoms may result from the development of a stone or infection within the diverticulum, presumably caused by urinary stasis.

Investigation

On IVU, a calyceal diverticulum appears as a rounded collection of contrast medium next to a papilla, although often, the connecting channel is too narrow to be clearly seen. They can be identified on CT, MRI, and USS; however, the distinction between a renal cyst and an obstructed calyx may be difficult on unenhanced images.

Treatment

Stones that form within the calyceal diverticulum may be treated by flexible ureteroscopy and laser lithotripsy or, if large, by percutaneous nephrolithotomy (PCNL) if percutaneous access is possible. Endoscopic dilatation or incision of the neck of the diverticulum may be attempted at the time of stone surgery to prevent recurrence and this technique can also be employed if the diverticulum is thought to be the cause of recurrent urinary infection. Open surgery has also been used to remove stones and to de-roof calyceal diverticula. Extracorporeal shock wave lithotripty (ESWL) therapy is not helpful. ESWL may result in stone fragmentation, but it may be difficult for the stone fragments to get out of the diverticulum and they may simply reform into a larger stone.

Medullary sponge kidney (MSK)

Definition

A congenital cystic disorder of the kidneys characterized by dilatation of the distal collecting ducts associated with the formation of multiple cysts and diverticula within the medulla of the kidney.

Prevalence

Difficult to know as it may be asymptomatic (diagnosed on an IVU performed for other reason or at post-mortem). Estimated to affect between 1 in 5000 to 1 in 20 000 people in the general population; 1 in 200 in those undergoing IVU (a select population). In 75% of cases, both kidneys are affected.

Pathology

The renal medulla resembles a sponge in cross section due to dilated collecting ducts in the renal papillae and the development of numerous small cysts. This is associated with urinary stasis and the formation of small calculi within the cysts. Some report a familial inheritance. It can be associated with other congenital or inherited disorders, including hemihypertrophy and Beckwith–Wiedemann syndrome*.

Presentation

The majority of patients are asymptomatic. When symptoms do occur, they include ureteric colic, renal stone disease (calcium oxalate ± calcium phosphate), UTI, and haematuria (microscopic or macroscopic). Up to 50% have hypercalciuria due to renal calcium leak or increased gastrointestinal calcium absorption. Renal function is normal unless obstruction occurs (secondary to renal pelvis or ureteric stones).

Differential diagnosis

Other causes of nephrocalcinosis (deposition of calcium in the renal medulla, e.g. TB, hyperparathyroidism, healed papillary necrosis, multiple myeloma).

Investigation

- **Midstream urine:** dipstick ± culture. Check for UTI and treat according to sensitivities.
- **Biochemistry:** 24h urinary calcium may be elevated (hypercalciuria). Detection of hypercalciuria requires further investigation to exclude other causes (i.e. raised serum parathyroid hormone (PTH) levels indicate hyperparathyroidism).
- **Imaging:** IVU is the principle method for diagnosing MSK, although CT and USS may also be used. The characteristic radiological features of MSK, as seen on IVU, are enlarged kidneys associated with dilatation of the distal portion of the collecting ducts, along with numerous associated cysts and diverticula (the dilated ducts are said to give the appearance of 'bristles on a brush'). The collecting ducts may become filled with calcifications, giving an appearance described as a 'bouquet of flowers' or 'bunches of grapes' (Fig. 8.1).

Treatment

Asymptomatic MSK disease requires no treatment. General measures to reduce urine calcium levels help reduce the chance of calcium stone formation (high fluid intake, vegetarian diet, low salt intake, consumption of fruit and citrus fruit juices). Thiazide diuretics may be required for hypercalciuria resistant to dietary measures and are designed to lower urine calcium concentration. Intrarenal calculi are often small and as such, may not require treatment, but if indicated, this can take the form of ESWL or flexible ureteroscopy and laser treatment. Ureteric stones are again usually small and will, therefore, pass spontaneously in many cases with a period of observation. Recurrent UTI may need prophylactic antibiotics. Renal function tends to remain stable in the long term. Rarely, recurrent infection and nephrocalcinosis may lead to the complication of renal impairment.

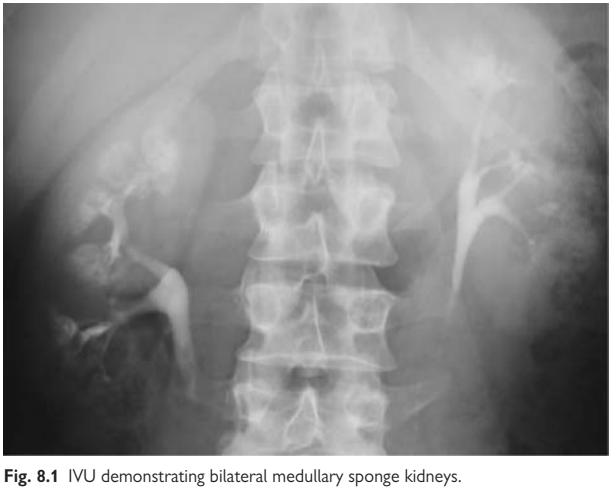

Fig. 8.1 IVU demonstrating bilateral medullary sponge kidneys.

* Beckwith–Wiedemann syndrome: a growth disorder characterized by macroglossia, macrosomia, visceromegaly, Wilm's tumour, neuroblastoma, omphalocele, and renal anomalies.

Acquired renal cystic disease (ARCD)

A cystic degenerative disease of the kidney with ≥5 cysts visualized on CT scan. By definition, this is an acquired condition, as opposed to ADPKD which is inherited (in an autosomal dominant fashion). It is predominantly associated with chronic and end-stage renal failure and as such, is commonly found in patients undergoing haemodialysis or peritoneal dialysis. Over one third of patients develop ARCD after 3y of dialysis. Clinically important because it may cause pain and haematuria and is associated with the development of benign and malignant renal tumours. The male to female ratio is 3:1.

Pathology

Usually multiple, bilateral cysts found mainly within the cortex of small, contracted kidneys. Cysts vary in size (average 0.5–1cm) and are filled with a clear fluid which may contain oxalate crystals. They usually have cuboidal or columnar epithelial linings and are in continuity with renal tubules (and, therefore, cannot be defined as simple cysts). Atypical cysts have a hyperplastic lining of epithelial cells, which may represent a precursor for tumour formation. Renal transplantation can cause regression of cysts in the native kidneys.

Aetiology

The exact pathogenesis is unknown, but several theories have been proposed. Obstruction or ischaemia of renal tubules may induce cyst formation. Renal failure may predispose to the accumulation of toxic endogenous substances or metabolites, alter the release of growth factors, and result in changes in sex steroid production or cause cell proliferation (secondary to immunosuppressive effects) which result in cyst formation.

Associated disorders

There is an increased risk of benign and malignant renal tumours. The chance of developing RCC is ~20%, 3–6 times greater than the general population (males > females). When on dialysis, RCC usually develops within the first 10y of treatment.

Presentation

Flank pain; UTI; visible haematuria; renal colic (stone disease); hypertension.

Investigation

This depends on the presenting symptoms.

- **For suspected UTI:** culture urine.
- **For haematuria:** urine cytology, flexible cystoscopy, and renal USS. On USS, the kidneys are small and hyperechoic, with multiple cysts of varying size, many of which show calcification. If the nature of the cysts cannot be determined with certainty on USS, arrange a renal CT.

Treatment

Persistent macroscopic haematuria can become problematic, exacerbated by heparinization (required for haemodialysis). Options include transferring to peritoneal dialysis, renal embolization or nephrectomy (acceptable as these patients already on dialysis by definition have non-functioning kidneys). Infected cysts, which develop into abscesses, require percutaneous or surgical drainage. Radical nephrectomy is indicated for renal masses with features suspicious of malignancy. Smaller asymptomatic masses require surveillance. Patients with ARCD on long-term dialysis should also be considered for renal surveillance with ultrasonography or CT.

Autosomal dominant polycystic kidney disease (ADPKD)

Definition

An autosomal dominant inherited disorder involving multiple expanding renal parenchymal cysts (Fig. 8.2).

Epidemiology

Incidence is 0.1–0.5%; 95% are bilateral. ADPKD can affect children and adults, although symptoms usually occur between ages 30–50y. ADPKD accounts for 10% of all renal failure (which usually manifests at >40y old).

Pathology

The kidneys reach an enormous size due to multiple fluid-filled cysts and can easily be palpated on abdominal examination. Expansion of the cysts results in ischaemic atrophy of the surrounding renal parenchyma and obstruction of normal renal tubules. End-stage renal failure occurs at around age 50y.

Associated disorders

Ten to thirty percent incidence of Circle of Willis berry aneurysms (associated with subarachnoid haemorrhage), cysts of the liver (33%), pancreas (10%), spleen (<5%) and seminal vesicles, mitral valve prolapse; aortic root dilatation, aortic aneurysms, and diverticular disease. Of note, the incidence of renal adenoma is ~20%; however, the risk of RCC is the same as the general population.

Aetiology

Two genes have been identified in ADPKD. The PKD1 gene is localized on the short arm of chromosome 16 (16p13.3) and accounts for 85% of cases. The PKD2 gene is on the long arm of chromosome 4 (4q21) and causes 15% of cases. A third gene, PKD3, is also implicated. Pathogenesis theories include intrinsic basement membrane abnormalities, tubular epithelial hyperplasia (causing tubular obstruction and basement membrane weakness), and alterations in the supportive extracellular matrix due to defective proteins, all of which may cause cyst formation.

Presentation

- Positive family history.
- Hypertension (75%).
- Palpable abdominal masses.
- Flank pain (due to mass effect, infection, stones or following acute cystic distension due to haemorrhage or obstruction).
- Haematuria (visible or non-visible).
- UTI.
- Renal failure which may present with lethargy, nausea, vomiting, anaemia, confusion, and seizures.

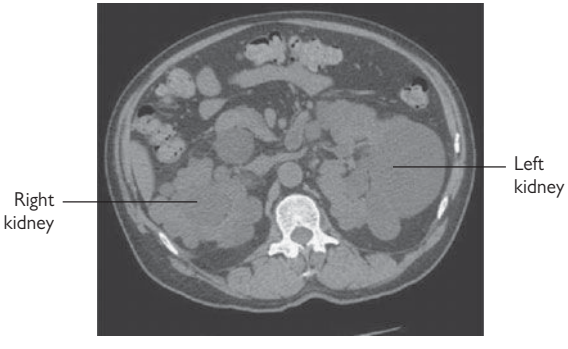

Fig. 8.2 Axial section from a non-contrast CT scan demonstrating bilateral ADPKD.

Differential diagnosis

Other forms of renal cystic disease (multiple simple cysts, autosomal recessive polycystic kidney disease (ARPKD), familial juvenile nephronophthisis, medullary cystic disease; see 🕮 p. 676).

Multiple renal cysts are also found in other autosomal dominant conditions:

- **Tuberous sclerosis:** has TSC1 and 2 gene mutations on chromosomes 9 and 16. It presents with adenoma sebaceum, epilepsy, learning difficulties, polycystic kidneys, and renal tumours (angiomyolipomas and, more rarely, RCC).
- **von Hippel–Lindau (**VHL**) syndrome:** has a VHL tumour suppressor gene mutation on the short arm of chromosome 3 (3p25) which causes hypoxia-inducible factor (HIF) to increase levels of growth factors (PDGF, TGF-α, VEGF), which can stimulate the formation of haemangioblastomas (cerebellar and retinal) and RCC. VHL syndrome also includes renal, pancreatic and epididymal cysts, and phaeochromocytoma.

Investigation

This depends on the presenting symptoms:

- **Adult patients with a family history of** ADPKD**:** first counsel the patient on the implications of a positive diagnosis. USS*, CT, and MRI of the renal tract are useful for initial diagnosis and investigation of complications. On USS, the kidneys are small and hyperechoic, with multiple cysts of varying size, many of which show calcification. If the nature of the cysts cannot be determined with certainty on USS, arrange a renal CT. Genetic testing can be done if imaging is equivocal or when a definite diagnosis is required in a young patient.
- **For suspected UTI:** culture urine.

- **For haematuria:** urine cytology, flexible cystoscopy, and renal USS.
- **Renal failure:** refer for management by a nephrologist. Renal failure may be associated with anaemia, although conversely, ADPKD can cause increased erythropoietin production and polycythaemia.

Treatment

The aim is to preserve renal function for as long as possible (monitor and control hypertension and UTI). Infected cysts should be drained. Persistent, heavy haematuria can be controlled by embolization or nephrectomy. Progressive renal failure requires dialysis and ultimately, renal transplantation.

Due to the high risk of inheritance of ADPKD, offsprings should be fully counselled and offered genetic testing or USS screening at an appropriate time.

* **USS diagnostic criteria.** Patients at 50% risk for developing ADPKD are:

≥2 unilateral or bilateral cysts if aged <30y old.

2 cysts in each kidney in patients aged 30–59y old.

4 cysts in each kidney in patients aged >60y.

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Vesicoureteric reflux in adults

Vesicoureteric reflux (VUR) is the retrograde flow of urine from the bladder into the upper urinary tract with or without dilatation of the ureter, renal pelvis, and calyces (see 📖 p. 662).

Pathophysiology

Reflux is normally prevented by low bladder pressures, efficient ureteric peristalsis, and the ability of the vesicoureteric junction (VUJ) to occlude the distal ureter during bladder contraction. This is assisted by the ureters passing obliquely through the bladder wall (the 'intramural' ureter) which is 1–2cm long. Normal intramural ureteric length to ureteric diameter ratio is 5:1. VUR of childhood tends to resolve spontaneously with increasing age because as the bladder grows, the intramural ureter lengthens.

Classification

Primary: a primary anatomical (and therefore, functional) defect, where the intramural length of the ureter is too short (ratio <5:1).

Secondary: to some other anatomical or functional problem.

- Bladder outlet obstruction (BPO, DSD, urethral stricture, missed posterior urethral valves), leading to elevated bladder pressures.
- Poor bladder compliance or the intermittently elevated pressures of neuropathic detrusor overactivity (due to neuropathic disorders,[1] e.g. SCI, spina bifida).
- Iatrogenic reflux. A relatively common cause would be direct ureteric reimplantation into the bladder without using an antirefluxing technique. Other causes include: ureteric meatotomy, i.e. incision of the ureteric orifice for removal of ureteric stones stuck at the VUJ; following incision of a ureterocele; following TURP or TURP; and post-pelvic radiotherapy.
- Inflammatory conditions affecting function of the VUJ—TB, schistosomiasis, UTI.

Associated disorders

VUR is commonly seen in duplex ureters (the Weigert–Meyer law)[2] and associated with PUJ obstruction. Cystitis can cause VUR through bladder inflammation, reduced bladder compliance, increased pressures, and distortion of the VUJ. Coexistence of UTI with VUR can cause pyelonephritis. Reflux of infected urine under high pressure may lead to reflux nephropathy, resulting in renal scarring, hypertension, and renal impairment—although this is much less common in adults compared to children. More commonly, this would manifest as loin pain in adults.

Presentation

- VUR may be asymptomatic. It may only be detected incidentally during investigations performed for other reasons, such as videourodynamics, IVU, or renal USS.
- Loin pain (sometimes associated with a full bladder or immediately after micturition).
- UTI symptoms.

Investigation

The definitive test for the diagnosis of VUR is cystography, which may be apparent during bladder filling or during voiding (micturating cystourethrography). Where clinically indicated, urodynamics establishes the presence of voiding dysfunction. If there is radiographic evidence of reflux nephropathy, check BP and the urine for proteinuria, measure serum creatinine, and arrange a ^{99m}Tc-DMSA renogram study to assess renal cortical scarring and determine split renal function.

Management

VUR is harmful to the kidney in the presence of infected urine and/or where bladder pressures are markedly elevated (due to severe BOO, poor compliance, or high-pressure overactive bladder contractions). In the absence of these factors, VUR is not harmful, at least in the short term (months). Subsequent management depends on:

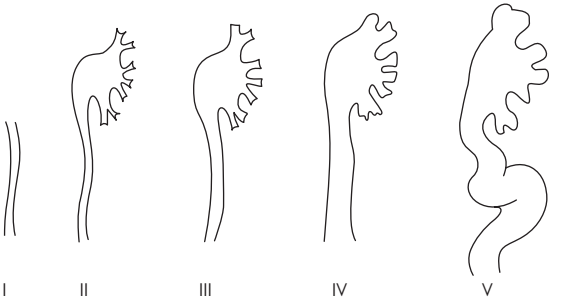
- The presence and severity of symptoms.
- The presence of recurrent, proven urinary infection.
- The presence of already established renal damage, as indicated by radiological evidence of reflux nephropathy, hypertension, impaired renal function, or proteinuria.

Primary VUR

- **For the patient with primary** VUR**, recurrent** UTI**s** with no symptoms between infections, no hypertension, and good renal function: treat the UTIs when they occur; consider low-dose antibiotic prophylaxis if UTIs occur frequently (>3 per year). If UTIs are regularly associated with systemic symptoms (acute pyelonephritis rather than uncomplicated cystitis), then ureteric reimplantation is indicated.
- **For the patient with primary** VUR **and objective evidence of deterioration** in the affected kidney: ureteric reimplantation.
- **Reflux into a non-functioning kidney** (<10% function on DMSA scan) with recurrent UTIs and/or hypertension: nephroureterectomy.
- **Primary reflux with severe recurrent loin pain:** ureteric reimplantation.

Secondary VUR

- VUR into a transplanted kidney: no treatment is necessary.
- VUR in association with the neuropathic bladder: treat the underlying cause—relieve BOO, improve bladder compliance (options: intravesical botulinum toxin injections, augmentation cystoplasty, sacral deafferentation).
- VUR with no symptoms, no UTI, no high bladder pressures, and no BOO: for grades I–II reflux, monitor for infection, hypertension, and evidence of deterioration in the appearance and function of the kidneys. For grades III–V, some urologists would recommend ureteric reimplantation or an endoscopic injection of bulking agent at the ureteric orifice (see Fig. 8.3 for VUR grading).



Grade I	Contrast into non-dilated ureter
Grade II	Contrast into renal pelvis and calyces; no dilatation
Grade III	Mild dilatation of ureter; pelvis, and calyces
Grade IV	Dilated ureter becomes slightly tortuous; moderate dilatation of pelvis and blunting of calyces
Grade V	Severe ureteric dilatation and tortuosity; gross dilatation of pelvis and calyces

Fig. 8.3 International reflux classification.

1 Neuropathic disorders cause VUR because they lead to intermittently or chronically raised bladder pressure (due to bladder outlet obstruction, poor compliance and/or detrusor overactivity).

2 The lower renal moiety ureter inserts into the bladder in a higher and more lateral location as compared to the upper moiety ureter, which inserts distally and medially, i.e. nearer the bladder neck. The lower moiety ureter has a shorter intramural length and therefore can be prone to reflux. The upper moiety ureter has a longer intramural length and tends to be at risk of obstruction.

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Pelviureteric junction obstruction in adults

Definition

PUJO is an obstruction of the proximal ureter at the junction with the renal pelvis, resulting in a restriction of urine flow (see 📖 p. 672); known as 'uretero-pelvic junction obstruction' (UPJO) in North America.

Aetiology

Congenital

- **Intrinsic:** smooth muscle defect results in an aperistaltic segment of ureter at the PUJ. The ureter can insert high on the renal pelvis (which may be a primary abnormality or secondary to the pelvic dilatation).
- **Extrinsic:** compression from the lower renal pole ('aberrant') vessel over which the PUJ runs. It is unlikely that these vessels are the primary cause of the obstruction. It is more probable that PUJO leads to a dilated PUJ and ballooning of the renal pelvis over the lower pole vessels, which may thus contribute to, but is not the primary cause of, the obstruction.

Acquired

PUJ stricture secondary to ureteric manipulation (e.g. ureteroscopy); trauma from passage of calculi; fibroepithelial polyps; TCC of urothelium at PUJ; external compression of ureter by retroperitoneal fibrosis or malignancy.

Presentation

Flank pain precipitated by diuresis (high fluid intake, especially after consumption of alcohol); flank mass; UTI; haematuria (after minor trauma). It may also be associated with VUR.

Investigation

- **Blood test:** for renal function (U&E, eGFR).
- **MSU:** to exclude infection.
- **Renal USS:** shows renal pelvis dilatation in the absence of a dilated ureter.
- **IVU:** demonstrates a delay of excretion of contrast and a dilated pelvicalyceal system.
- **CT:** shows a dilated renal pelvis and non-dilated ureter. Also helpful in excluding a small, radiolucent stone, urothelial TCC, or retroperitoneal pathology, which may be the cause of the obstruction at the PUJ.
- **MAG3 renogram** (with administration of furosemide to establish maximum diuresis): is the definitive diagnostic test for PUJO. Radioisotope accumulates in the renal pelvis and following intravenous furosemide, it continues to accumulate (a 'rising' curve). Also useful as it provides split renal function.

- **Retrograde pyelography:** to establish the exact site of the obstruction—often performed at the time of PUJ repair to avoid introducing infection into an obstructed renal pelvis.

Management

Surgery is indicated for recurrent episodes of bothersome pain, renal impairment, where a stone has developed in the obstructed kidney and where infection has supervened (an acutely infected obstructed kidney in a septic patient will require nephrostomy insertion). In the absence of symptoms, consider watchful waiting with serial MAG3 renograms. If renal function remains stable and the patient remains free of symptoms, there is no need to operate. A non-functioning 'burnt-out' kidney with PUJO may require nephrectomy to avoid the complication of pyonephrosis.

Pyeloplasty (see 🕮 p. 782)

- **Laparoscopic pyeloplasty:** the dismembered pyeloplasty is the most commonly performed technique using transperitoneal, retroperitoneal, or robotic-assisted approaches. Success rates are ~95%.
- **Open pyeloplasty:** success rates of 95%. Common techniques include dismembered or Anderson–Hynes pyeloplasty. The narrowed area of PUJ is excised, the proximal ureter is spatulated and anastomosed to the renal pelvis. Alternative techniques include flap pyeloplasty (Culp) and Y–V-plasty (Foley).

A double J ureteric stent is left for 6 weeks post-operatively, which can be removed with flexible cystoscopy as an outpatient procedure.

Endopyelotomy (or pyelolysis)

A minimally invasive technique to treat PUJO, but tends not to be offered as first-line therapy other than in older or frail patients. It can be utilized after pyeloplasty has failed. A full thickness incision is made through the obstructing proximal ureter from within the lumen of the ureter down into the peripelvic and periureteral fat, using a sharp knife or Holmium:YAG laser. The incision is stented for 4 weeks to allow re-epithelialization of the PUJ. Generally not used for PUJO >2cm in length. The incision may be made percutaneously or by a retrograde approach via a rigid or flexible ureteroscope or by using a specially designed endopyelotomy balloon, the Acucise® technique. Here, an angioplasty-type balloon (over which runs a cautery wire) is inflated across the PUJ. An electrical current heats the wire and this cuts through the obstructing ring of tissue at the PUJ.

The presence of a combination of PUJO and a renal stone that is suitable for PCNL is an indication for combined PCNL and percutaneous endopyelotomy.

Success rates in terms of relieving obstruction: percutaneous endopyelotomy, 60–100% (mean 70%); cautery wire balloon endopyelotomy, 70%; ureteroscopic endopyelotomy, 80%.

Follow-up

Repeat MAG3 renogram is usually performed 3 months post-operatively. If there has been no improvement, this can be repeated 6–12 months post-operatively. Failure may need re-do surgery or endopyelotomy.

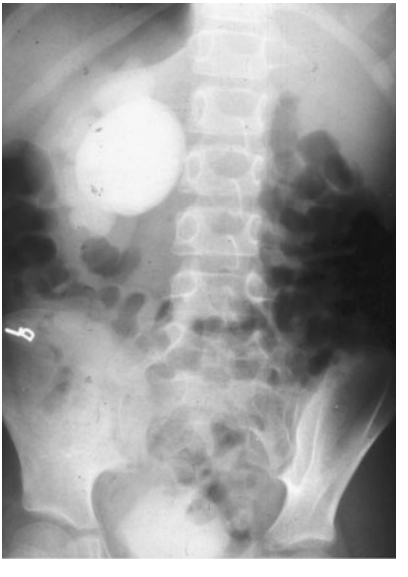


Fig. 8.4 IVU demonstrating a right PUJO (dilated pelvicalyceal system and non-dilated ureter). Image kindly provided with permissions from Mr P. Malone.

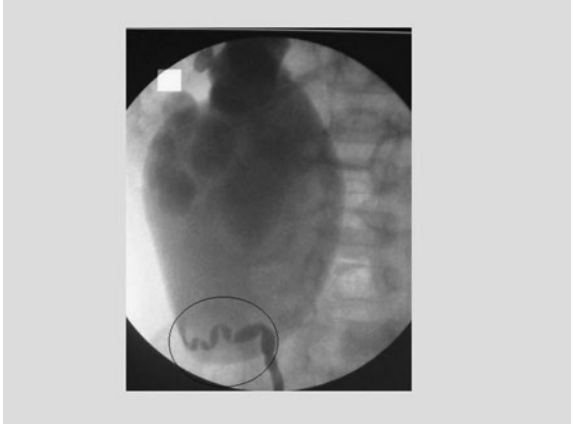


Fig. 8.5 Retrograde pyelogram demonstrating a right PUJO (circled). Image kindly provided with permissions from Mr P. Malone.

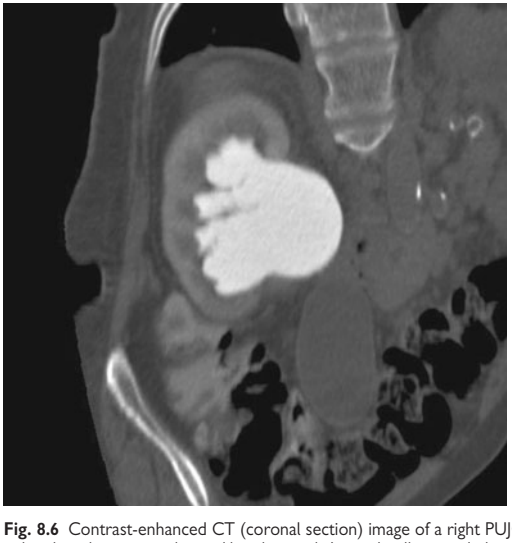


Fig. 8.6 Contrast-enhanced CT (coronal section) image of a right PUJO (dilated pelvicalyceal system and non-dilated ureter). Image kindly provided with permission from Mr A. Wedderburn.

Anomalies of renal fusion and ascent: horseshoe kidney, ectopic kidney

Abnormalities of renal fusion and ascent occur in weeks 6–9 of gestation, when the embryonic kidney is 'ascending' to its definitive lumbar position in the renal fossa ('ascending' as a result of rapid caudal growth of the embryo).

Horseshoe kidney

Most common example of renal fusion. Prevalence 1 in 400. Male to female ratio 2:1. The kidneys lie vertically (instead of obliquely) and are joined at their lower poles (in 95%) by midline parenchymal tissue (the isthmus). The inferior mesenteric artery obstructs ascent of the isthmus. Consequently, the horseshoe kidney lies lower in the abdomen (L3 or L4 vertebral level). Normal rotation of the kidney is also prevented and therefore, the renal pelvis lies anteriorly, with the ureters also passing anteriorly over the kidneys and isthmus (but entering the bladder normally). Blood supply is variable, usually from one or more renal arteries or their branches or from branches off the aorta or inferior mesenteric artery (Fig. 8.7).

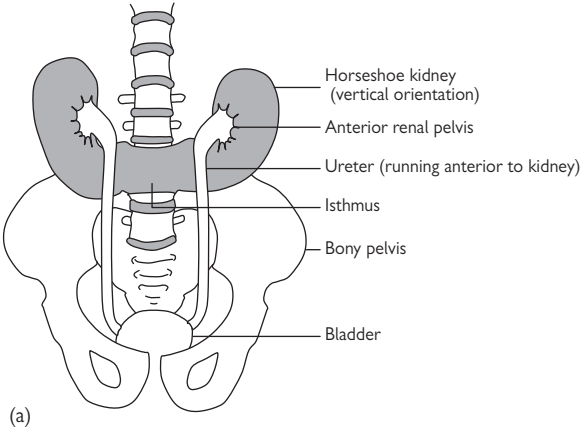
A proportion of individuals with horseshoe kidneys have associated congenital abnormalities (Turner's syndrome, trisomy 18, genitourinary anomalies, ureteric duplication), VUR, PUJ obstruction, and renal tumours (including Wilms' tumours).

Most patients with horseshoe kidneys remain asymptomatic; however, infection and calculi may develop and cause symptoms. The diagnosis is usually suggested on renal USS and confirmed by IVU (calyces of the lower renal pole are seen to point medially and lie medially in relation to the ureters) or CT. Renal function is usually normal.

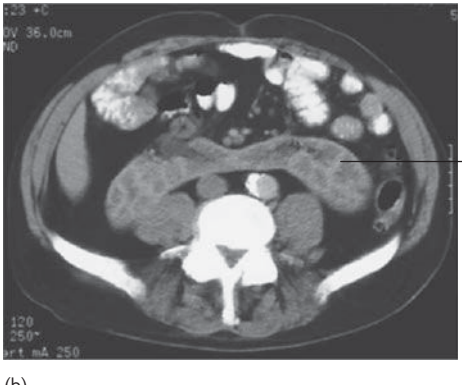
Ectopic kidney

The kidney fails to achieve its normal position and may be located in the thorax, abdomen, lumbar (in iliac fossa), or pelvis (on the contralateral side or crossed). The prevalence of renal ectopia is 1 in 900, with both sexes affected equally. The left kidney is affected more often than the right and bilateral cases are seen in <10%. The affected kidney is smaller, with the renal pelvis positioned anteriorly (instead of medially) and the ureter is short, but enters the bladder normally. Pelvic kidneys occur in 1 in 2000–3000 and lie opposite the sacrum and below the aortic bifurcation and are supplied by adjacent (aberrant) vessels (Fig. 8.8). Renal ectopia has an increased risk of congenital anomalies, including contralateral renal agenesis and genital malformations.

Most are asymptomatic. Diagnosis is made on renal USS, IVU, or renography. Complications include hydronephrosis (secondary to VUR, VUJ obstruction, and PUJO), stones, and infection.

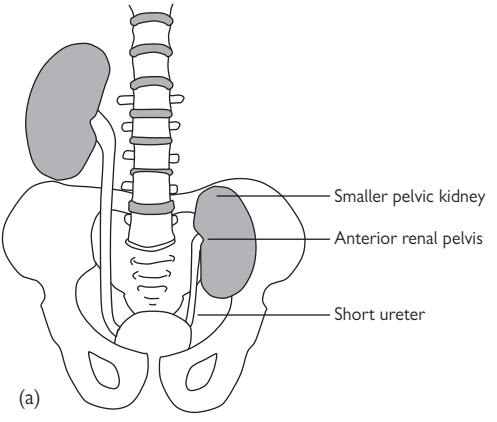


(a)

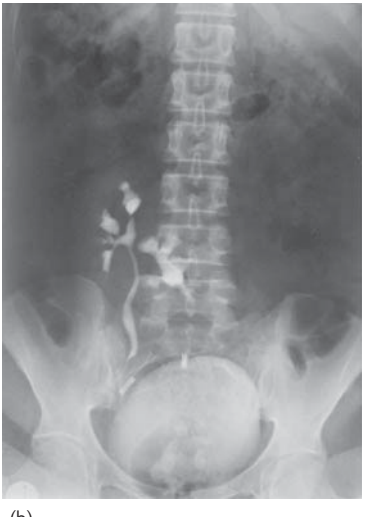


(b)

Fig. 8.7 (a) Horseshoe kidney; (b) Axial section of a CT scan demonstrating a horseshoe kidney.



(a)



(b)

Fig. 8.8 (a) Ectopic (pelvic) kidney; (b) IVU demonstrating ectopic kidneys. Sterilization clips are also seen. Image kindly provided with permission from Prof. S. Reif.

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Anomalies of renal number and rotation: renal agenesis and malrotation

Renal agenesis

Unilateral renal agenesis is the absence of one kidney due to embryological abnormality or absence of the ureteric bud. This results in failure of the ureteric bud to contact the metanephric blastema with failed induction of nephrogenesis. The incidence is 1 in 1000, left side > right, males > females. Absence of a kidney may also be caused by involution of a multicystic dysplastic kidney *in utero* or post-natally. Many patients are asymptomatic; however, it is associated with Turner's syndrome and cardiac, respiratory, gastrointestinal, and musculoskeletal abnormalities. Associated genitourinary anomalies include absence of the ipsilateral ureter, abnormal trigone, VUR, PUJO, VUJO, uterine abnormalities (unicornuate—one side has failed to develop; bicornuate—partially divided uterus; didelphys—double uterus), vaginal agenesis, anomalies of seminal vesicles, and absence of vas deferens. Often discovered as an incidental finding on USS performed for other reasons or during investigation of associated abnormalities. Long-term follow-up of renal function, urinalysis, and BP should be considered.

Bilateral renal agenesis is rare and incompatible with life. It is associated with complete ureteric atresia, bladder hypoplasia or absence, intrauterine growth retardation, pulmonary hypoplasia, and oligohydramnios (reduced amniotic fluid), causing characteristic 'Potter' facial features (blunted nose, low set ears, depression on the chin) and limb abnormalities.

Malrotation

The kidney is located in a normal position, but the renal pelvis fails to rotate to the normal medial orientation. Often seen with horseshoe kidneys and renal ectopia and associated with Turner's syndrome. The incidence is ~1 in 1000, with a male to female ratio of 2:1. The renal shape may be altered (flattened, oval, triangular, or elongated) and the kidney retains its foetal lobulated outline (Fig. 8.9). It is associated with increased deposition of fibrous tissue around the renal hilum, which can produce symptoms due to ureteric or PUJ obstruction (causing hydronephrosis, infection, or stone formation). Most patients, however, remain asymptomatic. The diagnosis is made on USS, IVU, or retrograde pyelography.

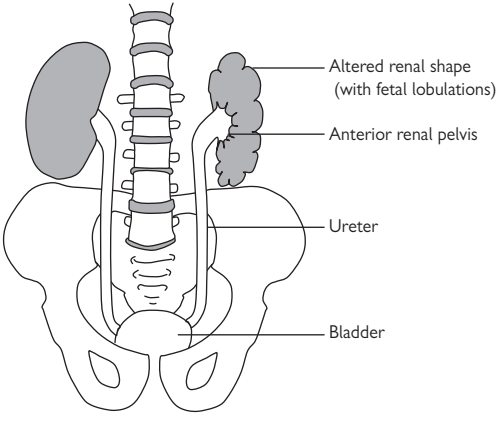

Fig. 8.9 Malrotation of the kidney.

Upper urinary tract duplication

Definitions

A duplex kidney has an upper renal moiety and a lower renal moiety, each with its own separate pelvicalyceal system and ureter. The two ureters may join to form a single ureter at the PUJ (bifid system; Fig. 8.10) or more distally (bifid ureter) before entering the bladder through one ureteric orifice. Alternatively, the two ureters may pass down individually to the bladder (complete duplication; Fig. 8.11). In this case, the Weigert–Meyer rule states that the upper moiety ureter always opens onto the bladder medially and inferiorly to the ureter of the lower moiety, thereby predisposing to ectopic placement of the ureteric orifice and obstruction (due to the longer intramural course of the ureter through the bladder wall). The lower moiety ureter opens onto the bladder laterally and superiorly, reducing the intramural ureteric length which predisposes to VUR (in up to 85%; Fig. 8.2).

Epidemiology

Ureteric duplication occurs in 1 in 125 individuals. Female to male ratio is 2:1. Unilateral cases are more common than bilateral, with right and left sides affected equally. Risk of other congenital malformations is increased.

Embryology

In duplication, two ureteric buds arise from the mesonephric duct (week 4 of gestation). The ureteric bud situated more distally (lower moiety ureter) enters the bladder first and so migrates a longer distance, resulting in the superior and lateral position of the ureteric orifice. The proximal bud (upper moiety ureter) has less time to migrate and consequently, the ureteric orifice is inferior and medial (ectopic) (see 📖 p. 668). Interaction of each ureteric bud with the same metanephric tissue creates separate collecting systems within the same renal unit. With bifid ureters, a single ureteric bud splits after it has emerged from the mesonephric duct.

Complications

Ectopic ureters are associated with upper renal moiety hydronephrosis (secondary to obstruction), renal hypoplasia or dysplasia (maldevelopment of the kidney correlating with the degree of ectopic displacement of ureteric orifice)[1], and ureteroceles (Fig. 8.10). Lower moiety ureters are prone to reflux, resulting in hydroureter and hydronephrosis. Bifid ureters can get urine continuously, passing from one collecting system to the other (yo-yo reflux), causing urinary stasis (and predisposing to infection).

Presentation

Symptoms of UTI, flank pain, or an incidental finding.

Investigation

- **Renal USS:** demonstrates ureteric duplication ± dilatation and hydronephrosis.
- **IVU:** decreased contrast excretion from renal upper pole ± hydronephrosis (which may displace the lower pole downwards and outwards, producing a 'drooping lily' appearance). Contrast in a ureterocele gives the appearance of a 'cobra head' (Fig. 8.10).
- **Micturating cystourethrography (MCUG):** will determine whether reflux is present.
- **Enhanced CT and MRI:** reveals detailed anatomical information.
- **^{99m}Tc-DMSA renogram:** assesses individual renal moiety function.

Management

Uncomplicated complete or incomplete ureteric duplication does not require any intervention. In symptomatic patients, the aim is to reduce obstruction and reflux and improve function. Where renal function is reasonable, common sheath ureteric reimplantation (where a cuff of bladder tissue is taken that encompasses both duplicated ureters) can treat both conditions. A poorly functioning renal moiety (i.e. upper moiety associated with ectopic ureter and/or reflux or lower moiety associated with a ureterocele) may require heminephrectomy and ureterectomy. Where both renal moieties have poor function or dysplasia, nephroureterectomy is indicated.

1 Mackie GG, Stephens FD (1975) Duplex kidneys: a correlation of renal dysplasia with position of the ureteric orifice. *J Urol* **114**:274–80.

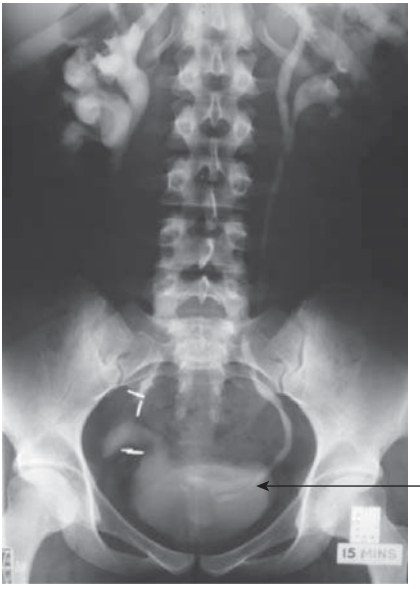

Fig. 8.10 IVU demonstrating bilateral (bifid system) renal duplication and a left ureterocele in the bladder ('cobra head' sign).

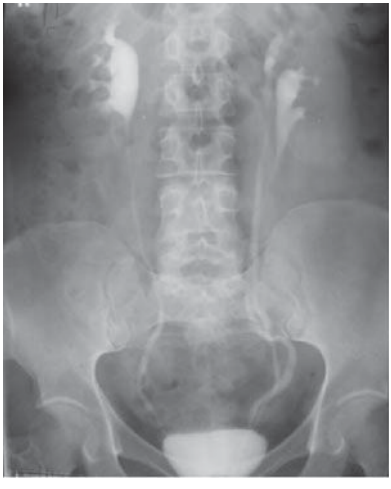

Fig. 8.11 IVU demonstrating complete left-sided renal and ureteric duplication.

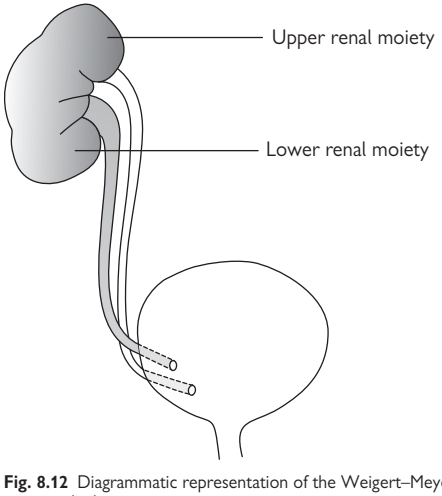

Fig. 8.12 Diagrammatic representation of the Weigert–Meyer rule with complete ureteric duplication.

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Chapter 9

Stone disease

Kidney stones: epidemiology

What is the risk of *de novo* stone formation?

Previous editions of this book have stated that ~10% of Caucasian men will develop a kidney stone by the age of 70. This is very much an average figure since lifetime stone risk is multifactorial, being dependent on a variety of intrinsic (inherent to the patient—sex, age, family history, comorbid conditions) and extrinsic factors (fluid intake, diet, lifestyle, climate, country of residence). In the United States of America (USA), the lifetime prevalence of stones is ~12% for men and ~7% for women. In other western countries, the lifetime risk is probably lower, but the gap between lifetime risk in the USA and that in other countries is probably narrowing as our lifestyles move closer to a USA one.

The prevalence of stone disease is increasing in all western societies. In the USA, the prevalence of stone disease increased from affecting 3.6% of the population in the period 1976–1980 to 5.2% between1988 and 1994.[1] While some of this increase may reflect better diagnostic tests (e.g. the advent of CTU) diagnosing asymptomatic stones, much of this increase is likely to be real. Certainly in the UK, rates of *treatment* for stones have shown a very substantial rise over the last 10y at a time when there have been no substantial changes in technology or technique of stone treatment. Thus, the use of ESWL for treating upper tract stones increased by 55% between 2000 and 2010 with a 127% increase in the number of ureteroscopic stone treatments, 49% of this increase occurring between the periods 2007–8 and 2009–10.[2]

Of 5047 men and women (mean age 57y) undergoing CT colonography screening in 2004–2008 and with no symptoms of stone disease, a staggering 395 (7.8%) had stones (an average of 2 stones per patient, mean stone size 3mm).[3] The prevalence in men was 9.7% and in women 6.3%, but was not (surprisingly) related to diabetes, obesity, and age >60. A substantial proportion of these initially asymptomatic stones became symptomatic over time. Over 10y of follow-up, 81 of these 395 patients (21%) went on to develop at least one symptomatic stone event.

What is the risk of recurrent stone formation in those who have already had a stone?

Once a stone has formed, the risk of future stone disease is very substantially increased. Within 1y of a calcium oxalate stone, 10% of men will form another calcium oxalate stone, ~27–50% will have formed another stone within a mean of 7.5[4] to 9y.[5]

Once a second stone has formed, the frequency of recurrences increases and the interval between relapses becomes smaller.

Factors affecting stone formation

The prevalence of renal tract stone disease is determined by factors *intrinsic* to the individual and by *extrinsic* (environmental) factors. A combination of factors often contributes to risk of stone formation.

Intrinsic factors

The prevalence of stone disease and incidence of new stone events is increasing. Much of this change may relate to the epidemic of obesity sweeping western societies (obesity is associated with increased urinary excretion of stone-promoting substances, e.g. calcium, oxalate, uric acid, and decreased excretion of stone-preventing substances, e.g. citrate). Obese patients have a lower urinary pH which encourages urate stone formation.

- **Age**: the peak incidence of stones occurs between the ages of 20–50y.
- **Sex**: previous editions of this book have stated that males are affected three times as frequently as females, but the gender gap is closing, at least in the USA so that between 1997 and 2002, the male : female ratio for treated stones fell from 1.7:1 to 1.3:1.[6] Testosterone may cause increased oxalate production in the liver (predisposing to calcium oxalate stones) and women have higher urinary citrate concentrations (citrate inhibits calcium oxalate stone formation).
- **Genetic**: kidney stones are relatively uncommon in Native Americans, Black Africans, and American Blacks and more common in Caucasians and Asians. About 25% of patients with kidney stones report a family history of stone disease (the relative risk of stone formation remaining high after adjusting for dietary calcium intake). Familial renal tubular acidosis (predisposing to calcium phosphate stones) and cystinuria (predisposing to cystine stones) are inherited.[7]

Extrinsic (environmental) factors

- **Geographical location, climate, and season**: the relationship between these factors and stone risk is complex. While renal stone disease is more common in hot climates, some indigenous populations of hot climates have a low incidence of stones (e.g. Black Africans, Aborigines) and many temperate areas have a high incidence of stones (e.g. Northern Europe and Scandinavia). This may relate to western lifestyle—excess food, inadequate fluid intake, limited exercise—combined with a genetic predisposition to stone formation.
- **Ureteric stones become more prevalent during the summer**: the highest incidence occurs a month or so after peak summertime temperatures, presumably because of higher urinary concentration in the summer (encourages crystallization). The number of patients presenting acutely with urinary calculi increases by 2.8% for each degree increase in temperature and 0.2% for each hour increase in sunlight hours.[8] Concentrated urine has a lower pH, encouraging cystine and uric acid stone formation. Exposure to sunlight may also increase endogenous vitamin D production, leading to hypercalciuria.
- **Water intake**: low fluid intake (<1200mL/day) predisposes to stone formation[9] and patients who relapse after experiencing a stone are less likely to have increased their fluid intake than those who remain stone-free. Increasing water 'hardness' (high calcium content) may reduce the risk of stone formation, by decreasing urinary oxalate.[10]

- **Diet**: high animal protein intake increases the risk of stone disease (high urinary oxalate, low pH, low urinary citrate).[11,12] High salt intake causes hypercalciuria (through a sodium:calcium co-transport mechanism). Contrary to conventional teaching, epidemiological studies show that in populations, low calcium diets predispose to calcium stone disease and high calcium intake is protective.[13]
- **Occupation**: sedentary occupations predispose to stones compared with manual workers.

1 Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC (2003) Time trends in reported prevalence of kidney stones in the United States: 1976–1994. *Kidney Int* **63**:1817–23.

2 Turney BW, Reynard JM, Noble JG, Keoghane SR. Trends in urological stone disease. *Br J Urol Int* 2011.

3 Boyce CJ, Pickhardt PJ, Lawrence EM, Kim DH, Bruce RJ (2010) Prevalance of urolithiasis in asymptomatic adults: objective determination using low dose non-contrast computerized tomography. *J Urol* **183**:1017–21.

4 *Trinchieri A*, Ostini F, Nespoli R, Rovera F, Montanari E, Zanetti G (1999) A prospective study of recurrence rate and risk factors for recurrence after a first renal stone. *J Urol* **162**:27–30.

5 *Sutherland JW,* Parks JH, Coe FL (1985) Recurrence after a single stone in a community practice. *Mineral Electrolyte Metab* **11**:267–9.

6 *Scales CD,* Curtis LH, Norris RD, *et al.* (2007) Changing gender prevalence of stone disease. *J Urol* **177**:979–82.

7 Curhan GC, Willett WC, Rimm EB, Stampfer MJ (1997) Family history and risk of kidney stones. *J Am Soc Nephrol* **8**:1568–73.

8 Lo SS, Johnston R, Al Sameraaii A, *et al.* (2009) Seasonal variation in the acute presentation of urinary calculi over 8y in Auckland, New Zealand. *BJU Int* **106**:96–101.

9 Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A (1996) Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J Urol* **155**:839–43.

10 Strauss AL, Coe FL, Deutsch L, Parks JH (1982) Factors that predict relapse of calcium nephrolithiasis during treatment. *Am J Med* **72**:17–24.

11 Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ (1997) Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Int Med* **126**:497–504.

12 Borghi L, Schianchi T, Meschi T, *et al.* (2002) Comparison of 2 diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* **346**:77–84.

13 Curhan GC, Willett WC, Rimm EB, Stampfer MJ (1993) A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* **328**:833–8.

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Kidney stones: types and predisposing factors

Stones may be classified according to composition (Table 9.1), X-ray appearance, size, and shape.

Table 9.1 Composition of stones

Stone composition	% of all renal calculi*
Calcium oxalate	80–85
Uric acid**	5–10
Calcium phosphate + calcium oxalate	10
Pure calcium phosphate	Rare
Struvite (infection stones)	2–20
Cystine	1

* The precise distribution of stone types will vary depending on the characteristics of the study population (geographical location, racial distribution, etc.). Hence, the quoted figures do not equate to 100.

** 80% uric acid stones are pure uric acid, and 20% contain some calcium oxalate as well.

Other rare stone types (all of which are radiolucent): indinavir (a protease inhibitor used for treatment of HIV), triamterene (a relatively insoluble potassium-sparing diuretic, most of which is excreted in urine), xanthine.

Radiodensity on X-ray

Three broad categories of stones are described, based on their X-ray appearance. This gives some indication of the likely stone composition and helps, to some extent, to determine treatment options. However, in only 40% of cases is the stone composition correctly identified from visual estimation of the radiodensity on plain X-ray.[3]

Radio-opaque

Opacity implies the presence of substantial amounts of calcium within the stone. Calcium phosphate stones are the most radiodense stones, being almost as dense as bone. Calcium oxalate stones are slightly less radiodense.

Relatively radiolucent on plain X-ray

Cystine stones are relatively radiodense because they contain sulphur (Fig. 9.1). Magnesium ammonium phosphate (struvite) stones are less radiodense than calcium-containing stones.

Completely radiolucent on plain X-ray

Uric acid, triamterene, xanthine, indinavir (cannot be seen even on CTU, hence if suspected, confirm by IVU).

Size and shape

Stones can be characterized by their size, in mm or cm. Stones which grow to occupy the renal collecting system (the pelvis and one or more renal calyces) are known as staghorn calculi since they resemble the horns of a stag (Fig. 9.2). They are most commonly composed of struvite—magnesium ammonium phosphate (being caused by infection and forming under the alkaline conditions induced by urea-splitting bacteria), but may be composed of uric acid, cystine, or calcium oxalate monohydrate.

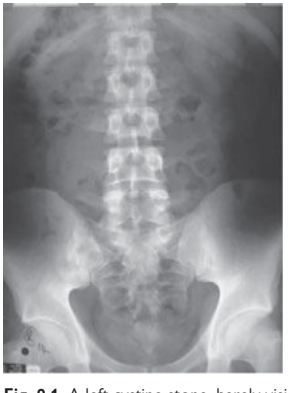

Fig. 9.1 A left cystine stone, barely visible, just below the midpoint of the 12th rib.

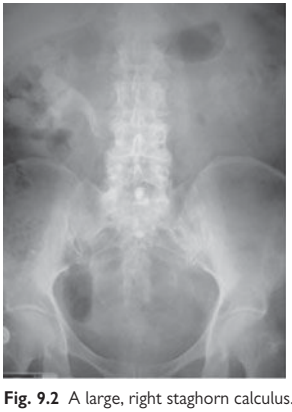

Fig. 9.2 A large, right staghorn calculus.

1 Ramakumar S, Patterson DE, LeRoy AJ, *et al.* (1999) Prediction of stone composition from plain radiographs: a prospective study. *J Endo Urol* **13**:397–401.

Kidney stones: mechanisms of formation

The driving force behind stone formation is the supersaturation of urine. Supersaturation is expressed as the ratio of urinary calcium oxalate (for example) to its solubility. Below a supersaturation of 1, crystals of calcium oxalate remain soluble. Above a supersaturation of 1, crystals of calcium oxalate nucleate and grow, thereby promoting stone formation.

Urine is said to be saturated with, for example, calcium and oxalate when the product of the concentrations of calcium and oxalate exceeds the *solubility product* (K_{sp}). Below K_{sp}, crystals of calcium and oxalate will not form and the urine is said to be *undersaturated*. Above K_{sp}, crystals of calcium and oxalate should form, but they do not because of the presence of *inhibitors* of crystal formation. However, above a certain concentration of calcium and oxalate, inhibitors of crystallization become ineffective and crystals of calcium oxalate start to form. The concentration of calcium and oxalate at which this is reached (i.e. at which crystallization starts) is known as the *formation product* (K_f) and the urine is said to be *supersaturated* with the substance or substances in question at concentrations above this level. Urine is described as being *metastable* for calcium and oxalate at concentrations between the K_{sp} of calcium and oxalate and the K_f (Box 9.1).

The ability of urine to hold more solute in solution than can pure water is due partly to the presence of various inhibitors of crystallization (e.g. citrate forms a soluble complex with calcium, preventing it from combining with oxalate or phosphate to form calcium oxalate or calcium phosphate stones). Other inhibitors of crystallization include magnesium, glycosaminoglycans, and Tamm–Horsfall protein. From a practical perspective, the only inhibitor of stone formation that is open to manipulation is citrate.

Periods of intermittent supersaturation of urine with various substances can occur as a consequence of dehydration and following meals.

The earliest phase of crystal formation is known as nucleation. Crystal nuclei usually form on the surfaces of epithelial cells or on other crystals. Crystal nuclei form into clumps—a process known as aggregation. Citrate and magnesium not only inhibit crystallization, but also inhibit aggregation. Calcium oxalate stones form over a nucleus of calcium phosphate (Randall's plaques on the surface of a renal papilla).

Box 9.1 Steps leading to stone formation

- Calcium and oxalate concentration < solubility product → NO STONE FORMATION.
- Metastable calcium and oxalate concentrations → NO STONE FORMATION.
- Calcium and oxalate concentrations > formation product → STONE.

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Factors predisposing to specific stone types

Calcium oxalate (~85% of stones)

Although most patients with calcium oxalate stones have at least one metabolic abnormality (e.g. hypercalciuria, hyperoxaluria, hypocitratruria), the majority of calcium oxalate stones are idiopathic, i.e. the cause of that metabolic abnormality is unknown.

Hypercalciuria: excretion of >7mmol of calcium per day in men and >6mmol per day in women. The major metabolic risk factor for calcium oxalate stone formation is that it increases the relative supersaturation of urine. Some series suggest that as many as 50% of patients with calcium stone disease have hypercalciuria although the proportion of hypercalciuric patients in other series is lower. There are three types:

- Absorptive: increased intestinal absorption of calcium.
- Renal: renal leak of calcium.
- Resorptive: increased demineralization of bone (due to hyperparathyroidism).

Diet has a major influence on hypercalciuria.

Hypercalcaemia: almost all patients with hypercalcaemia who form stones have primary hyperparathyroidism. Of hyperparathyroid patients, about 1% form stones (the other 99% do not because of early detection of hyperparathyroidism by screening serum calcium).

Hyperoxaluria: is due to the following.

- Altered membrane transport of oxalate, leading to increased renal leak of oxalate.
- **Primary hyperoxaluria:** increased hepatic oxalate production—rare.
- Increased oxalate absorption in short bowel syndrome or malabsorption (enteric hyperoxaluria): the colon is exposed to more bile salts and this increases its permeability to oxalate.

Ascorbic acid and high protein intake increase oxalate production.

Hypocitraturia: citrate forms a soluble complex with calcium (so-called chelation), thus preventing the complexing of calcium with oxalate to form calcium oxalate stones. Distal renal tubular acidosis, hypokalaemia, and carbonic anhydrase inhibitors lead to hypocitraturia.

Hyperuricosuria: high urinary uric acid levels lead to the formation of uric acid crystals on the surface of which calcium oxalate crystals form.

Uric acid (~5–10% of stones)

Humans (unlike birds) are unable to convert uric acid (which is relatively insoluble) into allantoin (which is very soluble). Human urine is supersaturated with insoluble uric acid. Uric acid exists in two forms in urine—uric acid and sodium urate. Sodium urate is 20 times more soluble than uric acid. At a urine pH of 5, <20% of uric acid is present as soluble sodium urate. At urine pH 5.5, half of the uric acid is ionized as sodium urate (soluble) and half is non-ionized as free uric acid (insoluble). At a urine pH of 6.5, >90% of uric acid is present as soluble sodium urate.

Thus, uric acid is essentially insoluble in acid urine and soluble in alkaline urine. Human urine is acidic (because the end products of metabolism are acid) and this low pH, combined with supersaturation of urine with uric acid, predisposes to uric acid stone formation.

About 20% of patients with gout have uric acid stones. Patients with uric acid stones may have:

- **Gout**: 50% of patients with uric acid stones have gout. The chance of forming a uric acid stone if you have gout is in the order of 1% per year from the time of the first attack of gout.
- **Myeloproliferative disorders**: particularly following treatment with cytotoxic drugs, cell necrosis results in release of large quantities of nucleic acids which are converted to uric acid. A large plug of uric acid crystals may form in the collecting system of the kidney in the absence of ureteric colic, causing oliguria or anuria.
- **Idiopathic uric acid stones**: no associated condition.

Calcium phosphate (calcium phosphate + calcium oxalate = 10% of stones)

Occur in patients with renal tubular acidosis (RTA)—a defect of renal tubular H^+ secretion resulting in an impaired ability of the kidney to acidify urine. The urine is, therefore, of high pH and the patient has a metabolic acidosis. The high urine pH increases supersaturation of the urine with calcium and phosphate, leading to their precipitation as stones.

Types of renal tubular acidosis

- **Type 1 or distal RTA**: the distal tubule is unable to maintain a proton gradient between the blood and the tubular fluid; 70% of such patients have stones. When the urine pH is >5.5, the patient has a metabolic acidosis and hypokalaemia, urinary citrate is low, and hypercalciuria is present.
- **Type 2 or proximal RTA**: due to failure of bicarbonate resorption in the proximal tubule. There is associated increased urinary citrate excretion which protects against stone formation.
- **Type 3**: a variant of type 1 RTA.
- **Type 4**: seen in diabetic nephropathy and interstitial renal disease. These patients do not make stones.

If urine pH is >5.5, use the ammonium chloride loading test. Urine pH that remains above 5.5 after an oral dose of ammonium chloride = incomplete distal RTA.

Struvite (infection or triple phosphate stones) (2–20% of stones)

These stones are composed of magnesium, ammonium, and phosphate. They form as a consequence of urease-producing bacteria which produce ammonia from the breakdown of urea (urease hydrolyses urea to carbon dioxide and ammonium) and in so doing, alkalinize urine as in the following equation:

$$NH_2–O–NH_2 + H_2O \rightarrow 2NH_3 + CO_2$$

Under alkaline conditions, crystals of magnesium, ammonium, and phosphate precipitate.

Cystine (1% of all stones)

Occur only in patients with cystinuria—an inherited (autosomal recessive) disorder of transmembrane cystine transport, resulting in decreased absorption of cystine from the intestine and in the proximal tubule of the kidney. Cystine is very insoluble so reduced absorption of cystine from the proximal tubule results in supersaturation with cystine and cystine crystal formation. Cystine is poorly soluble in acid urine (300mg/L at pH 5, 400mg/L at pH 7).

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Evaluation of the stone former

Determination of stone type and a metabolic evaluation allows the identification of the factors that led to stone formation so advice can be given to prevent future stone formation.

Metabolic evaluation depends, to an extent, on the stone type (Table 9.2). In many cases, a stone is retrieved. Stone type is analysed by polarizing microscopy, X-ray diffraction, and infrared spectroscopy rather than by chemical analysis. Where no stone is retrieved, its nature must be inferred from its radiological appearance (e.g. a completely radiolucent stone is likely to be composed of uric acid) or from more detailed metabolic evaluation.

In most patients, multiple factors are involved in the genesis of kidney stones and as a general guide, the following evaluation is appropriate in most patients.

Risk factors for stone disease

- **Diet**: enquire about volume of fluid intake, meat consumption (causes hypercalciuria, high uric acid levels, low urine pH, low urinary citrate), multivitamins (vitamin D increases intestinal calcium absorption, although in healthy post-menopausal women with no history of stone formation vitamin D supplementation does not increase urinary calcium excretion), high doses of vitamin C (ascorbic acid causes hyperoxaluria).
- **Drugs**: corticosteroids (increase enteric absorption of calcium, leading to hypercalciuria), chemotherapeutic agents (breakdown products of malignant cells leads to hyperuricaemia).
- **UTI**: urease-producing bacteria (*Proteus*, *Klebsiella*, *Serratia*, *Enterobacter*) predispose to struvite stones.
- **Mobility**: low activity levels predispose to bone demineralization and hypercalciuria.
- **Systemic disease**: gout, primary hyperparathyroidism, sarcoidosis.
- **Family history**: cystinuria, RTA.
- **Renal anatomy**: PUJO, horseshoe kidney, MSK (up to 2% of patients with calcium-containing stones have MSK).
- **Previous bowel resection or inflammatory bowel disease**: causes intestinal hyperoxaluria.

Metabolic evaluation of the stone former

Patients can be categorized as low risk and high risk for subsequent stone formation. High risk: previous history of a stone (i.e. multiple stone formers), bilateral stones, family history of stones, GI disease, uric acid stones or gout, chronic UTI, nephrocalcinosis, patients with solitary kidneys, staghorn calculi, children and young adults.

Low-risk patient evaluation

U & E, FBC (to detect undiagnosed haematological malignancy), serum calcium (corrected for serum albumin) and uric acid, urine culture, urine dipstick for pH.

Table 9.2 Characteristics of stone types

Stone type	Urine acidity	Mean urine pH (± SEM)
Calcium oxalate	Variable	6 (± 0.4)
Calcium phosphate	Tendency towards alkaline urine	>5.5
Uric acid	Acid	5.5 (± 0.4)
Struvite	Alkaline*	–
Cystine	Normal (5–7)	–

* Urine pH must be above 7.2 for deposition of struvite crystals.

High-risk patient evaluation

As for low-risk patients plus 24h urine for calcium, oxalate, uric acid, cystine; evaluation for RTA.

Urine pH

Urine pH in normal individuals shows variation from pH 5–7. After a meal, pH is initially acid because of acid production from metabolism of purines (nucleic acids in, for example, meat). This is followed by an 'alkaline tide', pH rising to >6.5. Urine pH can help establish what type of stone the patient may have (if a stone is not available for analysis) and can help the urologist and patient in determining whether preventative measures are likely to be effective or not.

- pH <6 in a patient with radiolucent stones suggests the presence of uric acid stones.
- pH consistently >5.5 suggests type 1 (distal) RTA (~70% of such patients will form calcium phosphate stones).

Evaluation for RTA

Evaluate for RTA if: calcium phosphate stones, bilateral stones, nephrocalcinosis, MSK, hypocitraturia.

- If fasting morning urine pH (i.e. first urine of the day) is >5.5, the patient has complete distal RTA.
- First and second morning urine pH are a useful screening test for thedetection of incomplete distal RTA, >90% of cases of RTA having a pH >6 on both specimens. The ammonium chloride loading test involves an oral dose of ammonium chloride (0.1g per kg; an acid load). If serum pH falls <7.3 or serum bicarbonate falls <16mmol/L, but urine pH remains >5.5, the patient has incomplete distal RTA.

Diagnostic tests for suspected cystinuria

Cyanide–nitroprusside colorimetric test ('cystine spot test'): if positive, a24h urine collection is done. A 24h cystine >250mg is diagnostic of cystinuria.[1]

1 Millman S, Strauss AL, Parks JH, Coe FL (1982) Pathogenesis and clinical course of mixed calcium oxalate and uric acid nephrolithiasis. *Kidney Int* **22**:366–70.

Kidney stones: presentation and diagnosis

Kidney stones may present with symptoms or be found incidentally during investigation of other problems. Presenting symptoms include pain or haematuria (microscopic or occasionally macroscopic). Struvite staghorn calculi classically present with recurrent UTIs. Malaise, weakness, and loss of appetite can also occur. Less commonly, struvite stones present with infective complications (pyonephrosis, perinephric abscess, septicaemia, xanthogranulomatous pyelonephritis).

Diagnostic tests

- **Plain abdominal radiography**: calculi that contain calcium are radiodense. Sulphur-containing stones (cystine) are relatively radiolucent on plain radiography.
- Radiodensity of stones in decreasing order: calcium phosphate > calcium oxalate > struvite (magnesium ammonium phosphate) >> cystine.
- Completely radiolucent stones (e.g. uric acid, triamterene, indinavir) are usually suspected on the basis of the patient's history and/or urine pH (pH <6—gout; drug history—triamterene, indinavir) and the diagnosis may be confirmed by USS, CT-KUB, or MRU.
- **Renal USS**: its sensitivity for detecting renal calculi is variable depending on the series. Some series suggest ~95% sensitivity for detecting stones, others just 50%.[1] A combination of plain abdominal radiography and renal ultrasonography is a useful screening test for renal calculi.
- **IVU**: virtually a historical investigation now having, to all intents and purposes, been replaced by CT-KUB. Useful for the rare patient with suspected indinavir stones (which are not visible on CT).
- **CTU**: a very accurate method of diagnosing renal and ureteric stones (except) indinavir stones. Allows accurate determination of stone size and location and good definition of pelvicalyceal anatomy.
- **MRU**: cannot visualize stones, but is able to demonstrate the presence of hydronephrosis.

1 Haddad MC, Sharif HS, Abomelha ME, *et al.* (1992) Management of renal colic: redefining the role of the urogram. *Radiology* **184**:35–6.

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Kidney stone treatment options: watchful waiting and the natural history of stones

The traditional indications for intervention are pain, infection, and obstruction. Haematuria caused by a stone is only very rarely severe or frequent enough to be the only reason to warrant treatment.

Before embarking on treatment of a stone which you think is the cause of the patient's pain or infections, warn them that though you may be able to remove the stone successfully, their pain or infections may persist (i.e. the stone may be coincidental to their pain or infections which may be due to something else). Remember, UTIs are common in women as are stones and it is not, therefore, surprising that the two may coexist in the same patient, but be otherwise unrelated.

Options for stone management are watchful waiting, ESWL, flexible ureteroscopy, PCNL, open surgery, and medical 'dissolution' therapy.

When to watch and wait—and when not to

It is not necessary to treat every kidney stone. As a rule of thumb, the younger the patient, the larger the stone and the more symptoms it is causing, the more inclined we are to recommend treatment. Thus, one would be inclined to do nothing about a 1cm symptomless stone in the kidney of a patient aged 95y. On the other hand, a 1cm stone in a symptomless patient aged 20y runs the risk over the remaining (many) years of the patient's life of causing problems. It could drop into the ureter, causing ureteric colic or it could increase in size and affect kidney function or cause pain.

The results of observational studies are conflicting, some suggesting most renal stones progress—increase in size, cause symptoms, or require intervention while others suggest many do not. In a series of 80 calyceal stones followed over 7.5y (stone size not reported), 45% of the stones increased in size and the authors concluded that 80% would require intervention within 5y.[1] Conversely, 68% of patients with small renal stones remained asymptomatic over 2.5y in Glowacki's study[2] and in Keeley's RCT of ESWL vs watchful waiting for small calyceal stones, only 9% required surgery over an average follow-up of 2y.[3]

Burger's paper[4] is helpful because it relates the risk of intervention to stone size and location, allowing a more tailored approach to decision making. Asymptomatic stones followed over a 3y period were more likely to require intervention (surgery or ESWL) or to increase in size or cause pain if they were >4mm in diameter or if located in a middle or lower pole calyx.[4] The approximate risks over 3y of follow-up of requiring intervention, developing pain, or of increase in stone size relative to stone size is shown in Table 9.3.

Another factor determining the need for treatment is the patient's job. Airline pilots are not allowed to fly if they have kidney stones for fear that the stones could drop into the ureter at 30 000 ft with disastrous consequences! They will only be deemed fit to fly when they are radiologically

stone-free. It is sensible to warn any one whose job entrusts them with the safety of others (pilots, train drivers, drivers of buses and lorries) that they are not fit to carry out these occupations until stone-free or, at the very least, that they should contact the relevant regulatory authority to seek guidance (the Civil Aviation Authority (CAA) for pilots and the Drivers Vehicle Licensing Agency (DVLA) for drivers).[5]

Some stones are definitely not suitable for watchful waiting. Untreated struvite (i.e. infection-related) staghorn calculi will eventually destroy the kidney if untreated and are a significant risk to the patient's life. Watchful waiting is, therefore, NOT recommended for staghorn calculi unless patient comorbidity is such that surgery would be a higher risk than watchful waiting. Historical series suggest that somewhere between 9 and 30% of patients with staghorn calculi who did not undergo surgical removal (from choice or because of comorbidity) died of renal-related causes—renal failure, urosepsis (septicaemia, pyonephrosis, perinephric abscess).[6-8] A combination of a neurogenic bladder and staghorn calculus seems to be particularly associated with a poor outcome.[9]

Table 9.3 Approximate 3-year risk of intervention, pain, or increase in stone size (from Burger 2004)[4]

	Stone size			
	<5mm	**5–10mm**	**11–15mm**	**>15mm**
% Requiring intervention	20	25	40	30
% Causing pain	40	40	40	60
% Increasing in size	50	55	60	70

1 Hubner WA, Porpaczy P (1990) Treatment of calyceal calculi. *Br J Urol* **66**:9–11.

2 Glowacki LS, Beecroft ML, Cook RJ, Pahl D, Churchill DN (1992) The natural history of asymptomatic urolithiasis. *J Urol* **147**:319–21.

3 Keeley FX, Tilling K, Elves A, *et al.* (2001) Preliminary results of a randomized controlled trial of prophylactic shock wave lithotripsy for small asymptomatic renal calyceal stones. *BJU Int* **87**:1–8.

4 Burgher A, Beman M, Holtzman JL, Monga M (2004) Progression of nephrolithiasis: long-term outcomes with observation of asymptomatic calculi *J Endourol* **18**:534–9.

5 Borley NC, Rainford D, Anson KM, Watkin N. (2007) What activities are safe with kidney stones? A review of occupational and travel advice in the UK. *Br J Urol Int* **99**:494–6.

6 Blandy JP, Singh M (1976) The case for a more aggressive approach to staghorn stones. *J Urol* **115**:505–6.

7 Rous SN, Turner WR (1977) Retrospective study of 95 patients with staghorn calculus disease. *J Urol* **118**:902.

8 Vargas AD, Bragin SD, Mendez R (1982) Staghorn calculi: clinical presentation, complications and management *J Urol* **127**:860–2.

9 Teichmann J (1995) Long-term renal fate and prognosis after staghorn calculus management. *J Urol* **153**:1403–7.

Stone fragmentation techniques: extracorporeal lithotripsy (ESWL)

The technique of focusing externally generated shock waves at a target (the stone). First used in humans in 1980. The first commercial lithotriptor, the Dornier HM3, became available in 1983.[1] ESWL revolutionized kidney and ureteric stone treatment.

Three methods of shock wave generation are commercially available—electrohydraulic, electromagnetic, and piezoelectric.

Electrohydraulic: application of a high voltage electrical current between two electrodes about 1mm apart under water causes discharge of a spark. Water around the tip of the electrode is vaporized by the high temperature, resulting in a rapidly expanding gas bubble. The rapid expansion and then the rapid collapse of this bubble generate a shock wave that is focused by a metal reflector shaped as a hemiellipsoid. Used in the original Dornier HM3 lithotriptor.

Electromagnetic: two electrically conducting cylindrical plates are separated by a thin membrane of insulating material. Passage of an electrical current through the plates generates a strong magnetic field between them, the subsequent movement of which generates a shock wave. An 'acoustic' lens is used to focus the shock wave.

Piezoelectric: a spherical dish is covered with about 3000 small ceramic elements, each of which expands rapidly when a high voltage is applied across them. This rapid expansion generates a shock wave.

X-ray, USS, or a combination of both are used to locate the stone on which the shock waves are focused. Older machines required general or regional anaesthesia because the shock waves were powerful and caused severe pain. Newer lithotriptors generate less powerful shock waves, allowing ESWL with oral or parenteral analgesia in many cases, but they are less efficient at stone fragmentation.

Efficacy of ESWL

The likelihood of fragmentation with ESWL depends on the stone size and location, anatomy of renal collecting system, degree of obesity, and stone composition. Most effective for stones <1cm in diameter and in favourable anatomical locations. Less effective for stones >1cm diameter, in lower pole stones in a calyceal diverticulum (poor drainage), and those composed of cystine or calcium oxalate monohydrate (very hard).

Randomized studies show that a lower shock wave rate (60 vs 120 per min) achieves better stone fragmentation and clearance. Animal studies also demonstrate less renal injury and a smaller decrease in renal blood flow from lower shock wave rates.[2]

There have been no randomized studies comparing stone-free rates between different lithotriptors. In non-randomized studies, rather surprisingly, when it comes to the efficacy of stone fragmentation, older (the original Dornier HM3 machine) is better (but with a higher requirement for analgesia and sedation or general anaesthesia). Less powerful (modern) lithotriptors have lower stone-free rates and higher retreatment rates.

Side effects of ESWL (see Fig. 9.3)

ESWL causes a certain amount of structural and functional renal damage (found more frequently the harder you look). Haematuria (microscopic, macroscopic—due to the rupture of intraparencyhmal vessels) and oedema are common, perirenal haematomas less so (0.5% detected on USS with modern machines, although reported in as many as 30% with the Dornier HM3). Effective renal plasma flow (measured by renography) has been reported to fall in ~30% of treated kidneys.

Renal injury during ESWL is significantly reduced by slowing the rate of shock wave delivery from 120 to 30 shock waves per min.[3]

There are data suggesting that ESWL may increase the likelihood of development of hypertension. Acute renal injury may be more likely to occur in patients with pre-existing hypertension, prolonged coagulation time, coexisting coronary heart disease, diabetes, and in those withsolitary kidneys. A retrospective case control study with 19y follow-up has raised the possibility that ESWL may cause pancreatic damage, leading to a higher risk of diabetes—diabetes developed in 16.8% of patients undergoing ESWL vs 6.6% of controls.[4]

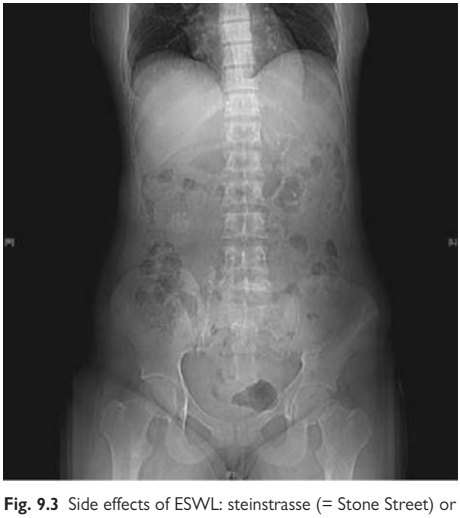

Fig. 9.3 Side effects of ESWL: steinstrasse (= Stone Street) or 'log-jam'.

Should a stent be inserted prior to ESWL to renal (or ureteric) calculi?

Is ESWL more effective in the *absence* of pre-ESWL stenting? Probably yes.[5] Does pre-ESWL stenting reduce the risk of ESWL complications? Probably not. When ESWL was first introduced, stones of all sizes were treated. It soon became apparent that multiple fragments from large stones could obstruct the ureter, causing a so-called steinstrasse (incidence of steinstrasse 2–3% for stones 1.5–2cm diameter; 56% for stones 3–3.5cm).

Whether stenting prior to ESWL can reduce the risk of steinstrasse remains controversial. Pre-ESWL stenting does not reduce the chances of spontaneous resolution of the steinstrasse (spontaneous passage of the stones). We nowadays see steinstrasse only rarely because ESWL tends to be reserved for smaller stones (<2cm) and PCNL for larger stones. Steinstrasse is managed expectantly (since 50% will resolve spontaneously), with ESWL of the so-called 'lead' fragment or ureteroscopy being required where the stones fail to pass.

The overall consensus is that pre-ESWL stenting is probably not necessary in most cases. For patients with solitary kidneys undergoing ESWL, prestenting is an option to reduce the risk of renal obstruction. The alternative is closer monitoring in the days and weeks after ESWL and emergency ureteroscopy where anuria develops.

Contraindications to ESWL

Absolute contraindications: pregnancy, uncorrected blood clotting disorders (including anticoagulation); known renal artery.

BAUS procedure-specific consent form: potential complications after ESWL

Common

- Bleeding on passing urine for short period after procedure.
- Pain in the kidney as small fragments of stone pass after fragmentation.
- UTI from bacteria released from the stone, needing antibiotic treatment.

Occasional

- Stone will not break as too hard, requiring an alternative treatment.
- Repeated ESWL treatments may be required.
- Recurrence of stones.

Rare

- Kidney damage (bruising) or infection, needing further treatment.
- Stone fragments occasionally get stuck in the tube between the kidney and the bladder, requiring hospital attendance and sometimes surgery to remove the stone fragment.
- Severe infection requiring IV antibiotics and sometimes drainage of the kidney by a small drain placed through the back into the kidney.

Alternative therapy

Telescopic surgery, open surgery, or observation to allow spontaneous passage.

What is the fate of the 'clinically insignificant fragment' after ESWL?

Clinically insignificant residual fragments (CIRFs) are residual stone fragments 4mm in size or less after ESWL. 'Clinically insignificant' is something of a misnomer for 12–46% of such fragments will increase in size over a period of 2–3y.[6-10] Given that there is a significant risk of increase in stone size and given our knowledge that stones that grow are likely to continue to do so and, therefore, require intervention or to become symptomatic and so require intervention, radiological follow-up of such patients seems to be sensible. How (plain X-ray if the stones are visible, USS or CT), how often and by whom (in primary care or by urologists) are contentious issues?

1 Chaussy CG, Brendel W, Schmidt E (1980) Extracorporeal induced destruction of kidney stones by shock waves. *Lancet* **2**:1265–8.

2 Semins MJ, Trock BJ, Matlaga BR (2008) The effect of shock wave rate on the outcome of shock wave lithotripsy: a meta-analysis. *J Urol* **179**:194–7.

3 Evan AP, McAteer JA, Connors BA, Blomgren PM, Lingeman JE (2007) Renal injury during shock wave lithotripsy is significantly reduced by slowing the rate of shock wave delivery. *BJU Int* **100**:624–7.

4 Kramback AE, Gettman MT, Rohlinger AL, *et al.* (2006) Diabetes mellitus and hypertension associated with shock wave lithotripsy of renal and proximal ureteric stones at 19y of follow-up. *J Urol* **175**:1742–7.

5 Haleblian, Kijvikai K, de la Rosette J, Preminger G (2008) Ureteral stenting and urinary stone management: a systematic review. *J Urol* **179**:424–30.

6 Candau C, Saussine C, Lang H, Roy C, Faure F, Jacqmin D (2000) Natural history of residual renal stone fragments after ESWL. *Eur Urol* **37:**18–22.

7 Streem SB, Yost A, Mascha E (1996) Clinical implications of clinically insignificant stone fragments after extracorporeal shock wave lithotripsy. *J Urol* **155:**1186–90.

8 El-Nahas AR, El-Assmy AM, Madbouly K, Sheir KZ. (2006) Predictors of clinical significance of residual fragments after extracorporeal shockwave lithotripsy for renal stones. *J Endourol* **20**:870–4.

9 Zanetti G, Seveso M, Montanari E, *et al.* (1997) Renal stone fragments following shock wave lithotripsy. *J Urol* **158**:352–5.

10 Buchholz N, Meier-Padel S, Rutishauser G (1997) Minor residual fragments after extracorporeal shockwave lithotripsy: spontaneous clearance or risk factor for recurrent stone formation. *J Endourol* **11**:227–32.

Intracorporeal techniques of stone fragmentation

Electrohydraulic lithotripsy (EHL)

The first technique developed for intracorporeal lithotripsy. A high voltage applied across a concentric electrode under water generates a spark. This vaporizes water and the subsequent expansion and collapse of the gas bubble generates a shock wave. An effective form of stone fragmentation. The shock wave is not focused so the EHL probe must be applied within 1mm of the stone to optimize stone fragmentation.

EHL has a narrower safety margin than pneumatic, ultrasonic, or laser lithotripsy and should be kept as far away as possible from the wall of the ureter, renal pelvis, or bladder to limit damage to these structures and at least 2mm away from the cystoscope, ureteroscope, or nephroscope to prevent lens fracture.

Principal uses: bladder stones (wider safety margin than in the narrower ureter).

Pneumatic (ballistic) lithotripsy

A metal projectile contained within the handpiece is propelled backwards and forwards at great speed by bursts of compressed air (Fig. 9.4a). It strikes a long, thin, metal probe at one end of the handpiece at 12Hz (12 strikes per second) transmitting shock waves to the probe which, when in contact with a rigid structure such as a stone, fragments the stone. Used for stone fragmentation in the ureter (using a thin probe to allow insertion down a ureteroscope) or kidney (a thicker probe may be used, with an inbuilt suction device—'Lithovac'—to remove stone fragments).

Pneumatic lithotripsy is very safe since the excursion of the end of the probe is about 1mm and it bounces off the pliable wall of the ureter. Ureteric perforation is, therefore, rare. Also low cost and low maintenance. However, its ballistic effect has a tendency to cause stone migration into the proximal ureter or renal pelvis where the stone may be inaccessible to further treatment. The metal probe cannot bend around corners so it cannot be used for ureteroscopic treatment of stones within the kidney.

Principal uses: ureteric stones.

Ultrasonic lithotripsy

An electrical current applied across a piezoceramic plate located in the ultrasound transducer generates ultrasound waves of a specific frequency (23 000–25 000Hz). The ultrasound energy is transmitted to a hollow metal probe which, in turn, is applied to the stone (Fig. 9.4b). The stone resonates at high frequency and this causes it to break into small fragments (the opera singer breaking a glass) which are then sucked out through the centre of the hollow probe. Soft tissues do not resonate when the probe is applied to them and, therefore, are not damaged. Can only be used down straight instruments.

Principal uses: fragmentation of renal calculi during PCNL.

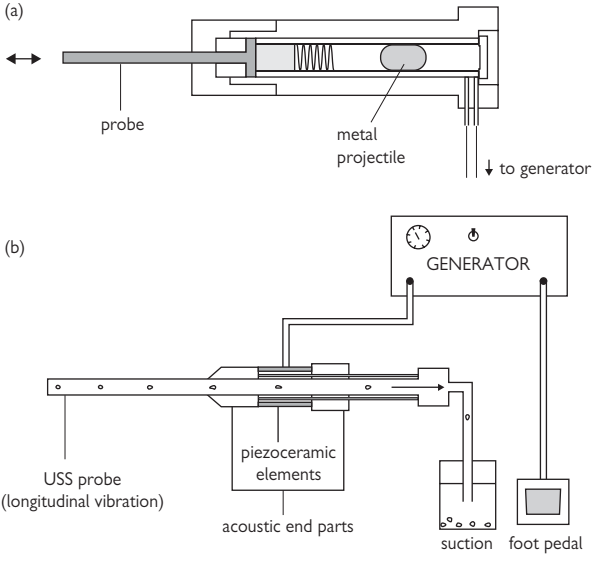

Fig. 9.4 (a) The Lithoclast: a pneumatic lithotripsy device (b) The Calcuson: an ultrasonic lithotripsy device. (Reproduced from Walsh PC, Retik AB, Vaughan D, et al. (2002) Campbell's Urology, 8th edn. Amsterdam: W.B. Saunders/Elsevier, pp. 3395–7 with permission from Elsevier).

Laser lithotripsy

The holmium:YAG laser. Principally, a photothermal mechanism of action, causing stone vaporization. Minimal shock wave generation and, therefore, less risk of causing stone migration. The laser energy is delivered down fibres which vary in diameter from 200 to 360μm. The 200μm fibre is very flexible and can be used to gain access to stones even within the lower pole of the kidney (Figs. 9.5 and 9.6). A 275μm fibre delivers more laser energy at the expense of a reduction in flexibility and, therefore, a reduced chance of lower pole access. The zone of thermal injury is limited from 0.5 to 1mm from the laser tip. No stone can withstand the heat generated by the Ho:YAG laser. Laser lithotripsy takes time, however, since the thin laser fibre must be 'painted' over the surface of the stone to vaporize it.

Principal uses: ureteric stones, small intrarenal stones.

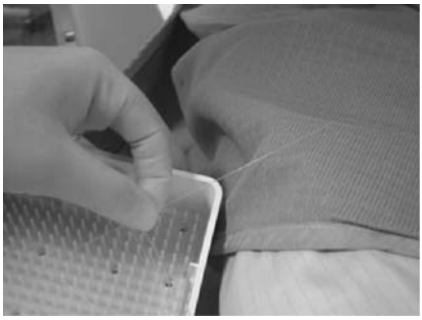

Fig. 9.5 A laser fibre.

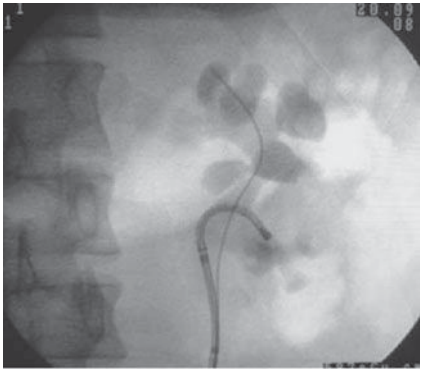

Fig. 9.6 Access to the lower pole of the kidney with a flexible ureteroscope.

Flexible ureteroscopy and laser treatment

The development of small calibre ureteroscopes with active deflecting mechanisms and instrument channels, in combination with the development of laser technology, small diameter laser fibres, and stone baskets and graspers, has opened the way for intracorporeal, endoscopic treatment of kidney stones. Access to virtually the entire collecting system is possible with modern instruments. The holmium:YAG laser has a minimal effect on tissues at distances of 2–3mm from the laser tip and so 'collateral' tissue damage is minimal with this laser type.

Flexible ureteroscopy and laser fragmentation offer a more effective treatment option compared with ESWL, with a lower morbidity than PCNL, but usually requires a general anaesthetic (some patients will tolerate it with sedation alone). It can also allow access to areas of the kidney where ESWL is less efficient or where PCNL cannot reach. It is most suited to stones <2cm in diameter.

Indications for flexible ureteroscopic kidney stone treatment

- ESWL failure.
- Lower pole stone (reduces the likelihood of stone passage post-ESWL—fragments have to pass 'uphill').
- Cystine stones.
- Obesity such that PCNL access is technically difficult or impossible (nephroscopes may not be long enough to reach the stone).
- Obesity such that ESWL is technically difficult or impossible. BMI >28 is associated with lower ESWL success rates. Treatment distance may exceed the focal length of the lithotripter.
- Musculoskeletal deformities such that stone access by PCNL or ESWL is difficult or impossible (e.g. kyphoscoliosis).
- Stone in a calyceal diverticulum (accessing stones in small diverticulae in upper and anterior calyces is difficult and carries significant risks).
- Stenosis of a calyceal infundibulum or 'tight' angle between the renal pelvis and infundibulum. The flexible ureteroscope can negotiate acute angles and the laser can be used to divide obstructions.
- Bleeding diathesis where reversal of this diathesis is potentially dangerous or difficult.
- Horseshoe or pelvic kidney. ESWL fragmentation rates are only 50% in such cases[1] due to difficulties of shock wave transmission through overlying organs (bowel). PCNL for such kidneys is difficult because of bowel proximity and variable blood supply (blood supply derived frommultiple sources).
- Patient's preference.

Disadvantages

Efficacy diminishes as stone burden increases—it simply takes a long time to 'paint' the surface of the stone with laser energy so destroying it. A dust cloud is produced as the stone fragments and this temporarily obscures

the view until it has been washed away by irrigation. Stone fragmentation rates for those expert in flexible ureteroscopy (not every stone surgeon will be able to achieve these results) are ~70–80% for stones <2cm in diameter and 50% for those >2cm in diameter[2] and ~10% of patients will require two or more treatment sessions.[2]

1 Kupeli B, Isen K, Biri H, *et al.* (1999) Extracorporeal shockwave lithotripsy in anomalous kidneys. *J Endourol* **13**:39–52.

2 Dasgupta P, Cynk MS, Bultitude MF, Tiptaft RC, Glass JM. (2004) Flexible ureterorenoscopy: prospective analysis of the Guy's experience. *Ann R Coll Surg* **86**:367–70.

Kidney stone treatment: percutaneous nephrolithotomy (PCNL)

Technique

PCNL is the removal of a kidney stone via a 'track' developed between the surface of the skin and the collecting system of the kidney. The first step requires 'inflation' of the renal collecting system (pelvis and calyces) with fluid or air instilled via a ureteric catheter inserted cystoscopically (Fig. 9.7). This makes subsequent percutaneous puncture of a renal calyx with a nephrostomy needle easier (Fig. 9.8). Once the nephrostomy needle is in the calyx, a guide wire is inserted into the renal pelvis to act as a guide over which the 'track' is dilated (Fig. 9.9). An access sheath is passed down the track and into the calyx and through this, a nephroscope can be advanced into the kidney (Fig. 9.10). An ultrasonic lithotripsy probe is used to fragment the stone and remove the debris.

A posterior approach is most commonly used, below the 12th rib (to avoid the pleura and far enough away from the rib to avoid the intercostals, vessels, and nerve). The preferred approach is through a posterolateral calyx rather than into the renal pelvis because this avoids damage to posterior branches of the renal artery which are closely associated with the renal pelvis. General anaesthesia is usual, though regional or even local anaesthesia (with sedation) can be used.

Indications for and outcomes of PCNL

PCNL is generally recommended for stones >3cm in diameter, those that have failed ESWL, and/or an attempt at flexible ureteroscopy and laser treatment. It is the first-line option for staghorn calculi,[1] with ESWL and/or repeat PCNL being used for residual stone fragments. For staghorn stones, the stone-free rate of PCNL, when combined with post-operative ESWL for residual stone fragments, is in the order of 80–85%.

For middle and upper pole stones 2–3cm in diameter, options include ESWL (with a JJ stent *in situ*), flexible ureteroscopy and laser treatment, and PCNL. PCNL gives the best chance of complete stone clearance with a single procedure, but this is achieved at a higher risk of morbidity. Some patients will opt for several sessions of ESWL or flexible ureteroscopy/laser treatment and the possible risk of ultimately requiring PCNL because of failure of ESWL or laser treatment rather than proceeding with PCNL 'up front'. About 50% of stones >2cm in diameter will be fragmented by flexible ureteroscopy and laser treatment.

For lower pole stones PCNL achieves substantially higher stone clearance than ESWL for all stones sizes (<1cm, 100% vs 63%; 1–2cm, 93% vs 23%; >2–3cm, 86% vs 14%)[2]. It is also achieves superior stone-free rates compared to flexible ureteroscopy/laser treatment for lower pole stones between 1–2.5cm (71% vs 37%).[3] Again, better stone-free rates must be balanced against higher morbidity.

Post-PCNL tube drainage vs tubeless PCNL?

PCNL is traditionally followed by the placement of a large bore nephrostomy tube, the rationale being to tamponade bleeding from the track (less frequently, the tube is used to keep the track patent to allow the option of check nephroscopy if post-operative imaging—a CT scan or nephrostogram—demonstrates residual stone). The disadvantage is more post-operative pain and requirement for analgesics and longer hospital stay (though some reports suggest tubed PCNL does not increase any of these parameters). As a consequence, tubeless PCNL is now in vogue—tubeless meaning no nephrostomy tube, but usually some form of ureteric drainage, e.g. a J stent or ureteric catheter (i.e. 'tubeless' PCNL is actually 'relatively tubeless'; there are occasional reports of 'totally tubeless' PCNL).

The use of track sealants has been suggested, but there is no convincing proof that they reduce bleeding or urinary extravasation. Track diathermy and cryoablation (a 10min freeze–thaw cycle) have also been reported.

A recent review[4] suggests that tubeless PCNL should be the default, but that the decision to place a tube should be individualized—partly based on the surgeon's experience and erring on the side of tube placement in cases with more than two access tracks; infection stones (most staghorns); significant intraoperative bleeding; collecting system perforation (though one could argue that antegrade J stent insertion or ureteric catheter drainage might be just as effective); where a second look is anticipated (e.g. especially large stone burden).

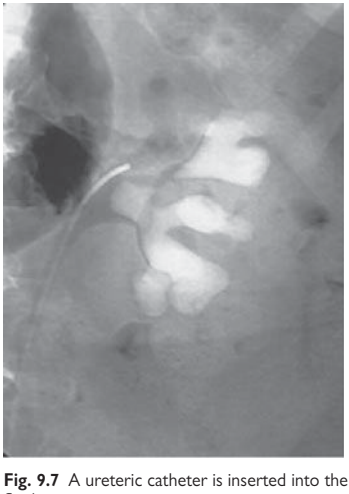

Fig. 9.7 A ureteric catheter is inserted into the renal pelvis to dilate it with air or fluid.

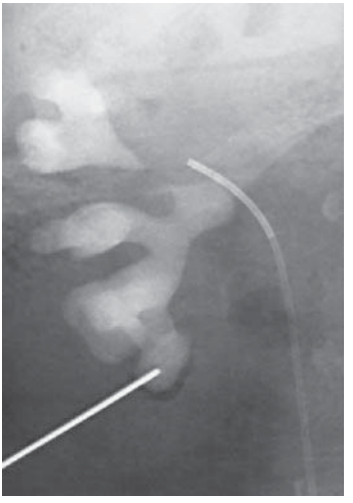

Fig. 9.8 A nephrostomy needle has been inserted into a calyx.

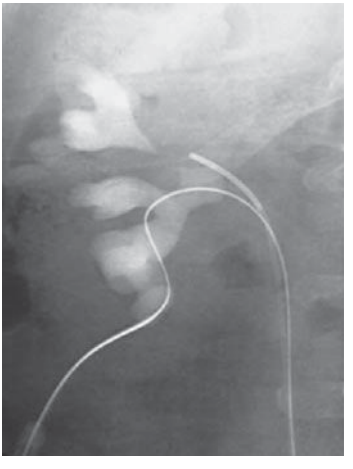

Fig. 9.9 A guide wire is inserted into the renal pelvis and down the ureter; over this guide wire, the track is dilated.

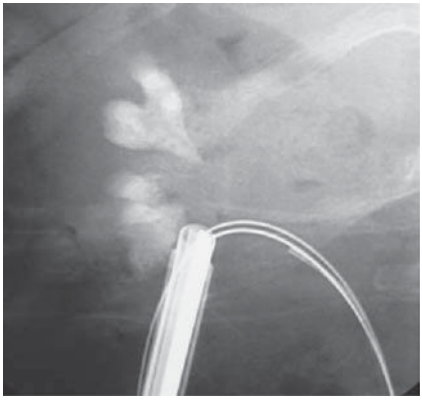

Fig. 9.10 An access sheath is passed down the track and into the calyx and through this, a nephroscope can be advanced into the kidney.

Supine vs prone PCNL?

Traditionally, PCNL is performed in the prone position (once access to the renal collecting system has been gained with the patient in the supine position, the patient is turned from supine to prone after the initial ureteric catheterization). 'Supine' PCNL (keeping the patient in the supine position throughout the procedure, rotated to one or other side to allow access to the appropriate flank) has recently been proposed as an alternative approach, the potential advantages being:[5] (1) reduced operating time (no time is wasted turning the patient), (2) lower anaesthetic morbidity (the prone position reduces cardiac output), (3) easier management of airway problems (it is difficult to access the airway in a prone patient), (4) should haemorrhage occur, arterial and central venous line insertion is easier, (5) it allows the potential for manipulating the renal stone burden not only percutaneously, but also ureteroscopically (the argument being that a 'two-handed' approach is better than a one-handed one). Whether the supine position will become the preferred option remains to be seen.

What treatment is best for the smaller (<3cm) lower pole kidney stone?

It is more difficult to achieve a stone-free status for lower pole kidney stones compared with stones in the upper and middle pole calyces because of poor clearance of stone fragments from the dependent lower pole. Lower Pole I[1] and another randomized study comparing stone-free rates for lower pole stones treated either by flexible ureterorenoscopy vs ESWL or flexible ureterorenoscopy vs PCNL inform treatment decisions (Tables 9.4 and 9.5).

Table 9.4 Stone-free rates for lower pole stones: PCNL vs ESWL[2]

Stone size (cm)	PCNL (%)	ESWL (%)
<1	100	63
1–2cm	93	23
>2–3cm	86	14

Table 9.5 Stone-free rates for lower pole stones: flexible ureterorenoscopy (F-URS) vs ESWL and flexible ureterorenoscopy vs PCNL[3]

Stone size (cm)	ESWL (%)	F-URS (%)	PCNL (%)
Group 1: <1	35	50	–
Group 2: 1–2.5	–	37	71

The convenience of ESWL over flexible ureterorenoscopy (outpatient procedure, no anaesthetic, much shorter recovery time) means that many patients prefer ESWL over flexible ureterorenoscopy if given the choice. Comparing flexible ureterorenoscopy vs PCNL, stone-free rates strongly favour PCNL. For stones <3cm, convalescence time is similar.

For the 1cm or smaller stones, ESWL or flexible ureterorenoscopy are reasonable first-line approaches, but warn the patient that stone clearance is relatively low for both (35% vs 50%).

For stones between 1 and 2cm, PCNL achieves higher clearance rates, although the potential for morbidity is higher. In the above well-designed study, flexible ureterorenoscopy was able to clear stones in only one-third of patients (no doubt this relatively low success rate was due to the use of very accurate non-enhanced CT scanning to determine stone-free status 3 months after treatment as opposed to plain radiography).[6]

For stones >2cm, PCNL achieves higher clearance rates than any other modality.

1 Segura JW, Preminger GM, Assimos DG, *et al.* (1994) Nephrolithiasis clinical guidelines panel summary report on the management of staghorn calculi. *J Urol* **151**:1648–51.

2 Albala DM, Assimos DG, Clayman RV, *et al.* (2001) Lower pole I: a prospective randomized trial of ESWL and PCNL for lower pole nephrolihiasis–initial results. *J Urol* **166**:2072.

3 Pearle MS, Lingeman JE, Leveillee R, *et al.* (2005) Prospective randomized trial comparing shock wave lithotripsy and ureteroscopy for lower pole calyceal calculi 1 cm or less. *J Urol* **173**:2005–9.

4 Zilberman DE, Lipkin ME, de la Rosette JJ, *et al.* (2009) Tubeless percutaneous nephrolithotomy – the new standard of care? *J Urol* **184**:1261–6.

5 Atkinson CJ, Turney BW, Noble JG, Reynard JM, Stoneham MD (2011) Supine v prone percutaneous nephrolithotomy: ananaesthetist's view. *BJU Int* **108**:306–8.

6 Dasgupta P, Cynk MS, Bultitude MF, Tiptaft RC, Glass JM (2004) Flexible ureterorenoscopy: prospective analysis of the Guy's experience. *Ann R Coll Surg Engl* **86**:367–70.

Kidney stones: open stone surgery

Indications

- Complex stone burden (projection of stone into multiple calyces such that multiple PCNL tracks would be required to gain access to all the stone).
- Failure of endoscopic treatment (technical difficulty gaining access to the collecting system of the kidney).
- Anatomic abnormality that precludes endoscopic surgery (e.g. retrorenal colon).
- Body habitus that precludes endoscopic surgery (e.g. gross obesity, kyphoscoliosis—open stone surgery can be difficult).
- Patient's request for a single procedure where multiple PCNLs might be required for stone clearance.
- Non-functioning kidney.

Non-functioning kidney

Where the kidney is not working, the stone may be left *in situ* if it is not causing symptoms (e.g. pain, recurrent urinary infection, haematuria). However, staghorn calculi should be removed unless the patient has comorbidity that would preclude safe surgery because of the substantial risk of developing serious infective complications. If the kidney is non-functioning, the simplest way of removing the stone is to remove the kidney.

Functioning kidneys—options for stone removal

Small- to medium-sized stones

- Pyelolithotomy.
- Radial nephrolithotomy.

Staghorn calculi

- Anatrophic (avascular) nephrolithotomy.
- Extended pyelolithotomy with radial nephrotomies (small incisions over individual stones).
- Excision of the kidney, 'bench' surgery to remove the stones, and autotransplantation.

Specific complications of open stone surgery

Wound infection (the stones operated on are often infection stones), flank hernia, wound pain. (With PCNL these problems do not occur, blood transfusion rate is lower, analgesic requirement is less, mobilization is more rapid, and discharge earlier—all of which account for PCNL having replaced open surgery as the mainstay of treatment of large stones.) There is a significant chance of stone recurrence after open stone surgery (as for any other treatment modality) and the scar tissue that develops around the kidney will make subsequent open stone surgery technically more difficult.

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Kidney stones: medical therapy (dissolution therapy)

Uric acid and cystine stones are potentially suitable for dissolution therapy. Calcium within either stone type reduces the chances of successful dissolution.

Uric acid stones

Urine is frequently supersaturated with uric acid (derived from a purine-rich diet, i.e. animal protein). Fifty percent of patients who form uric acid stones have gout. The other 50% do so because of a high protein and low fluid intake ('western' lifestyle). In patients with gout, the risk of developing stones is ~1% per year after the first attack of gout.

Uric acid stones form in concentrated acid urine. Dissolution therapy is based on hydration, urine alkalinization, allopurinol, and dietary manipulation—the aim being to reduce urinary uric acid saturation. Maintain a high fluid intake (urine output 2–3L/day), 'alkalinize' the urine to pH 6.5–7 (sodium bicarbonate 650mg tds or qds or potassium citrate 30–60mEq day, equivalent to 15–30mL of a potassium citrate solution tds or qds). In those with hyperuricaemia or urinary uric acid excretion >1200mg/day, add allopurinol 300–600mg/day (inhibits the conversion of hypoxanthine and xanthine to uric acid). Dissolution of large stones (even staghorn calculi) is possible with this regimen.

Cystine stones

Cystinuria is an inherited kidney and intestinal transepithelial transport defect for the amino acids cystine, ornithine, arginine, and lysine ('COAL'), leading to excessive urinary excretion of cystine. Autosomal recessive inheritance; prevalence of 1 in 700 are homozygous (i.e. both genes defective); occurs equally in both sexes. About 3% of adult stone formers are cystinuric and 6% of stone-forming children.

Most cystinuric patients excrete about 1g of cystine per day, which is well above the solubility of cystine. Cystine solubility in acid solutions is low (300mg/L at pH 5, 400mg/L at pH 7). Patients with cystinuria present with renal calculi, often in their teens or twenties. Cystine stones are relatively radiodense because they contain sulphur atoms. The cyanide nitroprusside test will detect most homozygote stone formers and some heterozygotes (false positives occur in the presence of ketones).

Treatment of existing stones and prevention of further stones

The aim is to:

- Reduce cystine excretion (dietary restriction of the cystine precursor amino acid methionine and also of sodium intake to <100mg/day).
- Increase solubility of cystine by alkalinization of the urine to pH >7.5, maintenance of a high fluid intake, and use of drugs which convert cystine to more soluble compounds.

D-penicillamine, N-acetyl-D-penicillamine, and mercaptopropionylglycine (Tiopronin) bind to cysteine as does captopril—the compounds so

formed are more soluble in urine than is cystine alone. D-penicillamine has potentially unpleasant and serious side effects (allergic reactions, nephrotic syndrome, pancytopenia, proteinuria, epidermolysis, thrombocytosis, hypogeusia). Therefore, reserved for cases where alkalinization therapy and high fluid intake fail to dissolve the stones.

Treatment for failed dissolution therapy

Cystine stones are very hard and are, therefore, relatively resistant to ESWL. Nonetheless, for small cystine stones, a substantial proportion will still respond to ESWL. Flexible ureteroscopy (for small) and PCNL (for larger) cystine stones are used where ESWL fragmentation has failed.

Ureteric stones: presentation

Ureteric stones usually present with sudden onset of severe flank pain which is colicky (waves of increasing severity are followed by a reduction in severity, but it seldom goes away completely). It may radiate to the groin as the stone passes into the lower ureter. About 50% of patients with classic symptoms for a ureteric stone do not have a stone confirmed on subsequent imaging studies nor do they physically ever pass a stone.

Examination

Spend a few seconds looking at the patient. Ureteric stone pain is colicky—the patient moves around, trying to find a comfortable position. They may be doubled up with pain. Patients with conditions causing peritonitis (e.g. appendicitis, a ruptured ectopic pregnancy) lie very still: movement and abdominal palpation are very painful.

Pregnancy test

Arrange a pregnancy test in premenopausal women (this is mandatory in any premenopausal woman who is going to undergo imaging using ionizing radiation). If positive, refer to a gynaecologist; if negative, arrange imaging to determine whether they have a ureteric stone.

Dipstick or microscopic haematuria

Many patients with ureteric stones have dipstick or microscopic haematuria (and more rarely, macroscopic haematuria), but 10–30% have no blood in their urine.[1,2] The sensitivity of dipstick haematuria for detecting ureteric stones presenting acutely is ~95% on the first day of pain, 85% on the second day, and 65% on the third and fourth days.[2] Therefore, patients with a ureteric stone whose pain started 3–4 days ago may not have blood detectable in their urine. Dipstick testing is slightly more sensitive than urine microscopy for detecting stones (80% vs 70%) because blood cells lyse and, therefore, disappear if the urine specimen is not examined under the microscope within a few hours. Both ways of detecting haematuria have roughly the same specificity for diagnosing ureteric stones (~60%).

Remember, blood in the urine on dipstick testing or microscopy may be a coincidental finding because of non-stone urological disease (e.g. neoplasm, infection) or a false positive test (no abnormality is found in ~70% of patients with microscopic haematuria despite full urological investigation).

Temperature

The most important aspect of examination in a patient with a ureteric stone confirmed on imaging is to measure their temperature. If the patient has a stone and a fever, they may have infection proximal to the stone. A fever in the presence of an obstructing stone is an indication for urine and blood culture, IV fluids and antibiotics, and nephrostomy drainage or J stent insertion if the fever does not resolve within a matter of hours.[1,2]

1 Luchs JS, Katz DS, Lane DS, *et al.* (2002) Utility of hematuria testing in patients with suspected renal colic: correlation with unenhanced helical CT results. *Urology* **59**:839.

2 Kobayashi T, Nishizawa K, Mitsumori K, Ogura K (2003) Impact of date of onset on the absence of hematuria in patients with acute renal colic. *J Urol* **1770**:1093–6.

Ureteric stones: diagnostic radiological imaging

The IVU, for many years the mainstay of imaging in patients with flank pain, has been superseded by CT-KUB, an unenhanced (i.e. no contrast) CT of the kidneys, ureters, and bladder (except in the rare situation of suspected indinavir stones which are not visible on CT-KUB) (Fig. 9.11). Compared with IVU, CT-KUB:

- Has greater specificity (97%) and sensitivity (94–100%) for diagnosing ureteric stones.[1] Can identify non-stone causes of flank pain (Fig. 9.12).
- Requires no contrast administration so avoiding the chance of a contrast reaction (risk of fatal anaphylaxis following the administration of low osmolality contrast media for IVU is in the order of 1 in 100 000).[2]
- Is faster, taking just a few minutes to image the kidneys and ureters. An IVU, particularly where delayed films are required to identify a stone causing high-grade obstruction, may take hours to identify the precise location of the obstructing stone.
- Is equivalent in cost to IVU in high CT volume hospitals.[3]

CT-KUB radiation dose: approximately 4.7mSv compared to 1.5mSv for IVU (fatal cancer risk is estimated at 1 in 2000 for a 10mSv radiation exposure). Ultra-low dose CT (ULDCT) lowers radiation exposure (0.6–2mSv), but at the expense of a lower sensitivity (68–86%) for small (<3mm) ureteric stones. Contrast-enhanced ultra-low dose CT (CEULDCT) uses contrast which increases sensitivity (97%) and specificity (100%) for detecting small ureteric stone disease while limiting radiation dose to levels comparable with IVU (1.7mSv vs 1.4mSv).[4]

If you only have access to IVU, remember it is contraindicated in patients with previous contrast reactions. Avoid in those with hay fever, a strong history of allergies or asthma who have not been pretreated with high-dose steroids 24h before the IVU. Patients taking metformin for diabetes should stop this for 48h prior to an IVU. Clearly, being able to perform an alternative test such as CT-KUB in such patients is very useful.

Where 24h CT-KUB access is not available, admit patients with suspected ureteric colic for pain relief and arrange a CT-KUB the following morning. When CTU is not immediately available, we arrange urgent abdominal ultrasonography in all patients aged >50y who present with flank pain suggestive of a possible stone to exclude serious pathology, e.g. a leaking abdominal aortic aneurysm and to demonstrate any other gross abnormalities due to non-stone associated flank pain.

Plain abdominal X-ray and renal USS are not sufficiently sensitive or specific for their routine use for diagnosing ureteric stones.

MR urography

Very accurate for identifying ureteric stones.[5] However, at the present time, cost and restricted availability limit its usefulness as a routine diagnostic method of imaging in cases of acute flank pain. This may change as MR scanners become more widely available.

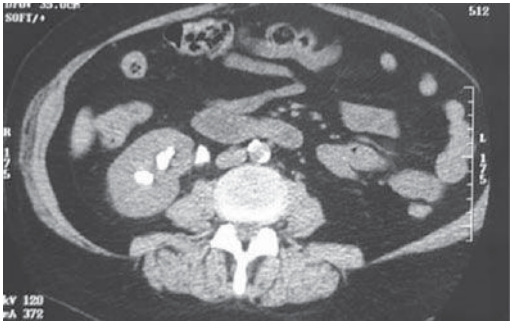

Fig. 9.11 A CT urogram.

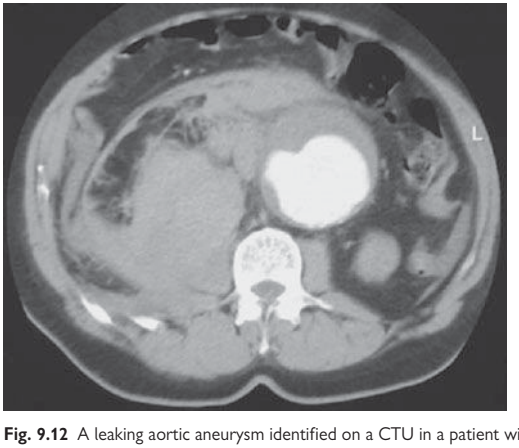

Fig. 9.12 A leaking aortic aneurysm identified on a CTU in a patient with loin pain.

1 Niemann T, Kollmann T, Bongartz G (2008) Diagnostic performance of low dose CT for the detection of urolithiasis. *AJR Am J Roentgenol* **191**:396–401.

2 Caro JJ, Trindale E, McGregor M (1991) The risks of death and severe non-fatal reactions with high vs low osmolality contrast media. *Am J Roentgen* **156**:825–32.

3 Thomson JM, Glocer J, Abbott C, *et al.* (2001) Computed tomography versus intravenous urography in diagnosis of acute flank pain from urolithiasis: a randomized study comparing imaging costs and radiation dose. *Australas Radiol* **45**:291–7.

4 Fowler JC, *et al.* (2011) Clinical evaluation of ultra-low dose contrast-enhanced CT in patients presenting with acute ureteric colic. *Br J Med Surg Urol* **4**:56–63.

5 Leyendecker JR, Gianini JW (2009) Magnetic resonance urography. *Abdominal Imaging* **34**: 527–40.

Ureteric stones: acute management

While appropriate imaging studies are being organized, pain relief should be given.

- NSAIDs (e.g. diclofenac) by intramuscular or IV injection, by mouth or per rectum. Provides rapid and effective pain control. Analgesic effect—partly anti-inflammatory, partly by reducing ureteric peristalsis.
- Where NSAIDs are inadequate, opiate analgesics such as pethidine or morphine are added.

There is no need to encourage the patient to drink copious amounts of fluids nor to give them large volumes of fluids intravenously in the hope that this will 'flush' the stone out. In a randomized trial of forced IV hydration vs minimal hydration, there was no significant difference in analgesic requirement, pain scores, or spontaneous stone passage rates.[1]

Renal blood flow and urine output from the affected kidney falls during an episode of acute partial obstruction due to a stone. Excess urine output will tend to cause a greater degree of hydronephrosis in the affected kidney, which may make ureteric peristalsis* even less efficient than it already is.

The exception to this rule may be those with radiolucent uric acid stones (suspected if low urinary pH and stones not visible on plain X-ray or with lower attenuation on CT compared with calcium, cystine, and struvite stones). High fluid intake and oral potassium citrate, sodium citrate, or sodium bicarbonate (to elevate urine pH to 6–7) may dissolve uric acid stones or at least reduce their size so increasing stone spontaneous passage rates.

Watchful waiting

In many instances, small ureteric stones will pass spontaneously within days or a few weeks, with analgesic supplements for exacerbations of pain.

Data on the rate of spontaneous stone passage are surprisingly limited.[2] Chances of spontaneous stone passage depend principally on stone size. Sixty-eight percent of stones 5mm or less will pass spontaneously (95% CI 46–85%; meta-analysis of 224 patients); 47% of stones 6–10mm in diameter will pass spontaneously (95% CI 36–59%; meta-analysis of 104 patients).[2] Average time for spontaneous stone passage for stones 4–6mm in diameter is 3 weeks.[3] Stones that have not passed in 2 months are unlikely to do so. Of those stones that do eventually pass, those 2mm or less do so within 30 days and those 2–6mm in size do so within 40 days (but not all stones do pass and we cannot predict the chance of spontaneous passage in the individual patient). Therefore, accurate determination of stone size (on plain abdominal X-ray or by CTU) helps predict chances of spontaneous stone passage.

Medical expulsive therapy (MET)

There is growing evidence for the efficacy of MET, the preferred agents being the smooth muscle relaxing α1-adrenergic adrenoceptor blockers.[2,4] These increase spontaneous stone passage rates, reduce stone passage time, and reduce frequency of ureteric colic.[4] The EAU/AUA Nephrolithiasis Guideline Panel meta-analysis showed that 29% more

patients (CI: 20–37%) taking tamsulosin passed their stones compared with controls.[2] Tamsulosin has been most studied in this setting, but terazosin and doxazosin seem to be equally effective. Whether stones in all segments of the ureter are equally responsive to α-blockers remains to be determined.

Another meta-analysis (7 studies, 484 patients)[5] suggests that tamsulosin also seems to encourage stone clearance after ESWL for ureteric (and possibly renal) stones, the pooled absolute risk difference being between 16–19% (0.2 vs 0.4mg) in favour of tamsulosin (so if 70% pass their stones spontaneously without tamsulosin, 89% pass their stones while on 0.4mg tamsulosin). Five patients needed to be treated with tamsulosin to achieve stone clearance in one. There was a mean difference of 8 days in terms of time to stone expulsion in favour of those on tamsulosin.

In the same meta-analysis, there was no significant difference in stone passage rates between those taking the calcium channel blocker, nifedipine, and control patients.

Glyceryl trinitrate patches do not aid stone passage or reduce the frequency of pain episodes and corticosteroids are of minimal, if any, benefit.[4,6]

A trial of MET is a very reasonable approach for many patients, but individual circumstances may dictate 'up front' ESWL or ureteroscopy, e.g. the possible disruption to work and daily living activities from episodes of pain occurring while a stone is progressing towards eventual spontaneous passage may prompt the patient to request ESWL or ureteroscopy (e.g. commercial airline pilots cannot fly until stone-free nor can those who fly for leisure).

MET is contraindicated where there is clinical evidence of sepsis (essentially fever) or deteriorating renal function. If you use a trial of MET, warn patients of the risks (drug side effects, possible need for intervention in the form of ESWL, ureteroscopy, or J stenting) and mention it is an 'off-label' (i.e. non-licensed) therapy. Arrange periodic follow-up imaging (usually a plain X-Ray) to monitor stone position.

* Peristalsis, the forward propulsion of a bolus of urine down the ureter, can only occur if the walls of the ureter above the bolus of urine can coapt, i.e. close firmly together. If they cannot, as occurs in a ureter distended with urine, the bolus of urine cannot move distally.

1 Springhart WP, Marguet CG, Sur RL, *et al.* (2006) Forced versus minimal intravenous hydration in the management of acute renal colic: a randomized trial. *J Endourol* **20**:713–6.

2 Preminger GM, Tiselius HG, Assimos DG, *et al.* (2007) 2007 Guideline for the management of ureteral calculi (Joint EAU/AUA Nephrolithiasis Guideline Panel. *J Urol* **178**:2418–34.

3 Miller OF, Kane CJ (1999) Time to stone passage for observed ureteral calculi. *J Urol* **162**:688–91.

4 Dellabella M, Milanese G, Muzzonigro G (2003) Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol* **170**:2202–5.

5 Zhu Y, Duijvesz D, Rovers MM, Lock TM (2009) Alpha blockers to assist stone clearance after extra-corporeal shock wave lithotripsy: a meta-analysis. *BJU Int* **106**:256–61.

6 Hussain Z, Inman RD, Elves AW, *et al.* (2001) Use of glyceryl trinitrate patches in patients with ureteral stones: a randomized, double-blind, placebo-controlled study. *Urology* **58**:521–5.

Ureteric stones: indications for intervention to relieve obstruction and/or remove the stone

- **Pain**: that fails to respond to analgesics or recurs and cannot be controlled with additional pain relief.
- **Bacteriuria**: in the presence of an obstructing stone can lead to the development of urosepsis. The EAU/AUA Nephrolithiasis Guideline Panel recommends that patients with ureteric stones and bacteriuria be treated with appropriate antibiotics (level IV evidence, i.e based on the opinions or clinical experience of respected authorities). Where intervention is planned (ESWL or ureteroscopy), appropriate antibiotics should be given in advance of the treatment.
- **Fever**: have a low threshold for draining the kidney (either percutaneous nephrostomy or JJ stent).[1]
- **Impaired renal function** (solitary kidney obstructed by a stone, bilateral ureteric stones, or pre-existing renal impairment which gets worse as a consequence of a ureteric stone): threshold for intervention is lower.
- **Prolonged unrelieved obstruction**: this can result in long-term loss of renal function.[1] How long it takes for this loss of renal function to occur is uncertain, but generally speaking, the period of watchful waiting for spontaneous stone passage tends to be limited to 4–6 weeks.
- **Social reasons**: young active patients may be very keen to opt for surgical treatment because they need to get back to work or because of their childcare duties whereas some patients will be happy to sit things out. Airline pilots and some other professions are unable to work until they are stone-free.

Emergency temporizing and definitive treatment of the stone

Where the pain of a ureteric stone fails to respond to analgesics or where renal function is impaired because of the stone, then temporary relief of the obstruction can be obtained by the insertion of a JJ stent or percutaneous nephrostomy tube. (Percutaneous nephrostomy tube can restore efficient peristalsis by restoring the ability of the ureteric wall to coapt.)

JJ stent insertion or percutaneous nephrostomy tube can be done quickly, but the stone is still present (Fig. 9.13). It may pass down and out of the ureter with a stent or nephrostomy *in situ*, but in many instances, it simply sits where it is and subsequent definitive treatment is still required. While JJ stents can relieve stone pain, they can cause bothersome irritative bladder symptoms (pain in the bladder, frequency, and urgency) (see Table 9.6). JJ stents do make subsequent stone treatment in the form of ureteroscopy technically easier by causing passive dilatation of the ureter.

The patient may elect to proceed to definitive stone treatment by immediate ureteroscopy (for stones at any location in the ureter) or ESWL (if the stone is in the upper and lower ureter—ESWL cannot be used for stones in the mid-ureter because this region is surrounded by bone,

which prevents penetration of the shock waves) (Fig. 9.14). Local facilities and expertise will determine whether definitive treatment can be offered immediately. Not all hospitals have access to ESWL or endoscopic surgeons 365 days a year.

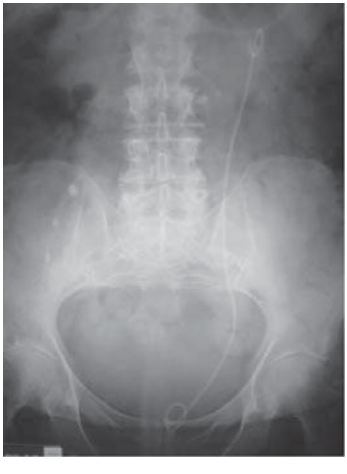

Fig. 9.13 A JJ stent.

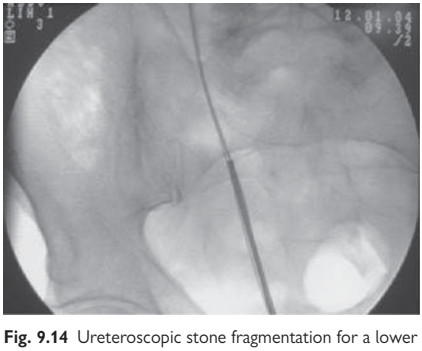

Fig. 9.14 Ureteroscopic stone fragmentation for a lower ureteric stone.

Emergency treatment of an obstructed infected kidney

Antibiotic delivery into an obstructed collecting system is impaired and so the septic patient with an obstructing stone should undergo urgent decompression of the collecting system and definitive stone treatment (ESWL or ureteroscopy) should be delayed until the sepsis has resolved.

The rationale for performing percutaneous nephrostomy, rather than JJ stent insertion for an infected obstructed kidney, is to reduce the likelihood of septicaemia occurring as a consequence of showering bacteria into the circulation. It has been theorized that this is more likely to occur with JJ stent insertion than with percutaneous nephrostomy insertion, that J stent insertion might damage the ureter (unlikely), and that monitoring of urine output and the facility for irrigation of a viscous pyonephrosis is possible with a nephrostomy, but with not a J stent. Nephrostomy insertion has the advantage that it avoids the need for a general anaesthetic, but in fact, J stent insertion can be done with sedation and avoids the risk of bleeding from inadvertent puncture of a branch of the renal artery.[1]

The EAU/AUA Nephrolithiasis Guideline Panel[2] recommends that the system of drainage—J stent or percutaneous nephrostomy—is left to the discretion of the urologist since both have been shown in a randomized trial of 42 patients with obstructing stones and a temperature of >38°C and/or WBC of 17 000/mm^{3*} to be equally effective for the management of presumed obstructive pyelonephritis or pyonephrosis[3] in terms of time to normalization of temperature and WBC (which takes approximately 2–3 days) and in-hospital stay. A 6 or 7 Ch J stent was used (with a Foley bladder catheter in 70%) or 8 Ch (occasionally larger) nephrostomy (plus a urethral catheter in 33%).

Table 9.6 Complications of and problems associated with nephrostomy insertion and drainage (n = 169)[4] and J stent[5,6] (none performed for relief of obstructed, infected kidney; n=226)

Complication	J stent (%)	Nephrostomy (%)
Failure of insertion	16	2
Sepsis in previously non-septic patient		3–4
Haemorrhage requiring transfusion		2
Stent occlusion	1–7	
Tube displacement (tube falling out or for J stent migrating up or down)	0.1–7	5
Pleural effusion		1
Pneumonia/atelectasis		2
Ureteric perforation	6%	
Stent symptoms	Flank pain, 15–20; suprapubic pain, 20; urinary frequency, 40; haema-turia, 40	

* An arbitrary definition of leukocytosis since patients with ureteric stones often have mildly elevated WBC.

1 Holm–Nielsen A, Jorgensen T, Mogensen P, Fogh J (1981) The prognostic value of probe renography in ureteric stone obstruction. *Br J Urol* **53**:504–7.

2 Preminger GM, Tiselius HG, Assimos DG, *et al.* (2007) 2007 Guideline for the management of ureteral calculi, Joint EAU/AUA Nephrolithiasis Guideline Panel. *J Urol* **178**:2418–34.

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Ureteric stone treatment

Almost 70% of stones 5mm or less and almost 50% of stones 6–10mm in diameter will pass spontaneously over a period of 3–6 weeks or thereabouts.[1] Stones that have not passed in 2 months are unlikely to do so, although much to the patient's and surgeon's surprise, large stones do sometimes drop out of the ureter at the last moment.

Indications for stone removal

- Pain that fails to respond to analgesics or recurs and cannot be controlled with additional pain relief.
- Impaired renal function (solitary kidney obstructed by a stone, bilateral ureteric stones, or pre-existing renal impairment which gets worse as a consequence of a ureteric stone).
- Prolonged unrelieved obstruction (generally speaking ~4–6 weeks).
- Social reasons: young active patients may be very keen to opt for surgical treatment because they need to get back to work or because of their childcare duties whereas some patients will be happy to sit things out. Airline pilots and some other professions are unable to work until they are stone-free.

These indications need to be related to the individual patient—their stone size, their renal function, the presence of a normal contralateral kidney, their tolerance of exacerbations of pain, their job and social situation, and local facilities (the availability of surgeons with appropriate skill and equipment to perform endoscopic stone treatment).

Twenty years ago, when the only options were watchful waiting or open surgical removal of a stone (open ureterolithotomy), surgeons, and patients were inclined to 'sit it out' for a considerable time in the hope that the stone would pass spontaneously. Nowadays, the advent of ESWL and of smaller ureteroscopes with efficient stone fragmentation devices (e.g. the holmium laser) has made stone treatment and removal a far less morbid procedure, with a far smoother and faster post-treatment recovery. It is easier for both the patient and the surgeon to opt for intervention, in the form of ESWL or surgery, as a quicker way of relieving them of their pain and a way of avoiding unpredictable and unpleasant exacerbations of pain.

It is clearly important for the surgeon to inform the patient of the outcomes and potential complications of intervention, particularly given the fact that many of stones would pass spontaneously if left a little longer, particularly now there is evidence for MET.

1 Preminger GM, Tiselius HG, Assimos DG, *et al.* (2007). 2007 Guideline for the management of ureteral calculi. Joint EAU/AUA Nephrolituiasis Guideline Panel. *J Urol* **178**: 2418–34.

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Treatment options for ureteric stones

- ESWL: *in situ* or after JJ stent insertion.*
- Ureteroscopy.
- PCNL.
- Open ureterolithotomy.
- Laparoscopic ureterolithotomy.
- Percutaneous antegrade ureteroscopy.

Basketing of stones (blind or under radiographic 'control') is a historical treatment (the potential for serious ureteric injury is significant).

For the purposes of decision making with regard to treatment options, the ureter can be divided into two halves (proximal and distal to the iliac vessels) or in thirds (upper third from the PUJ to the upper edge of the sacrum; middle third from the upper to the lower edge of the sacrum, i.e. the extent of the sacroiliac joint; lower third from the lower edge of the sacrum to the VUJ).

EAU/AUA Nephrolithiasis Guideline Panel recommendations 2007[1]

These should be interpreted in the light of local facilities and expertise. Some hospitals have access to and expertise in the whole range of treatment options. Others may have limited access to a lithotriptor or may not have surgeons skilled in the use of the ureteroscope.

Smaller ureteroscopes with improved optics and larger instrument channels and the advent of holmium laser lithotripsy have improved the efficacy of ureteroscopic stone fragmentation (to ~95% stone clearance) and reduced its morbidity. As a consequence, many surgeons and patients will opt for ureteroscopy, with its potential for a 'one-off ' treatment, over ESWL where more than one treatment will be required and post-treatment imaging is required to confirm stone clearance (with ureteroscopy, you can directly see that the stone has gone).

Many urology departments do not have unlimited access to ESWL and patients may, therefore, opt for ureteroscopic stone extraction.

The stone clearance rates for ESWL are stone size-dependent. ESWL is more efficient for stones <1cm in diameter compared with those >1cm in size. Conversely, the outcome of ureteroscopy is somewhat less dependent on stone size.

The bottom line seems to be that for stones <1cm in diameter, ESWL and ureteroscopy are able to achieve virtually equivalent stone-free rates, but ureteroscopy has the edge over ESWL for stones >1cm (although the difference in stone-free rates is not huge between these two treatments).[2,3]

* ESWL after 'push-back' of the stone into the kidney (i.e. into the renal pelvis or calyces) is a historical treatment for two reasons: (1) *In situ* ESWL (ESWL of the stone located within the ureter) is very effective in most cases without the need to push the stone back into the kidney; (2) If the ESWL fails to fragment the stone, a relatively straightforward operation of ureteroscopy has been converted into the technically more challenging one of flexible ureterorenoscopy. So try to avoid pushing the stone back into the kidney when inserting a J stent, but warn the patient of this possibility.

Efficacy outcomes (i.e. stone-free rates) of EAU/AUA Nephrolithiasis Guideline Panel 2007

Table 9.7 Median stone-free rates of ESWL and ureteroscopy (figures in brackets are 95% CI)1

Stone position and size	ESWL	Ureteroscopy
Distal ureter <10mm	86% (73–75)	97% (96–98)
Distal ureter >10mm	74% (80–90)	93% (88–96)
Mid ureter <10mm	84% (65–95)	91% (81–96)
Mid ureter >10mm	76% (36–97)	78% (61–90)
Proximal ureter <10mm	90% (85–93)	80% (73–85)
Proximal ureter >10mm	68% (55–79)	79% (71–87)

RCTs comparing ESWL and ureteroscopy are generally lacking. The EAU/AUA Nephrolithiasis Guideline Panel 2007 meta-analysis suggests that:

- **Proximal ureter <10mm**: ESWL marginally higher stone-free rate than ureteroscopy.
- **Proximal ureter >10mm**: ureteroscopy marginally higher stone-free rate than ESWL.
- **For all mid-ureteric stones**: ureteroscopy has a marginally higher stone-free rate than ESWL, but small patient numbers make comparison difficult.
- **For all distal stones ureteroscopy**: has a higher stone-free rate than ESWL.

Thus, there are no great differences in stone-free rates between ESWL and ureteroscopy (see Table 9.7). Precisely which technique one uses will depend to a considerable degree on local resources (e.g. ready access to ESWL) and local expertise at performing ureteroscopy, particularly for upper tract stones. Failed initial ESWL is associated with a low success rate for subsequent ESWL.[4] Therefore, if no effect after one or two treatments, change tactics.

Open ureterolithotomy and laparoscopic ureterolithotomy (less invasive than open ureterolithotomy) are used in the rare cases (e.g. very impacted stones) where ESWL or ureteroscopy have been tried and failed or were not feasible.[1] Laparoscopic ureterolithotomy for large, impacted stones has a stone-free rate averaging almost 90%.

Should a stent be inserted after ureteroscopic stone removal?

The standard advice, based on a number of RCTs, is that routine J stenting after an 'uncomplicated' ureteroscopy is unnecessary.[5] 'Uncomplicated ureteroscopy' has not been precisely defined. Definitions include minimal or no ureteral trauma during the process of stone extraction, minimal or no ureteral dilatation required in order to allow ureteroscope access, and no or minimal residual stone burden.

Meta-analyses of post-ureteroscopy complications (emergency room visit, readmission to hospital, requirement for secondary procedures) showed no significant difference in outcome in those stented post-ureteroscopy compared with those not stented.[6,7] Whether there are subgroups of patients who do benefit from stenting post-ureteroscopy remains to be determined.

It has been suggested that post-ureteroscopy stenting reduces ureteric stricture rates, but there is no convincing evidence to support this assertion.[6,7]

1 Preminger GM, Tiselius HG, Assimos DG, *et al.* (2007) 2007 Guideline for the management of ureteral calculi, Joint EAU/ AUA Nephrolithiasis Guideline Panel. *J Urol* **178**:2418–34.

2 Kijvikai K, Haleblian GE, Preminger GM, de la Rosette J (2008) Shock wave lithotripsy or ureteroscopy for the management of proximal ureteral calculi: an old discussion revisited. *J Urol* **178**:1157–63.

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4 Pace KT, Weir MJ, Tariq N, Honey RJ (2000) Low success rate of repeat shock wave lithotripsy for *ureteral* stones after failed initial treatment. *J Urol* **164**:1905–7.

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Prevention of calcium oxalate stone formation

The recurrent nature of stone disease emphasizes the importance of prevention. Recurrence is more likely in those with an onset of stone disease at a young age, a family history for stones, those with an underlying metabolic predisposition (cystinuria, gout), and in those who have had an infection stone (especially in those with neuropathic bladders).

A series of landmark papers from Harvard Medical School[1] and other groups allows us to give rational advice on reducing the risk of future stone formation. The Harvard studies were carried out in those with *no* prior history of stone disease, but are likely to be relevant to those who have already formed a stone (which, of course, is the group most interested in how to avoid the unpleasantness of another stone). The Harvard studies stratified the risk of stone formation based on intake of calcium and other nutrients (Nurses Health Study, n = 81 000 women; equivalent male study, n = 45 000).

Low fluid intake

Low fluid intake may be the single most important risk factor for recurrent stone formation. High fluid intake is protective,[2] by reducing urinary saturation of calcium, oxalate, and urate. Time to recurrent stone formation is prolonged from 2 to 3y in previous stone formers randomized to high fluid vs low fluid intake (averaging ~2.5 vs 1L/day) and over 5y, the risk of recurrent stones was 27% in low-volume controls compared with 12% in high-volume patients.[2]

Dietary calcium

Conventional teaching was that high calcium intake increases the risk of calcium oxalate stone disease. The Harvard Medical School studies have shown that low calcium intake is paradoxically associated with an increased risk of forming kidney stones in both men and women (relative risk of stone formation for the highest quintile of dietary calcium intake vs the lowest quintile = 0.65; 95% CI 0.5–0.83, i.e. high calcium intake was associated with a low risk of stone formation).

Calcium supplements

In the Harvard studies,[1,3] the relative risk of stone formation in women on supplemental calcium (most calcium supplements contain calcium carbonate) compared with those not on calcium was 1.2 (95% CI 1.02–1.4) and for men, it was 1.23 (95% CI 0.84–1.79). In 67% of women and 49% of men on supplements, the calcium was either not consumed with a meal or was consumed with a meal with low oxalate content. It is possible that consuming calcium supplements with a meal or with oxalate-containing foods could reduce this small risk of inducing kidney stones. A total of 650mg of calcium carbonate taken immediately after a meal is associated with a lower urinary oxalate and higher urinary citrate than when taken at bedtime. Urinary calcium excretion increased, but the net effect was a reduction in the activity product for calcium oxalate crystal formation.[4] The bottom line seems to be 'take your calcium supplement at mealtimes'.

In post-menopausal women, calcium citrate, 400 mg twice daily, increases urinary calcium and citrate excretion, reduces oxalate excretion, and does not change urine calcium oxalate saturation, which suggests calcium citrate neither increases nor decreases stone risk.[5]

Those few studies exploring the risk of calcium supplementation in those who have already formed a stone recruited so few subjects that few conclusions can be drawn. A reduction in urine saturation with calcium and oxalate was reported in 22 hyperoxaluric stone formers advised to consume calcium-containing foods or supplemental calcium citrate *with meals* (300–500mg of calcium), entirely in keeping with the protective effect of calcium noted in the Harvard studies (the risk of *actual* stone formation was not assessed).[6] The critical factor may be taking the supplement *at meal times*.

Other dietary risk factors related to stone formation

Increased risk of stone formation (relative risk of stone formation shown in brackets for highest to lowest quintiles of intake of particular dietaryfactor):

- Sucrose (1.5).
- Sodium (1.3): high sodium intake (leading to natriuresis) causes hypercalciuria.
- Potassium (0.65).

Animal proteins

High intake of animal proteins causes increased urinary excretion of calcium, reduced pH, high urinary uric acid, and reduced urinary citrate, all of which predispose to stone formation.[7,8]

Alcohol

Curhan's studies from Harvard[9] suggest small quantities of wine decrease the risk of stones.

Vegetarian diet

Vegetable proteins contain less of the amino acids, phenylalanine, tyrosine, and tryptophan, that increase the endogenous production of oxalate. A vegetarian diet may protect against the risk of stone formation.[10] A low animal protein, low sodium, and low oxalate diet with normal calcium intake (1200mg daily) is associated with a reduction in risk of stone formation of almost 50% over 5y when compared with a diet low in calcium (400mg daily) and oxalate[7].

Dietary oxalate

A small increase in urinary oxalate concentration increases calcium oxalate supersaturation much more than does an increase in urinary calcium concentration. Mild hyperoxaluria is one of the main factors leading to calcium stone formation.[11]

Potassium citrate

Potassium citrate results in a substantial reduction in the risk of stone formation.[12,13] Gastrointestinal side effects (nausea, vomiting, bloating, diarrhoea) are common. Calcium phosphate stones may form in the alkaline urine induced by citrate supplements (keep urine pH <6.5).

Thiazide diuretics

Reduce calcium stone disease by reducing urinary calcium excretion.[14] Hypokalaemia, glucose intolerance, hyperuricaemia, and increased total cholesterol, LDL and triglycerides are potential side effects, the latter predisposing to cardiovascular disease.

Allopurinol

Allopurinol 50–100mg daily reduces calcium oxalate stone recurrence in both urate stone formers and calcium oxalate stone formers.[15]

Calcium salts or calcium supplementation

May be helpful in those with hyperoxaluria or excessive GI oxalate absorption (inflammatory bowel disease, small bowel resection).

Magnesium and phosphate

Magnesium (an inhibitor of crystallization) and phosphate (which reduces GI calcium absorption) are probably not effective.

The bottom line in calcium stone prevention …

High fluid intake (aiming for >2.5L urine output daily); normal calcium intake; low sodium, oxalate, and protein; potassium citrate (e.g. lemon squash).

Prevention of other stone types

- **Uric acid stones**: high fluid intake aiming for urine output >3L/day; alkalinize urine (e.g. citrate), allopurinol (xanthine oxidase inhibitor).
- **Calcium phosphate stones**: usually due to RTA (inability to appropriately acidify the urine). Citrate increases urinary pH and helps reduce stone risk.
- **Cystine stones**: aim to increase free cystine solubility (by alkalinizing urine to pH >7 with citrate and bicarbonate) and reduce its urinary concentration to <500micromol/L (increase fluid intake to >4L/day; night time fluids help). Penicillamine, α-mercaptopropionlyglycine (Tiopronin), and captopril bind with cystine to form soluble dimers.
- **Infection stones**: a difficult one, especially in the neuropathic patient since sterilizing the urine may be impossible in the context of indwelling catheters. Consider low-dose antibiotics although whether they reduce stone recurrence rates is debatable (warn of rare, but serious, side effects: nitrofurantoin—pulmonary fibrosis; trimethoprim—haematological).

1 Curhan GC, Willett WC, Rimm EB, Stampfer MJ (1993) A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* **328**:833–8.

2 Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. (1996) Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: A 5-year randomized prospective study. *J Urol* **155**:839–43.

3 Curhan G, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ (1997) Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Int Med* **126**:497–504.

4 Domrongkitchaiporn S, Sopassathit W, Stitchantrakul W, Prapaipanich S, Ingsathit A, Rajatanavin R (2004) Schedule of taking calcium supplement and the risk of nephrolithiasis. *Kidney Int* **65**:1835-41.

5 Sakhaee K, Poindexter JR, Griffith CS, Pak CY (2004) Stone forming risk of calcium citrate supplementation in healthy postmenopausal women. *J Urol* **172**:958–61.

6 Penniston KL, Nakada SY (2009) Effect of dietary changes on urinary oxalate excretion and calcium oxalate supersaturation in patients with hyperoxaluric stone formation. *Urology* **73**:484–9.

7 Borghi, L (2002) Comparison of two diets for prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* **346**:77–84.

8 Kok DJ (1990) The effects of dietary excesses in animal protein and in sodium on the composition and crystallization kinetics of calcium oxalate monohydrate in urines of healthy men. *J Clin Endocrinol Metab* **71**:861–7.

9 Curhan G, Willett WC, Speizer FE, Stampfer MJ (1998) Beverage use and risk for kidney stones in women. *Ann Intern Med* **128**:534–40.

10 Robertson WG, Peacock M, Marshall DH (1982) Prevalence of urinary stone disease in vegetarians. *Eur Urol* **8**:334–9.

11 Robertson WG, Peacock M, Ouimet D, *et al.* (1981) The main risk for calcium oxalate stone disease in man: hypercalciuria or mild hyperoxaluria? In: Smith LH, Robertson WG, Finlayson B (eds) *Urolithiasis: Clinical and Basic Research*. New York: Plenum Press, pp. 3–12.

12 Ettinger B, Pak CY, Citron JT, Thomas C, Adams-Huet B, Vangessel A (1997) Potassium magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol* **158**:2069–73.

13 Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CY (1993) Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol* **150**:1761–4.

14 Pearle MS, Roehrborn CG, Pak CY (1999) Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* **13**:679.

15 Ettinger B, Tang A, Citron JT, Livermore B, Williams T (1986) Randomized trial of allopurinol in th eprevention of calcium oxalate calculi. *N Engl J Med* **315**:1386-9.

Bladder stones

Composition

Struvite (i.e. they are infection stones) or uric acid (in non-infected urine).

Adults

Bladder calculi are predominantly a disease of men aged >50 and with BOO due to BPE. They also occur in the chronically catheterized patient (e.g. SCI patients), where the chance of developing a bladder stone is 25% over 5y (similar risk whether urethral or suprapubic location of the stone).[1]

Children

Bladder stones are still common in Thailand, Indonesia, North Africa, the Middle East, and Burma. In these endemic areas, they are usually composed of a combination of ammonium urate and calcium oxalate. A low phosphate diet in these areas (a diet of breast milk and polished rice or millet) results in high peaks of ammonia excretion in the urine.

Symptoms

May be symptomless (incidental finding on KUB X-ray or bladder USS or on cystoscopy)—the common presentation in spinal patients who have limited or no bladder sensation). In the neurologically intact patient—suprapubic or perineal pain, haematuria, urgency, and/or urge incontinence, recurrent UTI, LUTS (hesitancy, poor flow).

Diagnosis

If you suspect a bladder stone, they will be visible on KUB X-ray or renal USS (Fig. 9.15).

Treatment

Most stones are small enough to be removed cystoscopically (endoscopic cystolitholapaxy), using stone-fragmenting forceps for stones that can be engaged by the jaws of the forceps and EHL or pneumatic lithotripsy for those that cannot. Large stones (Fig. 9.15) can be removed by open surgery (open cystolitholapaxy).[1]

1 Ord J (2003) Bladder management and risk of bladder stone formation in spinal cord injured patients. *J Urol* **170**:1734–7.

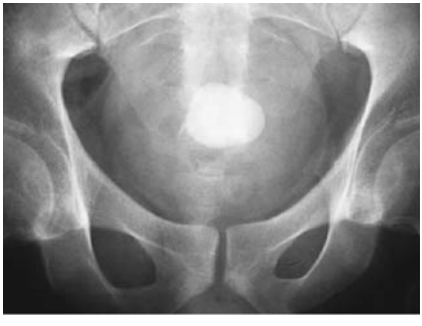

Fig. 9.15 A bladder stone.

Management of ureteric stones in pregnancy

While hypercalciuria and uric acid excretion increases in pregnancy (predisposing to stone formation), so too do urinary citrate and magnesium levels (protecting against stone formation). The 'net' effect—incidence of ureteric colic is the same as in non-pregnant women.[1] Ureteric stones occur in 1 in 1500–2500 pregnancies, mostly during second and third trimesters. They are associated with a significant risk of preterm labour[2] and the pain caused by ureteric stones can be difficult to distinguish from other causes.

Differential diagnosis of flank pain in pregnancy

Ureteric stone, placental abruption, appendicitis, pyelonephritis, and all the other (many) causes of flank pain in non-pregnant women.

Diagnostic imaging studies in pregnancy

Exposure of the fetus to ionizing radiation can cause fetal malformations, intrauterine growth retardation, malignancies in later life (leukaemia), and mutagenic effects (damage to genes, causing inherited disease in the offspring of the fetus). The fetus is most at risk during organogenesis (weeks 4–10 of gestation). Fetal radiation doses during various procedures are shown in Table 9.8. Radiation doses of <100mGy are reported as unlikely to have an adverse effect on the fetus.[3] In USA, the National Council on Radiation Protection has stated that 'fetal risk is considered to be negligible at <50mGy when compared to the other risks of pregnancy and the risk of malformations is significantly increased above control levels at doses >150mGy'.[4] The American College of Obstetricians and Gynaecologists has stated that 'X-ray exposure to <50mGy has not been associated with an increase in fetal anomalies or pregnancy loss'.[5] However, every effort should be made to limit exposure of the fetus to radiation.

Table 9.8 Fetal radiation dose after various radiological investigations (note lcGy is equivalent to 10mGy)

Procedure	Fetal dose (mGy)	Risk of inducing cancer (up to age 15y)
KUB X-ray	1.4	1 in 24 000
IVU 6 shot	1.7	1 in 10 000
IVU 3 shot	–	–
CT: abdominal	8	1 in 4000
CT: pelvic	25	1 in 1300
Fluoroscopy for JJ stent insertion	0.4	1 in 42 000

Adapted from the Joint Guidance from the National Radiographic protection Board, College of Radiographeres Royal College of Radiologists, 1998.

Plain radiography and IVU

Limited usefulness (fetal skeleton and the enlarged uterus obscure ureteric stones; delayed excretion of contrast limits opacification of ureter; theoretical risk of fetal toxicity from the contrast material). Recommendations are for a limited IVU (e.g. control film followed by a 30min film) with fetal shielding.

CT-KUB

Very accurate method for detecting ureteric stones, but most radiologists and urologists are unhappy to recommend this form of imaging in pregnant women due to increased fetal radiation exposure. Low and ultra-low dose CT protocols are being developed.

MRU

The American College of Obstetricians and Gynaecologists and the US National Council on Radiation Protection state that 'although there is no evidence to suggest that the embryo is sensitive to magnetic and radiofrequency at the intensities encountered in MRI, it might be prudent to exclude pregnant women during the first trimester'.[5,6] MRU can, therefore, potentially be used during the second and third trimesters, but not during the first trimester. Involves no ionizing radiation. Very accurate (100% sensitivity for detecting ureteric stones)[7], but expensive and not readily available in most hospitals, particularly out of hours.

Management

Most (70–80%) will pass spontaneously.[3]

- **Pain relief**: opiate-based analgesics; avoid NSAIDs (can cause premature closure of the ductus arteriosus by blocking prostaglandin synthesis).
- **Indications for intervention**: the same as in non-pregnant patients—pain refractory to analgesics, suspected urinary infection (high fever, high WBC), high-grade obstruction, and obstruction in a solitary kidney).

Options for intervention

Depend on the stage of pregnancy and on local facilities and expertise:

- JJ stent urinary diversion:[4] requires regular changing (approximately 6–8 weeks to avoid encrustation).
- Nephrostomy urinary diversion.
- Ureteroscopic stone removal with laser fragmentation.

Aim to minimize radiation exposure to the fetus and to minimize the risk of miscarriage and preterm labour. General anaesthesia can precipitate preterm labour and many urologists and obstetricians will err on the side of temporizing options such as nephrostomy tube drainage or JJ stent placement, rather than on operative treatment in the form of ureteroscopic stone removal. Avoid PCNL; ESWL is contraindicated.

1 Coe FL, Parks JH, Lindhermer MD (1978) Nephrolithiasis during pregnancy. *N Engl J Med* **298**:324–6.

2 Hendricks SK (1991) An algorithm for diagnosis and therapy of urolithiasis during pregnancy *Surg Gynecol Obst* **172**:49–54.

3 Hellawell GO, Cowan NC, Holt SJ, Mutch SJ (2002) A radiation perspective for treating loin pain in pregnancy by double-pigtail stents. *BJU Int* **90**:801–8.

4 National Council on Radiation Protection and Measurement (1997) *Medical radiation exposure of pregnant and potentially pregnant women.* NCRP Report no. 54. Bethesda, MD: NCRPM.

5 American College of Obstetricians and Gynaecologists Committee on Obstetric Practice (1995) *Guidelines for Diagnostic Imaging During Pregnancy*. ACOG Committee Opinion no. 158. Washington DC: ACOG.

6 Roy C (1996) Assessment of painful ureterohydronephrosis during pregnancy by MR urography. *Eur Radiol* **6**:334–8.

7 Watterson JD, Girvan AR, Beiko DT, *et al.* (2002) Ureteroscopy and holmium: an emerging definitive management strategy for symptomatic ureteral calculi in pregnancy. *Urology* **60**:383–7.

8 Sharp C, Shrimpton JA, Bury RF (1998) Joint Guidance from National Radiological Protection Board, College of Radiographers and Royal College of Radiologists. *Advice on Exposure to Ionizing Radiation during Pregnancy.* Produced by the National Radiological Protection Board, Chilton, Didcot [online]. Available from: http://www.nrpb.org.

Chapter 10

Upper tract obstruction, loin pain, hydronephrosis

Hydronephrosis

Dilatation of the renal pelvis and calyces (Fig. 10.1). When combined with dilatation of the ureters, known as hydroureteronephrosis.

Obstructive nephropathy is damage to the renal parenchyma, resulting from an obstruction to the flow of urine anywhere along the urinary tract.

Dilatation of the renal pelvis and calyces can occur without obstruction and therefore, hydronephrosis should not be taken to necessarily imply the presence of obstructive uropathy.

Ultrasound

- **False negative (i.e. obstruction present, no hydronephrosis):** acute onset of obstruction; in the presence of an intrarenal collecting system; with dehydration; misdiagnosis of dilatation of the calyces as renal cortical cysts (in acute ureteric colic, ultrasonography fails to detect hydronephrosis in up to 35% of patients with proven acute obstruction on IVU).
- **False positive (i.e. hydronephrosis, no obstruction):** capacious extrarenal pelvis; parapelvic cysts; VUR; high urine flow.

Diagnostic approach to the patient with hydronephrosis

Patients with hydronephrosis may present either as an incidental finding of hydronephrosis on USS or CT done because of non-specific symptoms or it may be identified in a patient with a raised creatinine or presenting with loin pain. Symptoms, if present, will depend on the rapidity of onset of obstruction of the kidney (if that is the cause of the hydronephrosis), whether the obstruction is complete or partial, unilateral or bilateral, and whether the obstruction to the ureter is extrinsic to the ureter or is within its lumen.

History

- Severe flank pain suggests a more acute onset of obstruction and if very sudden in onset, a ureteric stone may well be the cause. Pain induced by a diuresis (e.g. following consumption of alcohol) suggests a possible PUJO.
- Anuria (the symptom of bilateral ureteric obstruction or complete obstruction of a solitary kidney).
- If renal function is impaired, symptoms of renal failure may be present (e.g. nausea, lethargy, anorexia).
- Extrinsic causes of obstruction (e.g. compression of the ureters by retroperitoneal malignancy) usually have a more insidious onset whereas intrinsic obstruction (ureteric stone) is often present with severe pain of very sudden onset.
- An increase in urine output may be reported by the patient due to poor renal concentrating ability.
- Obstruction in the presence of bacterial UTI—signs and symptoms of pyelonephritis (flank pain and tenderness, fever) or sepsis.

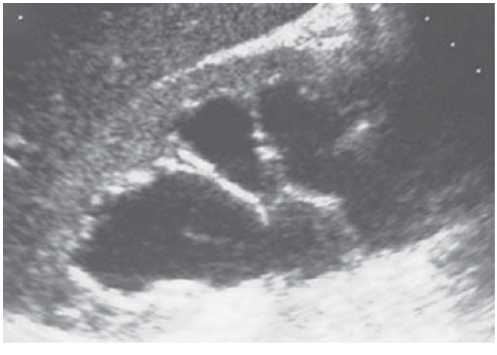

Fig. 10.1 Hydronephrosis as seen on renal ultrasonography.

Examination

- **Measure BP:** elevated in HPCR due to BPO (caused by fluid overload).
- Bilateral oedema (due to fluid overload).
- **Abdominal examination:** percuss and palpate for an enlarged bladder.
- DRE (? prostate or rectal cancer) and, in women, vaginal examination (? cervical cancer).
- Check serum creatinine to determine the functional effect of the hydronephrosis.
- Renal ultrasonography (if not already done).

IVU findings in renal obstruction

- An obstructive (dense) nephrogram.
- A delay in filling of the collecting system with contrast material.
- Dilatation of the collecting system.
- An increase in renal size.
- Rupture of fornices (junction between renal papilla and its calyx) with urinary extravasation.
- Ureteric dilatation and tortuosity.
- A standing column of contrast material in the ureter.

Unilateral hydronephrosis

KUB X-ray (a ureteric stone may be seen); CTU (or IVU) if stone suspected.

- If no stone seen, but hydronephrosis is confirmed and ureter is non-dilated, the obstruction must be at the PUJ. In the absence of a ureteric stone visible on CTU, the diagnosis must be PUJO.
- If no stone seen and the ureter is dilated as well as the kidney, ureteric TCC is likely. Arrange retrograde ureterography to identify site of obstruction and ureteroscopy/ureteric biopsy.

Bilateral hydronephrosis

- If the patient is in retention or has a substantial post-void residual urine volume, pass a catheter. If the elevated creatinine falls (and the hydronephrosis improves), the diagnosis is BOO due, for example, to BPH, prostate cancer, urethral stricture, DSD. If the creatinine remains elevated, the obstruction affecting both ureters is higher 'upstream'.
- TRUS and prostatic biopsy if prostate cancer suspected on DRE, CT scan looking for malignant bilateral ureteric obstruction, AAA.

Causes of hydronephrosis

Unilateral

- Obstructing ureteric stone.
- PUJO.
- Obstructing clot in ureter.
- Obstructing ureteric TCC.
- (Any of the causes listed below where the pathologic process has not yet extended to involve both ureters).

Bilateral

- BOO.
  - BPH.
  - Prostate cancer.
  - Urethral stricture.
  - DSD.
  - Posterior urethral valve.
- Bilateral ureteric obstruction at their level of entry into the bladder.
  - Locally advanced cervical cancer.
  - Locally advanced prostate cancer.
  - Locally advanced rectal cancer.
  - Poor bladder compliance (often combined with DSD): neuropathic bladder (spinal cord injury, spina bifida), post-pelvic radiotherapy.
- Periureteric inflammation.
  - From adjacent bowel involved with inflammatory bowel disease (e.g. Crohn's, ulcerative colitis) or diverticular disease.
- Retroperitoneal fibrosis.
  - Idiopathic (diagnosed following exclusion of other causes).
  - Periarteritis—aortic aneurysm, iliac artery aneurysm.
  - Post-irradiation.
  - Drugs—methysergide, hydralazine, haloperidol, LSD, methyldopa, beta blockers, phenacetin, amphetamines.
  - Malignant—retroperitoneal malignancy (lymphoma, metastatic disease from, e.g. breast cancer), post-chemotherapy.
  - Chemicals—talcum powder.
  - Infection—TB, syphilis, gonorrhoea, chronic UTI.
  - Sarcoidosis.
- Bilateral PUJO (uncommon).
- Hydronephrosis of pregnancy (partly due to smooth muscle relaxant effect of progesterone, partly obstruction of ureters by fetus).
- Hydronephrosis in association with an ileal conduit (a substantial proportion of patients with ileal conduit urinary diversion has bilateral hydronephrosis in the absence of obstruction).
- Bilateral ureteric stones (rare).

Management of ureteric strictures (other than PUJO)

Definition

A normal ureter undergoes peristalsis and therefore, at any one moment, at least one area of the ureter will be physiologically narrowed. A ureteric stricture is a segment of ureter that is narrowed and remains so on several images (i.e. it is a length of ureter that is constantly narrow).

Causes

Most ureteric strictures are benign and iatrogenic. Some follow the impaction of ureteric stone for a prolonged period; malignant strictures—within wall of ureter (e.g. TCC ureter), extrinsic compression from outside wall of ureter (e.g. lymphoma, malignant retroperitoneal lymphadenopathy); retroperitoneal fibrosis (RPF) which may be benign (idiopathic, aortic aneurysm, post-irradiation, analgesic abuse) or malignant (retroperitoneal malignancy, post-chemotherapy).

Mechanism of iatrogenic ureteric stricture formation

Normally ischaemic:

- Usually injury at time of open or endoscopic surgery (e.g. damage to ureteric blood supply or direct damage to the ureter at time of colorectal resection, AAA graft, hysterectomy); at ureteroscopy—mucosal trauma (from ureteroscope or electrohydraulic lithotripsy), perforation of ureter (urine extravasation, leading to fibrosis).
- Radiotherapy in the vicinity of the ureter.
- Stricture of ureteroneocystostomy of renal transplant.

Investigations

The stricture may be diagnosed following investigation for symptoms (loin pain, upper tract infection) or may be an incidental finding on an investigation done for some other reason. The stricture may be diagnosed on renal USS (hydronephrosis), IVU, or CTU. A MAG3 renogram will confirm the presence of obstruction (some minor strictures may cause no renal obstruction) and establish split renal function. Where ureteric TCC is possible, proceed with ureteroscopy and biopsy.

'Treatment' options

- Nothing (symptomless stricture in an old patient with significant comorbidity or <25% function in an otherwise healthy patient with a normally functioning contralateral kidney).
- Permanent JJ stent or nephrostomy, changed at regular intervals (symptomatic stricture in an old patient with significant comorbidity or <25% function in affected kidney with compromised overall renal function).
- Dilatation (balloon or graduated dilator) (Figs. 10.2 and 10.3).
- Incision + balloon dilatation (endoureterotomy by Acucise® balloon; ureteroscopy or nephrostomy and incision, e.g. by laser). Leave a 12 Ch stent for 4 weeks.
- Excision of stricture and repair of ureter (open or laparoscopic approach).
- Nephrectomy.

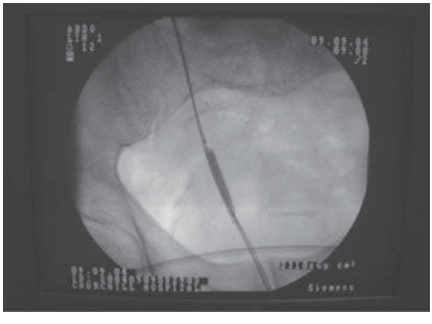

Fig. 10.2 Balloon dilatation of a lower ureteric stricture.

Fig. 10.3 The catheter used for balloon dilatation.

Factors associated with reduced likelihood of a good outcome after endoureterotomy

- <25% function in kidney.
- Stricture length >1cm.
- Ischaemic stricture.
- Midureteric stricture (compared with upper and lower)—tenuous blood supply.
- JJ stent size <12 Ch.

Ureteroenteric strictures (ileal conduits, ureteric implantation into neobladder)

These are due to ischaemia and/or periureteral urine leak in the immediate post-operative period, which leads to fibrosis in the tissues around the ureter. In ileal conduits, the left ureter is affected more than the right because greater mobilization is required to bring it to the right side and it may be compressed under the sigmoid mesocolon, both of which impair blood flow to the distal end of the ureter.

Pathophysiology of urinary tract obstruction

Effects of obstruction on renal blood flow and ureteric pressure

Acute unilateral ureteric obstruction (UUO)

Leads to a triphasic relationship between renal blood flow (RBF) and ureteric pressure.

- **Phase 1** (up to 1.5h post-obstruction): ureteric pressure rises, RBF rises (afferent arteriole dilatation).
- **Phase 2** (from 1.5–5h post-obstruction): ureteric pressure continues to rise, RBF falls (efferent arteriole vasoconstriction).
- **Phase 3** (beyond 5h): ureteric pressure falls, RBF continues to fall (afferent arteriole vasoconstriction).

Acute bilateral ureteric obstruction (BUO) or obstruction of a solitary kidney

- **Phase 1** (up to 1.5h post-obstruction): ureteric pressure rises, RBF rises (afferent arteriole dilatation).
- **Phase 2** (from 1.5–5h post-obstruction): ureteric pressure continues to rise, RBF is significantly lower than that during UUO.
- **Phase 3** (beyond 5h): ureteric pressure remains elevated (in contrast to UUO). By 24h, RBF has declined to the same level for both UUO and BUO.

In UUO, the decrease in urine flow through the nephron results in a greater degree of Na absorption so Na excretion falls. Water loss from the obstructed kidney increases.

Release of BUO is followed by a marked natriuresis, increased K excretion, and a diuresis (a solute diuresis).This is due to:

- An appropriate (physiological) natriuresis to excrete excessive Na which is a consequence of BUO.
- A solute diuresis from the accumulation of urea in ECF.
- A diminution of the corticomedullary concentration gradient, which is normally established by the countercurrent mechanism of the Loop of Henle, and is dependent on maintenance of flow through the nephron—reduction of flow, as occurs in BUO, reduces the efficiency of the countercurrent mechanism (effectively, the corticomedullary concentration gradient is 'washed out').

There may also be accumulation of natriuretic peptides (e.g. ANP) during BUO, which contributes to the natriuresis following release of the obstruction.

Likelihood of recovery of renal function after release of obstruction

In dogs with completely obstructed kidneys, full recovery of renal function after 7 days of UUO occurs within 2 weeks of relief of obstruction. A total of 14 days of obstruction leads to a permanent reduction in renal function to 70% of control levels (recovery to this level taking 3–6 months after reversal of obstruction). There is some recovery of function after 4 weeks of obstruction, but after 6 weeks of complete obstruction, there is no recovery. In humans, there is no clear relationship between the duration of BUO and the degree of recovery of renal function after relief of obstruction.

Physiology of urine flow from kidneys to bladder

Urine production by the kidneys is a continuous process. Its transport from the kidneys down the ureter and into the bladder occurs intermittently by waves of peristaltic contraction of the renal pelvis and ureter (peristalsis = wave-like contractions and relaxations). The renal pelvis delivers urine to the proximal ureter. As the proximal ureter receives a bolus of urine, it is stretched and this stimulates it to contract while the segment of ureter just distal to the bolus of urine relaxes. Thus, the bolus of urine is projected distally.

The origin of the peristaltic wave is from collections of pacemaker cells in the proximal most regions of the renal calyces. In species with multiple calyces such as humans, there are multiple pacemaker sites in the proximal calyces. The frequency of contraction of the calyces is independent of urine flow rate (it is the same at high and low flow rates) and it occurs at a higher rate than that of the renal pelvis. Precisely how the frequency of contraction of each calyx is integrated into a single contraction of the renal pelvis is not known. All areas of the ureter are capable of acting as a pacemaker. Stimulation of the ureter at any site produces a contraction wave that propagates proximally and distally from the site of stimulation, but under normal conditions, electrical activity arises proximally and is conducted distally from one muscle cell to another (the proximal most pacemakers are dominant over these latent pacemakers).

Peristalsis persists after renal transplantation and denervation and does not, therefore, appear to require innervation. The ureter does, however, receive both parasympathetic and sympathetic innervation and stimulation of these systems can influence the frequency of peristalsis and the volume of urine bolus transmitted.

At normal urine flow, the frequency of calyceal and renal pelvic contractions is greater than that in the upper ureter and there is a relative block of electrical activity at the PUJ. The renal pelvis fills; the ureter below it is collapsed and empty. As renal pelvic pressure rises, urine is extruded into the upper ureter. The ureteric contractile pressures that move the bolus of urine are higher than renal pelvic pressures. A closed PUJ may prevent back-pressure on the kidney. At higher urine flow rates, every pacemaker-induced renal pelvic contraction is transmitted to the ureter.

To propel a bolus of urine, the walls of the ureter must coapt (touch). Resting ureteric pressure is 0–5cmH_2O and ureteric contraction pressures range from 20 to 80cmH_2O. Ureteric peristaltic waves occur 2–6 times per min. The VUJ acts as a one-way valve under normal conditions, allowing urine transport into the bladder and preventing reflux back into the ureter.

Ureter innervation

Autonomic: the ureter has a rich autonomic innervation.

- **Sympathetic:** preganglionic fibres from spinal segments T10–L2; post-ganglionic fibres arise from the coeliac, aorticorenal, mesenteric, superior, and inferior hypogastric (pelvic) autonomic plexuses.
- **Parasympathetic:** vagal fibres via coeliac to upper ureter; fibres from S2–4 to lower ureter.

The role of ureteric autonomic innervation is unclear. It is not required for ureteric peristalsis (though it may modulate this). Peristaltic waves originate from intrinsic smooth muscle pacemakers located in minor calyces of the renal collecting system.

Afferent

Upper ureter—afferents pass (alongside sympathetic nerves) to T10–L2; *lower ureter*—afferents pass (alongside sympathetic nerves and by way of the pelvic plexus) to S2–4. Afferents subserve stretch sensation from the renal capsule, collecting system of kidney (renal pelvis and calyces), and ureter. Stimulation of the mucosa of the renal pelvis, calcyes, and ureter also stimulates nociceptors, the pain so felt being referred in a somatic distribution to T8–L2 (kidney T8–L1, ureter T10–L2), in the distribution of the subcostal, iliohypogastric, ilioinguinal, or genitofemoral nerves. Thus, ureteric pain can be felt in the flank, groin, scrotum or labia, and upper thigh, depending on the precise site in the ureter from which the pain arises.

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Retroperitoneal fibrosis

Retroperitoneal fibrosis (RPF) was first clearly described by the French urologist Albarran in 1905. Further cases were described by Ormond in 1948.

Benign causes

- Autoimmune: Idiopathic RPF (periaortitis) comprises two-thirds of cases. Considered to be a response to an insoluble lipid called ceroid that has leaked through a thinned arterial wall from atheromatous plaques, a fibrous plaque extends laterally and downwards from the renal arteries encasing the aorta, inferior vena cava and ureters, but rarely extends into the pelvis. The central portion of the plaque consists of woody scar tissue, while the growing margins have the histological appearance of chronic inflammation. It may be associated with abdominal aortic aneurysm (AAA), intra-arterial stents, and angioplasty; mediastinal, mesenteric, or bile-duct fibrosis.
- Drugs including methysergide, beta-blockers, hydralazine, haloperidol, amphetamines, and LSD; methyl methacrylate cement used for joint replacement.
- Chronic urinary infection including TB.
- Inflammatory conditions such as Crohn's disease, Reidel's thyroiditis, or sarcoidosis.

Amyloidosis and periaortic haematoma may mimic RPF.

Malignant causes

- Lymphoma is the most common cause, also sarcoma.
- Metastatic or locally infiltratative carcinoma of the breast, stomach, pancreas, colon, bladder, prostate, and carcinoid tumours.
- Radiotherapy may cause RPF, although rare in recent years with precise field localization.
- Chemotherapy, especially following treatment of metastatic testicular tumours, may leave fibrous masses encasing the ureters. These may or may not contain residual tumour.

Presentation

- Idiopathic retroperitoneal fibrosis classically occurs in the fifth or sixth decade of life.
- Men are affected twice as commonly as women.
- In the early stage, symptoms are relatively non-specific, including loss of appetite and weight, low-grade fever, sweating, and malaise. Lower limb swelling may develop. Dull, non-colicky abdominal or back pain is described in up to 90% of patients.
- Later, the major complication of the disease develops: bilateral ureteric obstruction, causing anuria and renal failure.
- Examination may reveal hypertension in up to 60% of patients and an underlying cause such as an abdominal aortic aneurysm.

Investigations

- Inflammatory serum markers are elevated in idiopathic RPF (60–90% elevated ESR).

- Pyuria or bacteriuria are common.
- Ultrasound will demonstrate uni- or bilateral hydronephrosis.
- CT, IVU, or ureterography reveal tapering medial displacement of the mid-ureters with proximal dilatation and will exclude calculus disease. Up to one third of patients will have a non-functioning kidney at the time of presentation due to long standing obstruction.
- CT-guided fine needle biopsy of the mass may confirm the presence of malignant disease or infection. A negative result does not exclude malignancy.

Management

- Emergency management of a patient presenting with established renal failure requires relief of the obstruction by percutaneous nephrostomy or ureteric stenting.
- Replacement of fluid and electrolyte losses following relief of bilateral ureteric obstruction is vital due to the frequent post-obstructive diuresis.
- Assess with daily weighing and measurement of blood pressure lying and standing.
- Steroids may decrease the oedema often associated with retroperitoneal fibrosis and in this way help reduce the obstruction. If used, they are usually discontinued when inflammatory markers return to normal. Azathioprine, tamoxifen, and cyclophosphamide have been used successfully in some patients.
- Surgical ureterolysis with omental wrap is often necessary to free and insulate the ureters from the encasing fibrous tissue.
- Monitor for recurrent disease with serum creatinine and ultrasound 3–6 monthly or annual DMSA renography for 5y.

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Chapter 11

Trauma to the urinary tract and other urological emergencies

Initial resuscitation of the traumatized patient

The resuscitation of the traumatized patient is usually initiated in the field by the paramedic team and is continued systematically once the patient reaches the emergency department by a rapid multidisciplinary priority-based approach.

Goals of resuscitation:

- Restoration of cardiac, pulmonary, and neurological function.
- Diagnosis of immediate life-threatening conditions.
- Prevention of complications from multisystem injuries.

The initial resuscitation process can be divided into three phases—the primary survey, the secondary survey, the definitive survey.

Primary survey

ABC: assess the patient's Airway, Breathing, and Circulation.

Airway and Breathing

- Establish a secure airway.
- Ventilate by oxygen mask or endotracheal intubation and mechanical ventilation.
- Immobilize the cervical spine.

Circulation

Assess circulatory function by pulse rate and BP.

The commonest cause of hypotension in the polytraumatized patient is hypovolaemia secondary to haemorrhage. With hypovolaemic shock, an immediate bolus of intravenous isotonic crystalloid solution should be given and the patient's response (pulse rate, BP) is assessed.

Radiological imaging

Determined by local facilities. Increasingly, in the severely traumatized patient, CT of chest, abdomen, and pelvis is used to identify significant chest, abdominal, and pelvic injuries. If not available, arrange supine chest, abdomen, and pelvic X-rays to identify the presence of rib and pelvic fractures and to identify the presence of significant quantities of blood in the chest, abdomen, and pelvis and in patients with persistent hypotension from presumed bleeding, search for occult haemorrhage using a diagnostic peritoneal lavage or focused abdominal USS.

Hypovolaemic shock is not always associated with hypotension. In young patients, compensatory mechanisms, e.g. rapid vasoconstriction can compensate for as much as a 35% volume loss without significant decreases in BP.

Remember non-hypovolaemic causes of hypotension:

- Tension pneumothorax.
- Cardiac tamponade.
- Myocardial infarction.
- Neurogenic (SCI).

Urinalysis

Routinely performed in every trauma patient because it provides valuable information regarding the likelihood of injuries to the upper and lower urinary tract. The absence of haematuria, however, does not exclude a urinary tract injury (e.g. haematuria may be absent in acceleration/deceleration renal injuries (see 🕮 p. 508)).

As life-threatening injuries are found during the primary survey, resuscitation efforts are initiated concurrently (e.g. chest drain for pneumothorax). The decision to transfer a patient from the emergency room to either the operating room or angiography suite is made during the primary survey.

Secondary survey

Performed after completion of the primary survey. Take a completehistory and perform a physical examination from head to toe. Arrange selective skeletal X-rays according to physical findings.

Definitive survey

During this phase, focus attention on identifying specific organ injuries using clinical and radiographic means. Genitourinary injuries are usually recognized during the definitive survey.

During all phases of the initial resuscitation, assess vital signs (BP, respiratory rate, blood gases, urinary output, and body temperature) continually. Vascular pressure monitoring, using central venous and pulmonary arterial catheters, can be performed selectively. Frequent re-evaluation should be performed to detect changes in the patient's condition and the appropriate actions taken.

Renal trauma: classification, mechanism, grading

Classification

Two categories—blunt and penetrating. See Table 11.1. Proportion of all renal injuries that are blunt—Europe 97%, United States 90%, South Africa 25–85%. Proportion depends on whether urban or non-urban community.

This classification is useful because it predicts the likely need for surgical exploration to control bleeding. Experience from large series shows that 95% of blunt injuries can be managed conservatively whereas 50% of stab injuries and 75% of gunshot wounds require exploration.

Blunt injures

- Direct blow to the kidney.
- Rapid acceleration or rapid deceleration.
- A combination of the above.

Rapid deceleration frequently causes renal pedicle injuries (renal artery and vein tears or thrombosis, PUJ disruption) because the renal pedicle is the site of attachment of the kidney to other fixed retroperitoneal structures.

Most common cause—motor vehicle accidents (e.g. pedestrian hit by a car, direct blow combined with rapid acceleration and then deceleration). Seemingly trivial injuries (e.g. fall from a ladder), direct falls onto the flank, or sporting injuries can lead to significant renal injuries.

Penetrating injuries

Stab or gunshot injuries to the flank, lower chest, and anterior abdominal area may inflict renal damage. Fifty percent of patients with penetrating trauma and haematuria have grade III, IV, or V renal injuries. Penetrating injuries anterior to the anterior axillary line are more likely to injure the renal vessels and renal pelvis, compared with injuries posterior to this line where less serious parenchymal injuries are more likely. Thus, renal injuries from stab wounds to the flank (i.e. posterior to the anterior axillary line) can often be managed non-operatively.

Wound profile of a low-velocity gunshot wound is similar to that of a stab wound. High-velocity gunshot wounds (>350m/s) cause greater tissue damage due to stretching of surrounding tissues ('temporary cavity').

Mechanism

The kidneys are retroperitoneal structures surrounded by perirenal fat, the vertebral column and spinal muscles, the lower ribs, and abdominal contents. They are, therefore, relatively protected from injury and a considerable degree of force is usually required to injure them (only 1.5–3% of trauma patients have renal injuries). Associated injuries are, therefore, common (e.g. spleen, liver, mesentery of bowel). Renal injuries may not initially be obvious, hidden as they are by other structures. To confirm or exclude a renal injury, imaging studies are required. In children, there is proportionately less perirenal fat to cushion the kidneys against injury and thus, renal injuries occur with lesser degrees of trauma.

Staging of the renal injury

Using CT, renal injuries can be staged according to the AmericanAssociation for the Surgery of Trauma (AAST) Organ Injury Severity Scale. Higher injury severity scales are associated with poorer outcomes.

Grade I Contusion (normal CT) or subcapsular haematoma with no parenchymal laceration.

Grade II <1cm deep parenchymal laceration of cortex, no extravasation of urine (i.e. collecting system intact).

Grade III >1cm deep parenchymal laceration of cortex, no extravasation of urine (i.e. collecting system intact).

Grade IV Parenchymal laceration, involving cortex, medulla and collecting system OR renal artery or renal vein injury with contained haemorrhage.

Grade V Completely shattered kidney OR avulsion of renal hilum.

Paediatric renal injuries

The kidneys are said to be more prone to injury in children because of the relatively greater size of the kidneys in children, the smaller protective muscle mass and cushion of perirenal fat, and the more pliable rib cage.

Table 11.1 Summary of mechanisms, causes, grading, and treatment of renal disease

Mechanisms and cause	**Blunt:** direct blow or acceleration/deceleration (RTAs, falls from a height, fall onto flank)
	Penetrating: knives, gunshots, iatrogenic (e.g. PCNL)
Imaging and grading	**CT:** accurate, rapid, images other intra-abdominal struc-tures
	Staging: AAST Organ Injury Severity Scale:
	I: contusion or subcapsular haematoma
	II: <1cm laceration without urinary extravasation
	III: >1cm laceration without urinary extravasation
	IV: laceration into collecting system, i.e. urinary extravasa-tion
	V: shattered kidney or avulsion of renal pedicle
Treatment	**Conservative:** 95% of blunt injuries, 50% of stab inju-ries, 25% of gunshot wounds can be managed non-operatively (cross-match, bed rest, observation)
	Exploration if:
	Persistent bleeding (persistent tachycardia and/or hy-potension not responding to appropriate fluid and blood replacement)
	Expanding perirenal haematuria
	Pulsatile perirenal haematoma

See also: Santucci RA, Wessells H, Bartsch G, et al. (2004) Consensus on genitourinary trauma. Evaluation and management of renal injuries: consensus statement of the renal trauma subcommittee. *Br J Urol Int* **93**:937–54.

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Renal trauma: clinical and radiological assessment

The haemodynamically stable patient

History: nature of trauma (blunt, penetrating)

Examination: pulse rate, systolic BP, respiratory rate, location of entry and exit wounds, flank bruising, rib fractures. The *lowest recorded systolic BP* is used to determine need for renal imaging.

Urinalysis: crucial for determining likelihood of renal injury and, therefore, of the need for radiological tests.

Haematuria (defined as >5 erythrocytes per high powered field or dipstick-positive) suggests the possibility of a renal injury; however, the amount of haematuria does not correlate consistently with the degree of renal injury.

Do FBC and serum chemistry profile.

Indications for renal imaging

- Macroscopic haematuria.
- Penetrating chest and abdominal wounds (knives, bullets).
- Microscopic (>5 RBCs per high powered field) or dipstick haematuria in a hypotensive patient (systolic BP <90mmHg recorded at any time since the injury).[1]
- A history of a rapid acceleration or deceleration (e.g. fall from a height, high speed motor vehicle accident). Falls from even a low height can cause serious renal injury in the absence of shock (systolic BP <90mmHg) and of haematuria (PUJ disruption prevents blood reaching the bladder).
- Any child with microscopic or dipstick haematuria who has sustained trauma.

Adult patients with a history of blunt trauma and microscopic or dipstick haematuria need not have their kidneys imaged as long as there is no history of acceleration/deceleration and no shock since the chances of a significant injury being found are <0.2%.

Degree of haematuria vs severity of injury

While significant renal injury is more likely with macroscopic haematuria, in some cases of severe renal injury, haematuria may be absent. Thus, the relationship between the presence, absence and degree of haematuria and the severity of trauma is not absolute. Broadly speaking, in *blunt* trauma, macroscopic haematuria predicts the likelihood of significant renal injury (Table 11.2). Conversely, in *penetrating* trauma, haematuria may be absent in severe renal injury (renal vascular injury, PUJ, or ureter avulsion).

Table 11.2 Blunt trauma in adults: chance of significant renal injury vs degree of haematuria and systolic BP (SBP)

Degree of haematuria; SBP (mmHg)	Significant renal injury (%)
Microhaematuria;* >90	0.2
Macroscopic haematuria; >90	10
Macroscopic haematuria; <90	10

* Dipstick or microscopic haematuria.

The haemodynamically unstable patient

Haemodynamic instability may preclude standard imaging such as CT, the patient having to be taken to the operating theatre immediately to control the bleeding. In this situation, an on-table IVU (Box 11.1) is indicated if:

- A retroperitoneal haematoma is found and/or
- A renal injury is found which is likely to require nephrectomy.

Box 11.1 What imaging study?

The IVU has been replaced by contrast-enhanced CT scan as the imaging study of choice in patients with suspected renal trauma. Compared with IVU, it provides clearer definition of the injury, allowing injuries to the parenchyma and collecting system to be more accurately graded and, therefore, determines subsequent management. An arterial-venous phase scan is done within minutes of contrast injection, followed by a repeat scan 10–20min after contrast administration to allow time for contrast to reach collecting system.

While ultrasound can establish the presence of two kidneys and identify blood flow in the renal vessels (power Doppler), it cannot accurately identify parenchymal tears, collecting system injuries, or extravasation of urine until a later stage when a urine collection has had time to accumulate.

Imaging is designed to:

- Grade injury.
- Document presence and function of contralateral kidney.
- Detect associated injuries.
- Detect pre-existing renal pathology in affected kidney.

On contrast enhanced CT look for:

- Depth of parenchymal laceration.
- Parenchymal enhancement (absence of enhancement suggests renal artery injury).
- Presence of urine extravasation (medial extravasation of contrast suggests disruption of PUJ or renal pelvis).
- Presence, size, and position of retroperitoneal haematoma (haematoma medial to the kidney suggests a vascular injury).
- Presence of injuries to adjacent organs (bowel, spleen, liver, pancreas, etc).
- Presence of a normal contralateral kidney.

On-table IVU

When, because of shock and need for immediate laparotomy, a patient is transferred immediately to the operating theatre without having hada CT scan and a retroperitoneal haematoma is found, a single shot abdominal X-ray, taken 10min after contrast administration (2mL/kg of contrast), can establish the presence/absence of a renal injury and the presence of a normally functioning contralateral kidney where the ipsilateral kidney injury is likely to necessitate a nephrectomy.

* Remember, in young adults and children, hypotension is a late manifestation of hypovolaemia: blood pressure is maintained until there has been substantial blood loss.

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Renal trauma: treatment

Conservative (non-operative) management

Most blunt (95%) and many penetrating renal injuries (50% of stab injuries and 25% of gunshot wounds) can be managed non-operatively.

Dipstick or microscopic haematuria: if systolic BP since injury has always been >90mmHg and no history of acceleration or deceleration, imaging and admission is not required.

Macroscopic haematuria: in a cardiovascularly stable patient, having staged the injury with CT, admit for bed rest (no hard and fast rules as to duration) and observation until the macroscopic haematuria, if present, resolves (cross-match in case BP drops); give antibiotics if urinary extravasation.

High-grade (IV and V) injuries: can be managed non-operatively if they are cardiovascularly stable. However, grade IV and, especially, grade V injuries often require nephrectomy to control bleeding (grade V injuries function poorly if repaired).

Surgical exploration

Is indicated (whether blunt or penetrating injury) if:

- The patient develops shock which does not respond to resuscitation with fluids and/or blood transfusion.
- The haemoglobin decreases (there are no strict definitions of what represents a 'significant' fall in haemoglobin).
- There is urinary extravasation and associated bowel or pancreatic injury.
- Expanding perirenal haematoma (again the patient will show signs of continued bleeding).
- Pulsatile perirenal haematoma.

An expanding and/or pulsatile perirenal haematoma suggests a renal pedicle avulsion. Haematuria is absent in 20%.

Technique of renal exploration

Midline incision allows:

- Exposure of renal pedicle, so allowing early control of the renal artery and vein.
- Inspection for injury to other organs.

Lift the small bowel upwards to allow access to the retroperitoneum. Incise the peritoneum over the aorta, above the inferior mesenteric artery. A large peri-renal haematoma may obscure the correct site for this incision. If this is the case, look for the inferior mesenteric vein and make your incision medial to this. Once on the aorta, the inferior vena cava may be exposed, then the renal veins and the renal arteries. Pass slings around all of these vessels. Expose the kidney by lifting the colon offof the retroperitoneum. Bleeding may be reduced by applying pressure to the vessels via the slings. Control bleeding vessels within the kidney with 4/0 vicryl or monocryl sutures. Close any defects in the collecting system with 4/0 vicryl. If your sutures cut out, place a strip of Surgicel over the site of bleeding, place your sutures through the capsule on either side

of this, and tie them over the Surgicel. This will stop them from cutting through the friable renal parenchyma.

Finding a non-expanding, non-pulsatile retroperitoneal haematoma at laparotomy

The finding of an expanding and/or pulsatile retroperitoneal haematoma at laparotomy will often indicate a renal pedicle injury (avulsion or laceration), and nephrectomy may be required to stop further haemorrhage.

Controversy surrounds the correct management of the finding at laparotomy of a non-expanding, non-pulsatile retroperitoneal haematoma. Most can be left alone. Remember, exploration increases the chances of loss of the kidney (because of bleeding which can becontrolled only by nephrectomy). The decision to explore is based on whether pre-operative or on-table imaging has been done and is normal or abnormal:

Pre-operative or intra-operative imaging	Action
Normal	Leave the haematoma alone
Abnormal; contralateral kidney normal	Explore and repair renal injury
Abnormal; abnormal or absent contralateral kidney	Leave the haematoma alone*
None	Explore and repair renal injury

* Exploration increases the chances of loss of the kidney (because of bleeding that can be controlled only by nephrectomy), which is a disaster if the contralateral kidney is absent or damaged.

Urinary extravasation

Not in itself necessarily an indication for exploration. Almost 80–90% of these injuries will heal spontaneously. The threshold for operative repair is lower with associated bowel or pancreatic injury—bowel contents mixing with urine is a recipe for overwhelming sepsis. In these situations, the renal repair should be well drained and omentum interposed between the kidney and bowel or pancreas.

If there is substantial contrast extravasation, consider placing a JJ stent. Repeat renal imaging if the patient develops a prolonged ileus or a fever since these signs may indicate the development of a urinoma which can be drained percutaneously. Renal exploration is required for a persistent leak.

Devitalized segments

Exploration is usually not required for patients with devitalized segments of kidney and with urinary extravasation.[1]

Complications of renal injury[2–4]

Early

- **Delayed bleeding:** 1.5% of surgically treated patients, 4% of surgically treated penetrating injuries, 1–6% of paediatric blunt injuries managed non-operatively, 20% of conservatively managed stab injuries. 75%require surgery and of these, 60% require nephrectomy.

- **Urinary extravasation and urinoma formation:** blunt injury 2–20%; penetrating injury 10–25%. If low volume and non-infected, often heal spontaneously; large volume—consider a trial of JJ stenting with renal repair if extravasation persists.
- **Abscess formation:** flank pain, fever, ileus. CT or USS is diagnostic. Treat by percutaneous drainage.
- **Renal arteriovenous fistulas:** commonest cause is percutaneous renal biopsy, i.e. iatrogenic. Often small and heal spontaneously, but may manifest with retroperitoneal bleeding; collecting system bleeding (heavy haematuria); microscopic haematuria; abdominal bruit; hypertension; tachycardia; high output heart failure. Diagnosis is confirmed by selective renal arteriography. Treat by arterial embolization (treatment of choice); partial nephrectomy; complete nephrectomy.

Late

- Decreased renal function.
- Hypertension.

Hypertension and renal injury

Excess renin excretion occurs following renal ischaemia from renal artery injury or thrombosis or renal compression by haematoma or fibrosis (so-called 'Page' kidney). This can lead to hypertension months or years after renal injury. The exact incidence of post-traumatic hypertension is uncertain. It may occur in <1% of individuals.

Iatrogenic renal injury: renal haemorrhage after percutaneous nephrolithotomy (PCNL)

Significant renal injuries can occur during PCNL for kidney stones. This is the surgical equivalent of a stab wound and serious haemorrhage results in 1% of cases.[5]

Bleeding during or after a PCNL can occur from vessels in the nephrostomy track itself, from an arteriovenous fistula, or from a pseudoaneurysm which has ruptured. Track bleeding will usually tamponade around a large-bore nephrostomy tube. Traditionally, persistent bleeding through the nephrostomy tube is managed by clamping the nephrostomy tube and waiting for the clot to tamponade the bleeding. While this may control bleeding in some cases, in others, a rising or persistently elevated pulse rate (with later hypotension) indicates the possibility of persistent bleeding and is an indication for renal arteriography and embolization of the arteriovenous fistula or pseudoaneurysm (Figs 11.1 and 11.2). Failure to stop the bleeding by this technique is an indication for renal exploration.

Arteriovenous fistulae can sometimes occur following open renal surgery for stones or tumours and arteriography with embolization again can be used to stop the bleeding in these cases. However, the bleeding usually occurs over a longer time course (days or even weeks) rather than as an acute haemorrhage causing shock.

1 Toutouzas KG (2002) Non-operative management of blunt renal trauma: a prospective study. *Am Surg* **68**:1097–103.

2 McAninch JW, Carroll PR, Klosterman PW, *et al.* (1991) Renal reconstruction after injury. *J Urol* **145**:932.

3 Carroll PR, McAninch JW. (1985) Operative indications in penetrating renal trauma. *J Trauma* **25**:587.

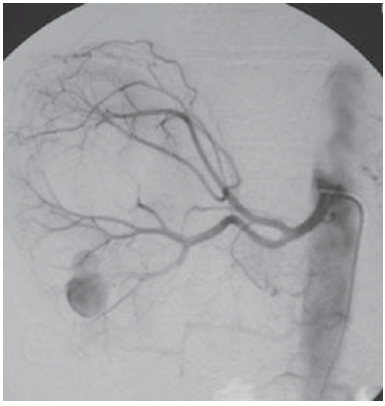

Fig. 11.1 Renal arteriography after PCNL where severe bleeding was encountered. An arteriovenous fistula was found and embolized.

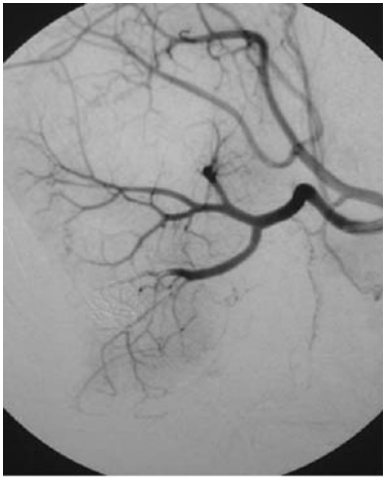

Fig. 11.2 Post-embolization of arteriovenous fistula. Note the embolization coils in the lower pole.

4 Bernath AS, Shutte H, Fernandez RRD, *et al.* (1983) Stab wounds of the kidney: conservative management in flank penetration. *J Urol* **129**:468.

5 Martin X (2000) Severe bleeding after nephrolithotomy: results of hyperselective embolization. *Eur Urol* **37**:136–9.

Ureteric injuries: mechanisms and diagnosis

Types, causes, and mechanisms

- **External:** rare—blunt (e.g. high-speed road traffic accidents, fall from a height); penetrating (knife or gunshot wounds).
- **Internal trauma** (= iatrogenic): during pelvic or abdominal surgery, e.g. hysterectomy, colectomy, AAA repair; ureteroscopy. The ureter may be divided, ligated, or angulated by a suture; a segment excised or damaged by diathermy.

External injury: diagnosis

Based on a high index of suspicion for the possibility of ureteric injury in the types of scenarios (see Types, causes, and mechanisms). *Imaging studies:* IVU or CT can be used to determine the presence of a ureteric injury. If doubt remains regarding the integrity of the ureters, retrograde ureterography should be done.

Internal (iatrogenic) injury: diagnosis

The injury may be suspected at the time of surgery, but injury may not become apparent until some days or weeks post-operatively.

Intraoperative diagnosis

For ureteric contusions and perforations seen at the time of ureteroscopy, insert a JJ stent. During abdominal or pelvic surgery, first optimize exposure of the suspected injury site by packing bowel out of the way, controlling bleeding, and ensuring the theatre lights are appropriately positioned. Examine both ureters (bilateral injuries can occur).

Direct inspection of the ureter

A good way of inspecting the ureter for injury, but requires exposure of a considerable length of ureter to establish that it has not been injured. Lower ureteric exposure is more difficult than upper ureteric.

Extravasation after injection of methylene blue into the ureter

Look for leakage of dye from a more distant section of ureter.

On-table IVU

Technically difficult; does not always demonstrate the presence or site of injury.

On-table retrograde ureterography

Via an incision made in the bladder or via a cystoscope. A very accurate method of establishing the presence or absence of a ureteric injury (see Fig. 11.3). Both ureters can easily be examined.

Post-operative diagnosis

The diagnosis is usually apparent in the first few days following surgery (Box 11.2), but it may be delayed by weeks, months, or years (presentation: flank pain, post-hysterectomy incontinence—a continuous leak of urine suggests a ureterovaginal fistula).

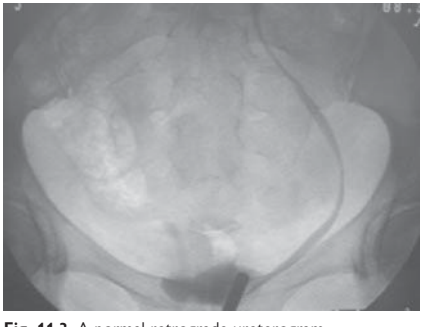

Fig. 11.3 A normal retrograde ureterogram.

Box 11.2 Symptoms and signs of ureteric injury

May include:

- An ileus (due to urine within the peritoneal cavity).
- Prolonged post-operative fever or overt urinary sepsis.
- Persistent drainage of fluid from drains, the abdominal wound, or the vagina. Send this for creatinine estimation. Creatinine level higher than that of serum = urine (creatinine level will be at least 300μmol/L).
- Flank pain if the ureter has been ligated.
- Abdominal mass, representing a urinoma (a collection of urine).
- Vague abdominal pain.
- The pathology report on the organ that has been removed may note the presence of a segment of ureter!

Investigation: IVU or retrograde ureterogram. Ultrasonography may demonstrate hydronephrosis, but hydronephrosis may be absent when urine is leaking from a transected ureter into the retroperitoneum or peritoneal cavity. The IVU usually shows an obstructed ureter or occasionally, a contrast leak from the site of injury.

Ureteric injuries: management

When to repair the ureteric injury

Generally, the best time to repair the ureter is as soon as the injury has been diagnosed.

Delay definitive ureteric repair when:

- The patient is unable to tolerate a prolonged procedure under general anaesthetic.
- There is evidence of active infection at the site of proposed ureteric repair (infected urinoma).

A percutaneous nephrostomy should be placed, the infection drained radiologically (percutaneous drain), intravenous antibiotics given, and ureteric repair delayed until the patient is apyrexial.

Traditional teaching held that surgical repair should be delayed when the injury was diagnosed between roughly days 7 and 14 after ureteric injury, the time when maximal oedema and inflammation at the site of repair was believed to occur. However, favourable outcomes have been demonstrated after early repair and the time of the original injury is nowadays seen as a less important determinant of time of definitive repair.[1]

Definitive treatment of ureteric injuries

The options depend on:

- Whether the injury is recognized immediately.
- Level of injury.
- Other associated problems.

The options are:

- JJ stenting for 3–6 weeks (e.g. ligature injury recognized immediately).
- Primary closure of partial transection of the ureter.
- Direct ureter to ureter anastomosis (primary uretero-ureterostomy)—if the defect between the ends of the ureter is of a length where a tension-free anastomosis is possible.
- Reimplantation of the ureter into the bladder (uretero-neocystostomy), either using a psoas hitch or a Boari flap (see Figs. 11.4 and 11.5).
- Transuretero-ureterostomy (see Fig. 11.6).
- Autotransplantation of the kidney into the pelvis—where the segment of damaged ureter is very long.
- Replacement of the ureter with ileum—where the segment of damaged ureter is very long.
- Permanent cutaneous ureterostomy—where the patient's life expectancy is very limited.
- Nephrectomy—traditionally advocated for ureteric injury during vascular graft procedures (e.g. aortobifemoral graft for AAA), but the trend is towards ureteric repair and renal preservation, reserving nephrectomy only where a urine leak develops post-operatively (continuing drainage of urine from the drain placed at the site of ureteric anastomosis).[2]

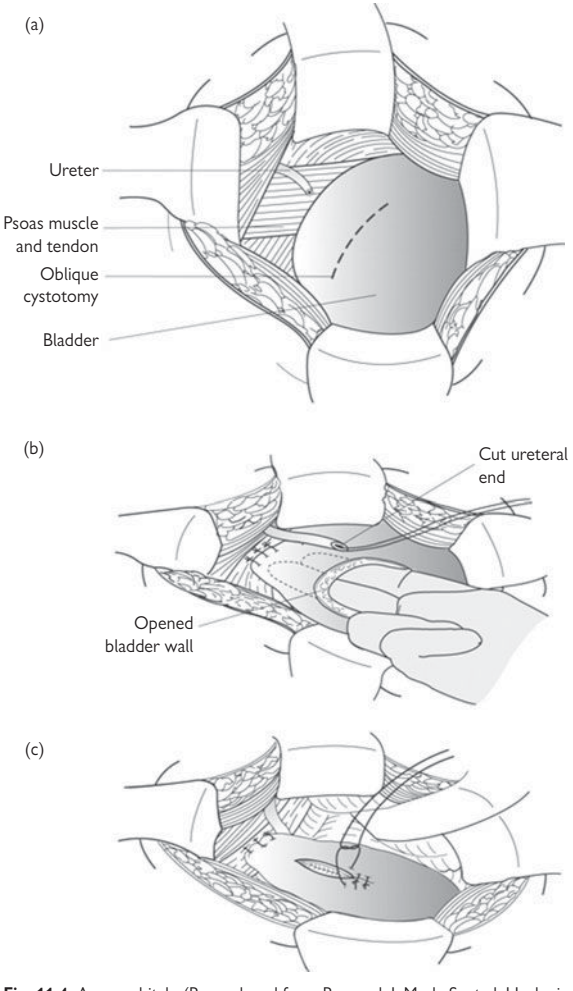

Fig. 11.4 A psoas hitch. (Reproduced from Reynard, J, Mark, S. et al, Urological Surgery. Oxford University Press, with permission from OUP.)

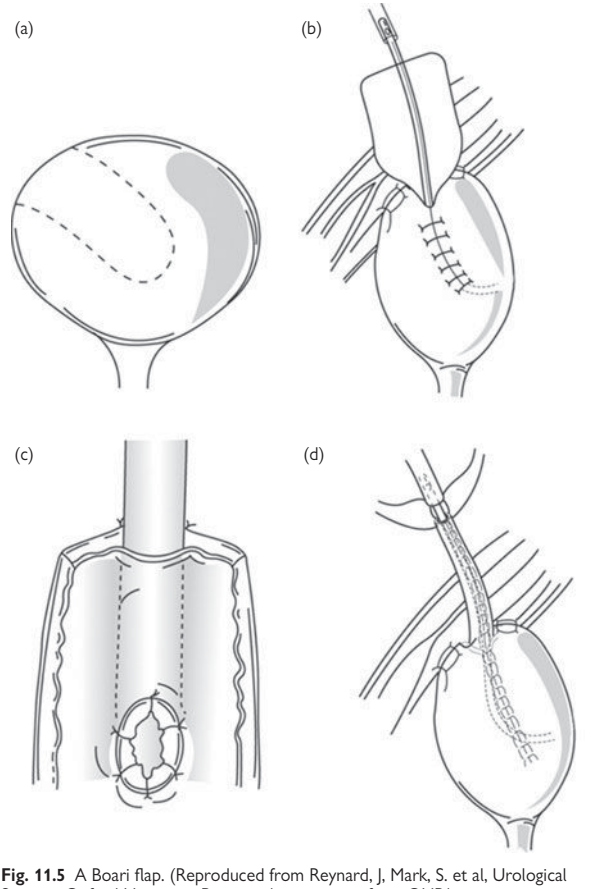

Fig. 11.5 A Boari flap. (Reproduced from Reynard, J, Mark, S. et al, Urological Surgery. Oxford University Press, with permission from OUP.)

JJ stenting

For some injuries, JJ stenting may be adequate for definitive treatment, particularly where the injury does not involve the entire circumference of the ureter and continuity is, therefore, maintained across the region of the ureteric injury. In situations where a ligature has been applied around the ureter and this has been immediately recognized such that viability of the ureter has probably not been compromised, remove the ligature and place a JJ stent (cystoscopically if this is feasible or, if not, by opening the

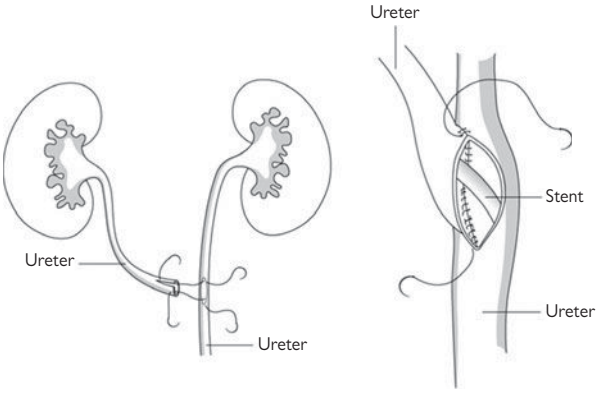

Fig. 11.6 Transuretero-ureterostomy. (Reproduced from Reynard, J, Mark, S. et al, Urological Surgery. Oxford University Press, with permission from OUP.)

bladder). If there has been a delay in recognition of a ligature injury to the ureter, it is probably safer to remove the affected segment of ureter and perform a uretero-ureterostomy. Generally speaking, the stent is maintained in position for somewhere between 3 and 6 weeks (no hard and fast rules). At the time of stent removal, perform a retrograde ureterogram to confirm that there is no persistent leakage of contrast from the original site of injury and to see if there is evidence of ureteric stricturing.

Factors other than the level of injury are important in determining the type of repair. Blast injuries characteristically cause considerable 'collateral' damage to the ureter and surrounding tissues and this may not be apparent at the time of surgery. Delayed necrosis can occur in such apparently normal-looking ureters.

General principles of ureteric repair

- The ends of the ureter should be debrided so that the edges to be anastomosed are bleeding freely.
- The anastomosis should be tension-free.
- For complete transection, the ends of the ureter should be spatulated to allow a wide anastomosis to be done.
- A stent should be placed across the repair.
- Mucosa to mucosal anastomosis should be done to achieve a watertight closure.
- Use 4/0 absorbable suture material.
- A drain should be placed around the site of anastomosis.

1 Blandy JP, Badenoch DF, Fowler CG, Jenkins BJ, Thomas NW (1991) Early repair of iatrogenic injury to the ureter and bladder after gynecological surgery. *J Urol* **146**:761–5.

2 McAninch JW (2002) In: Walsh PC, Retik AB, Vaughan ED, Wein AJ (eds) *Campbell's Urology*, 8th edn. Philadelphia: WB Saunders pp. 3703–14.

Pelvic fractures: bladder and ureteric injuries

Pelvic fractures are usually due to run-over or crush injuries where massive force is applied to the pelvis. Associated head, chest, intra-abdominal (spleen, liver, mesentery of bowel), pelvic (bladder, urethra, vagina, rectum), and genital injuries are common and these injuries and the massive blood loss from torn pelvic veins and arteries account for the substantial (20%) mortality after pelvic fracture.

Initial assessment

Pelvic fractures are often occult. Screen run-over or crush victims with a pelvic X-ray. Assess:

- Vital signs (pulse rate, systolic BP).
- Neurovascular integrity of lower limb (lumbosacral plexus, peripheral nerves, and major vessels may be damaged).
- Examine for head, chest, abdominal, and perineal injuries.
- Determine stability/instability of the fracture from pelvic X-rays.

Is the fracture stable or unstable?

See Box 11.3.

Abdominal and pelvic imaging in pelvic fracture

- **Abdominal/pelvic CT:** establishes presence/absence of associated pelvic (rectum, bladder) and abdominal organ injury (liver, bowel, spleen).
- **Retrograde urethrogram:** to detect urethral injury. Some hospitals perform retrograde urethrography only when blood is present at the meatus; others do this in all pelvic fracture patients where the pubic rami have been disrupted.
- If the urethra is intact, a retrograde cystogram is done to assess theintegrity of the bladder.

Box 11.3 Is the fracture stable or unstable?

Stable = the fracture can withstand normal physiologic forces.
Unstable = the fracture cannot withstand normal physiologic forces.

Instability suggests a greater degree of trauma to the pelvis and increases the likelihood of serious associated injuries. In addition, fixation of an unstable fracture reduces blood loss, mortality, hospital stay, leg length discrepancy, and long-term disability; makes nursing care easier; and reduces analgesic consumption. Stability can be defined according to the Tile classification system of pelvic ring fractures (Table 11.3).

Of unstable pelvic fractures, 70% are B2 and B3, 10–20% are open book type (B1), and 10–20% are type C.

- **Open book pelvic fracture (B1):** caused by anteroposterior compression. A dramatic rise in pelvic volume stretches vessels, nerves, and organs (e.g. bladder) (Figs. 11.7 and 11.8).
- **Closed book pelvic fracture (B2 or B3):** caused by a lateral compression force to the pelvis. The pubic rami fracture and overlap and the ilium and sacral wings may be fractured. Nerves and vessels are not stretched, but the urethra is more likely to be damaged by scissors like action of overlapping pubic rami.
- **Vertically unstable pelvic fracture (C):** vessels and nerves can be damaged by stretching.

Radiological determination of stability

Based on inlet (for anteroposterior displacement) and outlet views (for vertical displacement) of the pelvis, the X-ray beam being angled accordingly. CT provides better definition of sacral, sacroiliac, and acetabular fractures and dislocations.

Is urethral catheterization of a pelvic fracture patient safe?

If there is no blood present at the meatus, a gentle attempt at urethral catheterization may be made. It has been suggested that this could convert a partial urethral rupture into a complete rupture. However, leading trauma centres in the United States state 'We and others have not seen any evidence that this can convert an incomplete into a complete transection … and we usually make one gentle attempt to place a urethral catheter in suspected urethral disruption'.[1] If any resistance is encountered, stop and obtain a retrograde urethrogram. If the retrograde urethrogram demonstrates a normal urethra, proceed with another attempt at catheterization, using plenty of lubricant. If there is a urethral rupture, insert an SPC via a formal open approach to allow inspection of the bladder (and repair of injuries if present).

Bladder injuries associated with pelvic fractures

Ten percent of male and 5% of female pelvic fractures are associated with a bladder injury (fracture type leading to bladder injury is usually an anteroposterior pelvic compression fracture, i.e. open book pelvic fracture; Tile classification B1). Sixty percent of pelvic fracture bladder ruptures are extraperitoneal, 30% intraperitoneal, and 10% combined extraperitoneal and intraperitoneal.

Table 11.3 The Tile classification system of pelvic ring fractures

Type A—stable	A1: fracture of pelvis not involving the pelvic ring
	A2: minimal displacement of pelvic ring with no instability
Type B—rotationally (horizontally) unstable	B1: open book
	B2: closed book
	Lateral compression: ipsilateral fracture B3 closed book
	Lateral compression: contralateral fracture (bucket handle fracture)
Type C—rotationally (horizontally) and vertically unstable	C1: unilateral
	C2: bilateral
	C3: with acetabular fracture

Urethral injuries associated with pelvic fractures

The posterior urethra (essentially the membranous urethra) is injured with roughly the same frequency as the bladder in subjects who sustain a pelvic fracture, occurring in 5–15% of such cases. Most posterior urethral injuries occur in association with pelvic fractures.[2] Cass found bladder ruptures in 6% of pelvic fractures, urethral rupture in 2%, and combined bladder and urethral rupture in 0.5%.[3]

Combined bladder and posterior urethral injuries following pelvic fracture

One-third of patients with a traumatic bladder rupture have injuries to other urinary structures, most commonly the urethra. Ten to twenty percent of patients with a pelvic fracture and bladder rupture also have a posterior urethral rupture.

Symptoms and signs of bladder or urethral injury in pelvic fracture

- Blood at meatus—in 40–50% of patients (no blood at meatus in 50–60%).
- Gross haematuria.
- Inability to pass urine.
- Perineal or scrotal bruising.
- 'High riding' prostate.
- Inability to pass a urethral catheter.

'High riding prostate'

The prostate and bladder become detached from the membranous urethra and are pushed upwards by the expanding pelvic haematoma. The high riding prostate is said to be a classic sign of posterior urethral rupture. Traditional teaching states that a DRE should be done in cases of pelvic

trauma to determine prostatic position. However, the presence of a high riding prostate is an unreliable sign.[4] The pelvic haematoma may make it impossible to feel the prostate so the patient may be thought to have a high riding prostate when, in fact, it is in a normal position. Conversely, what may be thought to be a normal prostate in a normal position may actually be the palpable pelvic haematoma. In pelvic fracture, a DRE is done not to identify a high riding prostate, but rather to establish the presence of an associated rectal injury (blood seen on the examining finger). However, rectal injury can still occur in the absence of rectal blood.

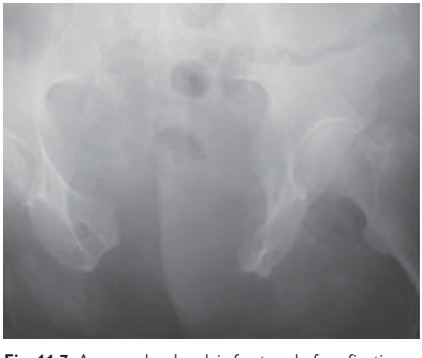

Fig. 11.7 An open book pelvic fracture before fixation.

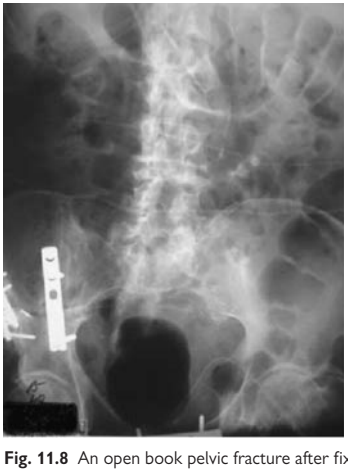

Fig. 11.8 An open book pelvic fracture after fixation.

Management of bladder injuries associated with pelvic fractures

Extraperitoneal: urethral catheter until the bladder has healed (usually 2–3 weeks).
Intraperitoneal: open surgical repair.

Management of urethral injuries associated with pelvic fractures

Suprapubic catheter: placement via an open approach is generally better than a percutaneous approach, partly because it allows inspection of the bladder for associated injuries which may require repair, but also because the catheter may inadvertently be placed into the large pelvic haematoma which always accompanies such fractures. Not only does this mean that the bladder is not being drained (so urine will leak into the pelvic haematoma and fracture site), but the suprapubic can also act as a potential source of infection of the pelvic haematoma, which can lead to life-threatening sepsis.

Management of combined urethral and bladder injuries associated with pelvic fractures

If a urethral catheter can be passed and a cystogram shows an extraperitoneal bladder rupture, leave a urethral catheter in place until the bladder has healed (usually 2–3 weeks).

If a urethral catheter cannot be passed (because of a complete urethral rupture), a suprapubic catheter should be placed via an open approach (rather than percutaneously) to allow inspection of the bladder (and repair if the bladder has been torn) at the same time that the suprapubic catheter is placed. The urethral rupture will prevent a cystogram from being done so *direct* inspection of the bladder is required to establish the presence/absence of a bladder injury.

1 McAninch JW (2002) In: Walsh PC, Retik AB, Vaughan ED, Wein AJ (eds) *Campbell's Urology*, 8th edn. Philadelphia: WB Saunders pp. 3703–14.

2 Cass AS (1984) Simultaneous bladder and prostato membranous urethral rupture from external trauma. *J Urol* **132**:907–8.

3 Cass AS (1988) *Genitourinary Trauma.* Boston: Blackwell Scientific Publications.

4 Elliott DS, Barrett DM (1997) Long-term follow-up and evaluation of primary realignment of posterior urethral disruptions. *J Urol* **157**:814–6.

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Bladder injuries

Situations in which the bladder may be injured

TURBT (Figs. 11.9 and 11.10), cystoscopic bladder biopsy, TURP, cystolitholapaxy, penetrating trauma to the lower abdomen or back, Caesarean section (especially as an emergency), blunt pelvic trauma—in association with pelvic fracture or 'minor' trauma in the inebriated patient, rapid deceleration injury (e.g. seat belt injury with full bladder in the absence of a pelvic fracture), spontaneous rupture after bladder augmentation, total hip replacement (very rare).

Types of perforation

- **Intraperitoneal perforation:** the peritoneum overlying the bladder is breached, allowing urine to escape into the peritoneal cavity.
- **Extraperitoneal perforation:** the peritoneum is intact and urine escapes into the space around the bladder, but not into the peritoneal cavity.

Making the diagnosis

During endoscopic urological operations (e.g. TURBT, cystolitholapaxy), the diagnosis is usually obvious on visual inspection alone—a dark hole is seen in the bladder and loops of bowel may be seen on the other side. No further diagnostic tests are required.

In cases of trauma, the classic triad of symptoms and signs suggesting a bladder rupture is:

- Suprapubic pain and tenderness.
- Difficulty or inability in passing urine.
- Haematuria.

Additional signs:

- Abdominal distension.
- Absent bowel sounds (indicating an ileus from urine in the peritoneal cavity).

These symptoms and signs are an indication for a retrograde cystogram.

The diagnosis may be made only at operation for fixation of a pelvic fracture.

Imaging studies

Retrograde cystography or CT cystography

- Ensure the bladder is adequately distended with contrast. With inadequate distension, a clot, omentum, or small bowel may 'plug' the perforation,which may not, therefore, be diagnosed. Use at least 400mL of contrast in an adult and 60mL plus 30mL per year of age in children up to a maximum of 400mL in children.
- Obtain images after the contrast agent has been completely drained from the bladder (a post-drainage film). A whisper of contrast from a posterior perforation may be obscured by a bladder distended with contrast.

In extraperitoneal perforations, extravasation of contrast is limited to the immediate area surrounding the bladder. In intraperitoneal perforations, loops of bowel may be outlined by the contrast.

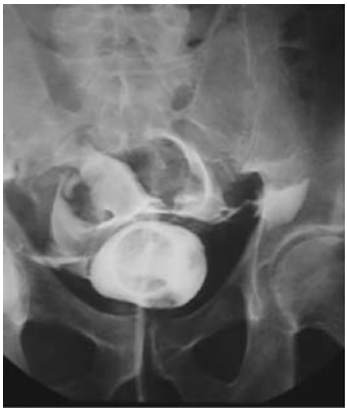

Fig. 11.9 An intraperitoneal bladder perforation following a TURBT, as demonstrated on a cystogram (anteroposterior view).

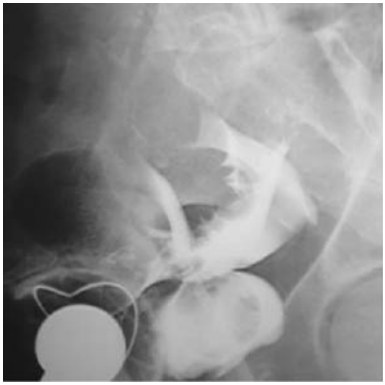

Fig. 11.10 A bladder perforation following a TURBT, as demonstrated on a cystogram (lateral view).

Treatment of bladder rupture

Extraperitoneal: bladder drainage with a urethral catheter for 2 weeks followed by a cystogram to confirm the perforation has healed.

Indications for surgical repair of extraperitoneal bladder perforation:

- If you have opened the bladder to place a suprapubic catheter for a urethral injury.
- A bone spike protruding into the bladder on CT.
- Associated rectal or vaginal perforation.
- Where the patient is undergoing open fixation of a pelvic fracture, the bladder can be simultaneously repaired.

Intraperitoneal: usually repaired surgically to prevent complications from leakage of urine into the peritoneal cavity.

Spontaneous rupture after bladder augmentation: spontaneous bladder rupture occasionally occurs months or years after bladder augmentation and usually with no history of trauma. If the patient has spina bifida or a spinal cord injury, they usually have limited awareness of bladder fullness and pelvic pain. Their abdominal pain may, therefore, be mild and vague in onset and nature. Fever or other signs of sepsis may be present. Have a high index of suspicion in patients with augmentation who present with non-specific signs of illness. A cystogram usually, although not always, confirms the diagnosis. If doubt exists, consider exploratory laparotomy.

Posterior urethral injuries in males and urethral injuries in females

Mechanisms

- **External blunt**: pelvic fracture—road traffic accidents, falls from a height, crush injuries—most common cause.
- **External penetrating**: gunshot—rare; stab—rare.
- **Internal, iatrogenic**: endoscopic surgery; radical prostatectomy; TURP (more likely with vascular prostate, prostate cancer, inexperienced surgeon).
- **Internal, self-inflicted**: foreign bodies inserted into urethra—rare.

Male posterior urethral injuries

The great majority of posterior urethral injuries are an associated injury following pelvic fracture, and their diagnosis and initial management are discussed on 📖 p. 530. Immediate (within 48h) open repair of posterior urethral injuries is associated with a high incidence of urethral strictures (70%) and subsequent restenosis after stricture repair, incontinence (20%), and impotence (40%). The surrounding haematoma and tissue swelling make it difficult to identify structures and to mobilize the two ends of the urethra to allow tension-free anastomosis.

In the majority of male posterior urethral injuries, treatment should be deferred for 3 months to allow the oedema and haematoma to completely resolve. As this occurs, the two distracted ends of the urethra come closer together, thereby reducing the amount of mobilization that the surgeon has to do. Most such injuries can be repaired by an anastomotic urethroplasty. Optical urethrotomy (division of the stricture using an endoscopic knife or laser via a cystoscope inserted into the urethra) is generally not recommended.

Immediate repair is indicated where there is an open wound as long as the urethral ends are close (i.e. not distracted by a large haematoma).

Urethral injuries in females

Rare because the female urethra is short and its attachments to the pubic bone are weak such that it is less prone to tearing during pubic bone fracture. When they do occur, such injuries are usually associated with rectal or vaginal injuries. In developing countries, prolonged labour can cause ischaemic injury to the urethra and bladder neck, leading to urethrovaginal or vesicovaginal fistula formation.

Anterior urethral injuries

These injuries are uncommon.

Mechanisms

- External blunt: straddle injury (e.g. forceful contact of perineum with bicycle cross-bar*)—most common cause of injury; kick to perineum; penile fracture.
- External penetrating: gunshot; stab.
- Internal, iatrogenic: catheter balloon inflated in urethra; endoscopic surgery; penile surgery.
- Internal, self-inflicted: foreign bodies inserted into urethra.

History and examination

The patient usually presents with difficulty in passing urine and frank haematuria in the context of a straddle injury. Blood may be present at the end of the penis and a haematoma around the site of the rupture. If Buck's fascia has been ruptured (the deep layer of the superficial fascia of penis), urine and blood track into the scrotum causing swelling and a 'butterfly wing' pattern of bruising, reflecting the anatomical attachments of Colles' fascia—the membranous layer of the superficial fascia of the groin and perineum(see Fig. 11.11).

Confirming the diagnosis and subsequent management

Retrograde urethrography delineates the extent of urethral injury.

Extravasation of urine can create a collection of urine around the urethra (a urinoma) and generates an inflammatory reaction, with subsequent stricture formation. Superadded infection can lead to abscess formation which may burst onto the surface of the skin, leading to a urethrocutaneous fistula. More rarely, Fournier's gangrene supervenes. Urinary diversion (urethral or suprapubic catheter) prevents further extravasation of urine and antibiotics may reduce the likelihood of superadded infection.

Anterior urethral contusion

Typical history: blood at meatus, *no* extravasation of contrast on retrograde urethrogram. Pass a small gauge urethral catheter (12 Ch in an adult) and remove a week or so later.

Partial rupture of anterior urethra

Leak of contrast from urethra with retrograde flow into bladder. Most can be managed by a period of suprapubic urinary diversion. Seventy percent heal without stricture formation (primary closure can be difficult because of oedema and of haematoma at the site of injury and can convert a short area of urethral injury into a longer one). Give a broad-spectrum antibiotic to prevent infection of extravasated urine and blood. If a voiding cystogram 2 weeks later confirms urethral healing, remove SPC. If contrast still extravasates, leave it in place a little longer.

* Bulbar urethra being crushed against pubic bone.

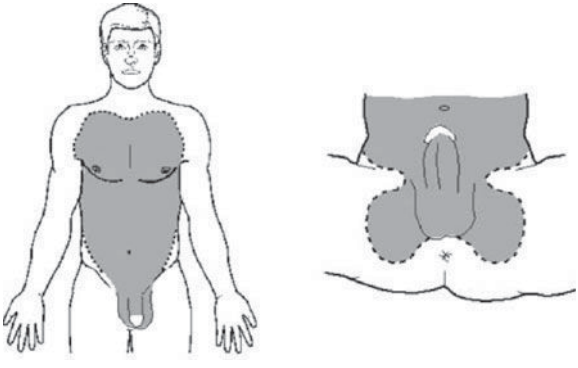

Fig. 11.11 Butterfly bruising following rupture of Buck's fascia.

Suprapubic catheterization (percutaneously) is preferred over urethral catheterization because a partial rupture can be converted to a complete rupture. If the bladder cannot be palpated such that an SPC cannot be safely inserted, then perform open suprapubic cystostomy (under general anaesthetic).

Complete rupture of anterior urethra

Leak of contrast from the urethra on retrograde urethrogram, no filling of the posterior urethra or bladder. The urethra may either be immediately repaired (if a surgeon with sufficient experience is available) or an SPC can be placed with delayed repair.

Penetrating partial and complete anterior urethral injuries

Knife or gunshot wound: primary (i.e. immediate) repair may be carried out if a surgeon experienced in these techniques is available; if not,suprapubic diversion and subsequent repair by an appropriate surgeon.

Immediate surgical repair of anterior urethral injuries is only done in the context of penile fracture or where there is an open wound.

The anatomical explanation for 'butterfly wing' pattern of bruising in anterior urethral rupture

Fascial layers of penis from superficial to deep:

- Penile skin.
- Superficial fascia of the penis (= dartos fascia)—continuous with the membranous layer of the superficial fascia of the groin and perineum (= Colles' fascia).
- Buck's fascia (= the deep layer of the superficial fascia).
- Deep fascia of the penis (the tunica albuginea) which covers the two dorsal rods of erectile tissue, the corpora cavernosa, and the ventrally located corpus spongiosum that surrounds the urethra (Fig. 11.12).

If Buck's fascia is intact, bruising from a urethral rupture is confined in a sleeve-like configuration along the length of the penis. If Buck's fascia has ruptured, the extravasation of blood, and thus the subsequent bruising, is limited by the attachments of Colles' fascia which forms a 'butterfly'-like pattern in the perineum and is continuous in the upper abdomen and chest with Scarpa's fascia.

How to perform a retrograde urethrogram

- Aseptic technique.
- Urografin 150® (sodium amidotrizoate and meglumine amidotrizoate), but other contrast agents can be used.
- Position the patient at an oblique angle (bottom leg flexed at the hip and knee)
- A 12 Ch catheter is placed in the fossa navicularis of the penis 1–2cm from the external meatus, with the catheter balloon with 2mL of water or with a penile clamp applied to prevent contrast spilling out of the urethra and to hold the catheter in place.
- Continuous screening (fluoroscopy) is done as contrast is instilled until the entire length of the urethra is demonstrated. Remember, as the urethra passes through the pelvic floor (the membranous urethra), there is a normal narrowing and similarly, the prostatic urethra is narrower than the bulbar urethra.

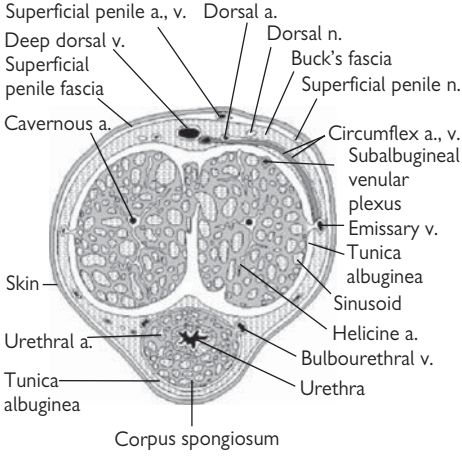

Fig. 11.12 The fascial layers of the penis.

Testicular injuries

Testicular injuries are uncommon.

Mechanisms

Blunt or penetrating. Most in civilian practice are blunt, a blow forcing the testicle against the pubis or the thigh. Bleeding occurs into the parenchyma of the testis and if sufficient force is applied, the tunica albuginea of the testis (the tough fibrous coat surrounding the parenchyma) ruptures, allowing extrusion of seminiferous tubules.

Penetrating injuries occur as a consequence of gunshot and knife wounds and from bomb blasts; associated limb (e.g. femoral vessel), perineal (penis, urethra, rectum), pelvic, abdominal, and chest wounds may occur.

Where bleeding is confined by the tunica vaginalis, a *haematocele* is said to exist. Intraparenchymal (intratesticular) haemorrhage and bleeding beneath the parietal layer of tunica vaginalis will cause the testis to enlarge slightly. The testis may be under great pressure as a consequence of the intratesticular haemorrhage confined by the tunica vaginalis. This can lead to ischaemia, necrosis, and atrophy of the testis.

The force is usually sufficient to rupture the tunica albuginea and the tunica vaginalis and the seminiferous tubules and blood extrude into the layers of the scrotum. This is a *haematoma*.

History and examination

Severe pain is common as are nausea and vomiting. If the testis is surrounded by haematoma, it will not be palpable. If it is possible to palpate the testis, it is usually very tender. The resulting scrotal haematoma can be very large and the bruising and swelling so caused may spread into the inguinal region and lower abdomen.

Testicular ultrasound in cases of blunt trauma

A normal parenchymal echo pattern suggests there is no significant testicular injury (i.e. no testicular rupture). Hypoechoic areas within the testis (indicating intraparenchymal haemorrhage) suggests testicular rupture.

Indications for exploration in scrotal trauma

- **Testicular rupture:** exploration allows evacuation of the haematoma, excision of extruded seminiferous tubules, and repair of the tear in the tunica albuginea.
- **Penetrating trauma:** exploration allows repair to damaged structures (e.g. the vas deferens may have been severed and can be repaired).

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Penile injuries

Amputation

Blood loss can be severe; resuscitate the shocked patient and cross-match blood. Place the penis, if found, in a wet swab inside a plastic bag which is then placed inside another bag containing ice ('bag in a bag'). It can survive for 24h.

Knife and gunshot wounds

Associated injuries are common (e.g. scrotum, major vessels of the lower limb). Most injuries, other than minor ones, should undergo primary repair. Remove debris from wound (e.g. particles of clothing) and debride necrotic tissue and repair as for penile fractures (Box 11.4).

Penile fracture

Rupture of the tunica albuginea of the erect penis (i.e. rupture of one or both corpora cavernosa ± rupture of the corpus spongiosum with rupture of the urethra). The tunica albuginea is 2mm thick in the flaccid penis. It thins to 0.25mm during erection and is, therefore, vulnerable to rupture if the penis is forcibly bent (e.g. during vigorous sexual intercourse). The patient usually reports a sudden 'snapping' or 'popping' sound and/or sensation with sudden penile pain and detumescence of the erection.

The penis is swollen and bruised, sometimes resembling an aubergine. If Buck's fascia has ruptured, bruising extends onto the lower abdominal wall and into the perineum and scrotum. A tender, palpable defect may be felt over the site of the tear in the tunica albuginea. If the urethra is damaged, there may be blood at the meatus or haematuria (dipstick/ microscopic or macroscopic) and pain on voiding or urinary retention. Arrange a retrograde urethrogram in such cases.

Treatment

There has been a trend away from conservative management towards surgical repair (lower complication rate, e.g. reduced penile deformity, less chance of penile scar tissue, and prolonged penile pain).

Conservative: application of cold compresses to the penis; analgesics and anti-inflammatory drugs; abstinence from sexual activity for 6–8 weeks to allow healing.

Surgery: expose the fracture site in the tunica albuginea, evacuate the haematoma, and close the defect in the tunica.

Box 11.4 Surgical re-implantation of amputated penis

Repair the urethra first over a catheter to provide a stable base for subsequent neurovascular repair. Close the tunica albuginea of the corpora (4/0 absorbable suture). Cavernosal artery repair is technically very difficult and does not improve penile viability. Anastomose the dorsal artery of the penis (11/0 nylon), then the dorsal vein (9/0 nylon) to provide venous drainage, and finally, the dorsal penile nerve (10/0 nylon).

Surgical repair of penile fracture

Expose the fracture site by degloving the penis via a circumcising incision around the subcoronal sulcus or by an incision directly over the defect, if palpable. A degloving incision allows better exposure of the urethra for associated urethral injuries. Alternatively, use a midline incision extending distally from the midline raphe of the scrotum along the shaft of the penis. This latter incision, along with a degloving incision, allows excellent exposure of both corpora cavernosa so that an unexpected bilateral injury can be repaired easily as can a urethral injury should this have occurred.

Close the defect in the tunica with absorbable sutures or by non-absorbable sutures (bury the knots so that the patient is unable to palpate them). Non-absorbable sutures may possibly be associated with prolonged post-operative pain. Leave a urethral catheter (voiding can be difficult immediately post-operatively). Repair a urethral rupture, if present, with a spatulated single or two-layer urethral anastomosis and splint repair with a urethral catheter for 3 weeks.

Penile bites

Clean the wound. Give broad-spectrum antibiotics (e.g. cephalosporin and amoxicillin).

Zipper injuries

If the penis is still caught in the zipper, use lubricant jelly and gently attempt to open it. The zipper may have to be cut with orthopaedic cutters or prised apart with a pair of surgical clips on either side of the zipper.

Torsion of the testis and testicular appendages

Definition

A testicular torsion is a twist of the spermatic cord, resulting in strangulation of the blood supply to the testis and epididymis. Testicular torsion occurs most frequently between the ages of 10–30 (peak incidence 13–15y of age), but any age group may be affected.

History and examination

Sudden onset of severe pain in the hemiscrotum, sometimes waking the patient from sleep. It may radiate to the groin, loin, or epigastrium (reflecting its origin from the dorsal abdominal wall of the embryo and its nerve supply from T10/11). There is sometimes a history of minor trauma to the testis. Some patients report previous episodes with spontaneous resolution of the pain (suggesting previous torsion with spontaneous detorsion). The patient may have a slight fever. The testis is usually slightly swollen and very tender to touch. It may be high riding (lying at a higher than normal position in the testis) and may be in a horizontal position due to twisting of the cord. The cremasteric reflex is usually, but not always, absent (positive Rabinowitz's sign). The cremasteric reflex may normally be elicited by stroking the finger along inside of the thigh, which results in upwards movement of the ipsilateral testis. Elevation of the involved testicle does not ameliorate the symptoms (negative Prehn's sign).

Differential diagnosis and investigations

Epididymo-orchitis, torsion of a testicular appendage, and causes of flank pain with radiation into the groin and testis (e.g. a ureteric stone). Colour Doppler USS (reduced arterial blood flow in the testicular artery) and radionuclide scanning (decreased radioisotope uptake) can be used to diagnose testicular torsion, but in many hospitals, these tests are not readily available and the diagnosis is based on symptoms and signs.

Surgical management

Scrotal exploration should be undertaken as a matter of urgency. Delay in relieving the twisted testis results in permanent ischaemic damage to the testis, causing atrophy, loss of hormone and sperm production, and as the testis undergoes necrosis and the blood–testis barrier breaks down, an autoimmune reaction against the contralateral testis (sympathetic orchidopathia). Fix **BOTH** testes since the bell-clapper abnormality, which predisposes to torsion, can occur bilaterally.

Torsion of testicular appendages

The appendix testis (hydatid of Morgagni—a remnant of the Müllerian duct) and the appendix epididymis (a remnant of a cranial mesonephric tubule of the Wolffian duct) can undergo torsion, causing pain that mimicks a testicular torsion. At scrotal exploration, they are easily removed with scissors or a diathermy probe.

Paraphimosis

Definition and presentation

This is where the foreskin is retracted from over the glans of the penis, becomes oedematous, and cannot then be pulled back over the glans into its normal anatomical position. It occurs most commonly in teenagers or young men and also in elderly men (who have had the foreskin retracted during catheterization, but where it has not been returned to its normal position). Paraphimosis is usually painful. The foreskin is oedematous and a small area of ulceration of the foreskin may have developed.

Treatment

The 'iced glove' method: apply topical lignocaine gel to the glans and foreskin for 5min. Place ice and water in a rubber glove and tie a knot in the cuff of the glove to prevent the contents from pouring out. Invaginate the penis into the thumb of the glove. This may reduce the swelling and allow reduction of the foreskin.

Granulated sugar: placed in a condom or glove and applied over the end of the penis has been used to reduce the oedema by osmosis.

The Dundee technique:[1] give the patient a broad-spectrum antibiotic such as 500mg of ciprofloxacin by mouth. Apply a ring block to the base of the penis using a 26 G needle and 10–20mL of 0.5% plain bupivacaine (children usually require general anaesthesia). Clean the skin of the foreskin and the glans with cleaning solution. Using a 25 G needle, make approximately 20 punctures into the oedematous foreskin. Squeeze the oedema fluid out of the foreskin and return to its normal position. Approximately one-third of patients subsequently require elective circumcision for an underlying phimosis.

If this fails, the traditional surgical treatment is a dorsal slit under general anaesthetic or ring block. A longitudinal incision is made in the tight band of constricting tissue and the foreskin pulled back over the glans. Close the incision transversely to lengthen the circumference of the foreskin and prevent recurrences.

1 Reynard JM, Barua JM (1999) Reduction of paraphimosis the simple way—the Dundee technique. *BJU Int* **83**: 859–60.

Malignant ureteric obstruction

Locally advanced prostate cancer, bladder or ureteric cancer may cause unilateral or bilateral ureteric obstruction. Locally advanced non-urological malignancies can also obstruct the ureters (e.g. cervical cancer, rectal cancer, lymphoma).

Unilateral obstruction: is often asymptomatic; an incidental USS finding that requires no specific treatment in the presence of a normal contralateral kidney. Occasionally, loin pain and systemic symptoms may develop due to infection of the obstructed upper urinary tract. In this circumstance, drainage by nephrostomy or stenting is required.

Bilateral ureteric obstruction: is a urological emergency. The patient presents either with symptoms and signs of renal failure or anuric without a palpable bladder. A mass will probably be palpable on rectal examination. ***Investigations:*** renal USS will demonstrate bilateral hydronephrosis and an empty bladder; CT-KUB will confirm the presence of dilated ureters down to a mass at the bladder base.

Immediate treatment of bilateral ureteric obstruction

After treating any life-threatening hyperkalaemia, options include bilateral percutaneous nephrostomy or ureteric stenting. A clotting screen is required prior to nephrostomy insertion. Insertion of retrograde ureteric stents in this setting is usually unsuccessful because tumour involving the trigone obscures the location of the ureteric orifices. More successful is antegrade ureteric stenting following nephrostomy insertion, both of which are performed under sedo-analgesia. The full-length double-J silicone or polyurethane ureteric stents require periodic (4–6 monthly) changes to prevent calcification or blockage. In the case of prostate cancer, hormone therapy should be commenced, if not previously used; even in patients with androgen-independent disease, high-dose parenteral oestrogens may relieve ureteric obstruction.

Long-term treatment of bilateral ureteric obstruction

Longer term treatment options include urinary diversion by formation of ileal conduit, ureteric reimplantation, insertion of short 'permanent' metallic ureteric stents, or ureteric replacement with isolated ileal segments or prosthetic graft material. Such procedures are often complicated and inappropriate in these patients with poor prognosis.

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Metastatic spinal cord and cauda equina compression

Metastatic spinal cord compression (MSCC)

This is an oncological emergency; failure to diagnose and treat promptly can lead to permanent paraplegia and autonomic dysfunction. It is defined as spinal cord or cauda equina compression by direct pressure and/or induction of vertebral collapse or instability by metastatic spread or direct extension of malignancy that threatens or causes neurological disability[1].

Ninety-five percent of patients will complain of back or nerve root pain and have a positive bone scan. Five percent of patients do not exhibit these features because their disease is paravertebral. The majority of urological cases of MSCC are due to prostate cancer. Patients with back or nerve root pain should be examined neurologically and evaluated radiologically. Pain, sometimes worsened by straining or coughing, usually precedes clinical cord compression by ~4 months. Clinical features include sensory changes and muscle weakness in the lower limbs; 50% of patients present unable to stand or walk. Only two-thirds of patients presenting as such will recover any function within one month.

If cord compression is suspected, the patient should be nursed flat with neutral spine alignment (including 'log rolling' or turning beds, with use of a slipper pan for toilet) until bony and neurological stability are ensured and cautious remobilisation may begin. Every acute UK NHS Cancer Centre should have access to a MSCC coordinator who should be informed. The investigation of choice is *emergency spinal MRI*. STIR and sagittal T2-weighted sequences will reveal the bone deposits and level (multiple in 20% of cases) of the soft-tissue cord compression. If MRI is not possible, CT scan or myelography should be considered.

Initial treatment is with high-dose intravenous *corticosteroids*, for example dexamethasone 16mg followed by 4mg 6-hourly for 2–3 weeks. Analgesics and bisphosphonates are administered for pain relief. Within 24 hours, definitive treatment is with fractionated *radiotherapy* or *neurosurgical decompression*. Surgery to achieve decompression and spinal stability is considered preferable if there is pathological fracture, unknown tissue diagnosis or a history of previous radiotherapy. Subsequently, care should include pressure sore and venous thromboembolism prophylaxis measures. Bladder and bowel dysfunction may also occur, requiring catheterisation, stool softeners. Rehabilitation and community support will also be required.

Cauda equina compression

The adult spinal cord tapers below L2 vertebral level into the conus medullaris. The cauda equina consists of the nerve roots of all spinal cord segments below L2, as they run in the subarachnoid space to their exit levels in the lower lumbar and sacral spines.

Pathophysiology: the cauda equina may be compressed by central intervertebral disc prolapse (1–15% of cases), spinal stenosis, or by a benign or malignant tumour within the lower lumbar or sacral vertebral canal.

Symptoms: the diagnosis should be considered in any female or young male presenting with difficulty voiding or in urinary retention. There may be back pain.

Signs: palpable bladder, loss of perianal (S2-4) and lateral foot sensation (S1-2), reduced anal tone; priapism.

Investigations: MRI lumbosacral spine; urodynamic studies reveal a normally-compliant but areflexic bladder.

Treatment: intermittent self-catheterisation, neurosurgery.

1 UK NICE (2008) Clinical guideline 75 – Metastatic spinal cord compression.

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Chapter 12

Infertility

Male reproductive physiology

Hypothalamic–pituitary–testicular axis

The hypothalamus secretes luteinizing hormone-releasing hormone (LHRH), also known as gonadotrophin-releasing hormone (GnRH). This causes the pulsatile release of anterior pituitary gonadotrophins called follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which act on the testis. FSH stimulates the seminiferous tubules to secrete inhibin and produce sperm; LH acts on Leydig cells to produce testosterone (Fig. 12.1).

Testosterone is secreted by the interstitial ***Leydig cells***, which lie adjacent to the seminiferous tubules in the testis. It promotes the development of the male reproductive system and secondary sexual characteristics. Steroidogenesis is stimulated by a cAMP–protein kinase C mechanism which converts cholesterol to pregnenolone. Further steps in the biosynthesis pathway produce intermediary substances (dehydroepiandrosterone and androstenedione) prior to producing testosterone. In blood, 60% of testosterone is attached to sex hormone-binding globulin (SHBG), 38% bound to albumin and 2% is free. At androgen-responsive target tissues, testosterone is converted into a potent androgen, dihydrotestosterone (DHT), by intracellular 5α-reductase (see 🕮 p. 672; Fig. 16.7).

Spermatogenesis Seminiferous tubules are lined with ***Sertoli cells***, which surround developing germ cells (spermatogonia) and provide nutrients and stimulating factors as well as secreting androgen-binding factor and inhibin (Fig. 12.2). Primordial germ cells divide to form primary spermatocytes. These undergo a first meiotic division to create secondary spermatocytes (46 chromosomes), followed by a second meiotic division to form spermatids (23 chromosomes). Finally, these differentiate into spermatozoa. This process takes 72 days. The non-motile spermatozoa leave the seminiferous tubules and pass to the epididymis for storage and maturation (until ejaculation). Spermatozoa that are not released are reabsorbed by phagocytosis.

Mature sperm has a head, middle piece and tail (Fig. 12.3). The head is composed of a nucleus covered by an acrosome cap containing vesicles filled with lytic enzymes. The middle piece contains mitochondria and contractile filaments which extend into the tail to aid motility. After deposition at the cervix, sperm penetrate cervical mucus and travel through the uterus to the site of fertilization in the Fallopian tube, during which time they undergo functional maturation (capacitation). Sperm start to penetrate the oocyte and bind to the zona pellucida. The activation phase is initiated (by ZP3), triggering hyperactivated motility and the acrosomal reaction which leads to enzyme release, penetration into the cytoplasm of the oocyte, fusion, and fertilization.

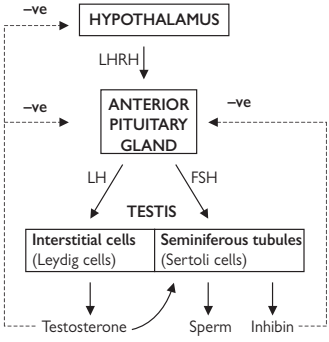

Fig. 12.1 Hypothalamic–pituitary–testicular axis.

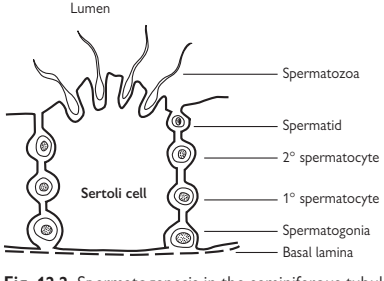

Fig. 12.2 Spermatogenesis in the seminiferous tubules of the testis.

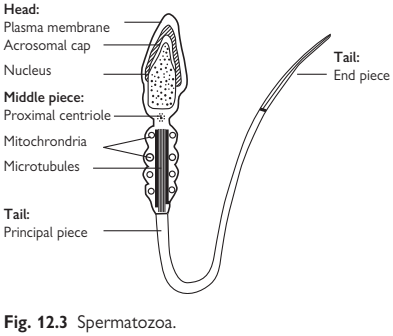

Fig. 12.3 Spermatozoa.

Aetiology and evaluation of male infertility

Definition of subfertility

Failure of conception after at least 12 months of regular unprotected intercourse. The chance of a normal couple conceiving is estimated at 20–25% per month, 75% by 6 months, and 90% at 1y.

Epidemiology

Up to 50% of infertility is due to male factors. An estimated 14–25% of couples may be affected at some point in their reproductive years. Twenty-five percent of subfertile couples will have oligozoospermia and 10% azoospermia. Azoospermia exists in 1% of the male population.

Pathophysiology

Failed fertilization of the normal ovum due to defective sperm development, function, or inadequate numbers. There may be abnormalities of morphology (teratozoospermia, <4% normal forms), motility (asthenozoospermia, <40% motile sperm), low sperm numbers (oligozoospermia, $<15 \times 10^6$ per mL), or absent sperm (azoospermia). Abnormal epididymal function may result in defective spermatozoa maturation or transport or induce cell death.

Aetiology of male factor infertility

- **Idiopathic** (25%).
- **Varicocele** (present in ~40%).
- **Undescended testes**.
- **Functional sperm disorders:** immunological infertility (antisperm antibodies); head or tail defects; Kartagener's syndrome (immotile cilia); dyskinetic cilia syndrome.
- **Erectile dysfunction.**
- **Ejaculatory problems:** retrograde ejaculation causes absent or low volume ejaculate.
- **Testicular injury:** orchitis (post-pubertal bilateral mumps orchitis); testicular torsion; trauma; radiotherapy.
- **Endocrine disorders:** Kallmann's syndrome (isolated gonadotrophin deficiency causing hypogonadism); Prader–Willi syndrome . (hypogonadism, short stature, hyperphagia, obesity); pituitary gland adenoma, radiation, or infection.
- **Hormone excess:** excess prolactin (pituitary tumour); excess androgen (adrenal tumour, congenital adrenal hyperplasia, anabolic steroids); excess oestrogens.
- **Genetic disorders:** including Klinefelter's syndrome (47XXY) with azoospermia, ↑ FSH/LH and ↓ testosterone; XX male and XYY syndromes. Deletions in the azoospermic factor (AZF) gene on the Y chromosome are associated with abnormal spermatogenesis, which can be inherited by male offspring. Microdeletions of region AZFa has associations with Sertoli cell only syndrome; AZFb with maturation arrest and AZFc with azoospermia/severe oligozoospermia.

- **Male genital tract obstruction:** congenital absence of vas deferens; agenesis of seminal vesicles/Wolffian duct abnormalities; epididymal obstruction or infection; Müllerian prostatic cysts; inguinoscrotal or pelvic surgery.
- **Systemic disease:** renal failure; liver cirrhosis; cystic fibrosis.
- **Drugs:** chemotherapy; steroids; alcohol; marijuana; sulphasalazine; smoking.
- **Environmental factors:** pesticides; heavy metals; hot baths.
- **Infection:** genital tract infections are found in 10–20%. *Chlamydia trachomatis* can attach to and penetrate sperm; *Ureaplasma urealyticum* reduces sperm motility. HIV infection, previous prostatitis, and bilateral epididymitis reduce semen quality.

History

- **Sexual and reproductive:** duration of problem; frequency and timing of intercourse; use of vaginal lubricants (adversely affects sperm function); previous successful conceptions; previous birth control; erectile or ejaculatory dysfunction.
- **Partner's history:** age; previous pregnancies; previous investigation for subfertility; medical history.
- **Developmental:** age at puberty; history of undescended testes; gynaecomastia.
- **Medical and surgical:** detailed assessment for risk factors—recent febrile illness; post-pubertal mumps orchitis; varicocele; testicular torsion, orchidopexy, trauma or tumour; sexually transmitted infections; UTI; genitourinary and pelvic surgery; radiotherapy; respiratory diseases associated with ciliary dysfunction; diabetes.
- **Drug and environmental:** previous chemotherapy; exposure to substances which impair spermatogenesis or erectile function; alcohol consumption; smoking habits; hot baths.
- **Family history:** hypogonadism; undescended testes.

Examination

Perform a full assessment of all systems, with attention to general appearance (evidence of secondary sexual development; signs of hypogonadism; gynaecomastia). ***Urogenital examination*** should include assessment of the penis (phimosis, hypospadias, chordee); the presence of testes; measurement of testicular consistency, tenderness and volume with a Prader orchidometer (normal >20mL—varies with race); palpate epididymis (tenderness, swelling) and spermatic cord (vas deferens present or absent; varicocele); DRE of prostate.

Of note, the patient's partner should also undergo full screening and assessment for infertility by a gynaecologist, in either a separate consultation or in a joint clinic.

Investigation of male infertility

Basic investigations

Semen analysis: 2–3 specimens over several weeks, collected after 2–7 days of sexual abstinence. Deliver specimens to the laboratory within 1h (ideally keeping the specimen warm in a shirt or trouser pocket). Ejaculate volume, liquefaction time, and pH are noted (Table 12.1). Microscopy techniques measure sperm concentration, total numbers, morphology, and motility (Table 12.2). The mixed agglutination reaction (MAR) test is used to detect antisperm antibodies (useful for asthenozoospermia which can be associated with immunological infertility). The presence of leucocytes (>1 x 10^6/mL in semen) suggests infection and cultures should be requested. Low or absent ejaculate volume may suggest abnormality of seminal vesicles, ejaculatory duct obstruction, hypogonadism, or retrograde ejaculation.

Hormone measurement: serum FSH, LH and testosterone (Table 12.3). In cases of isolated low testosterone level, it is recommended to test early morning and free testosterone levels. Raised prolactin is associated with sexual dysfunction and may indicate pituitary disease.

Special investigations

Karyotype: 5–10% of azoospermic patients have Klinefelter's syndrome.

Y chromosome microdeletion assay: to assess AZF—regions a, b, and c.

- AZFa: microdeletion predicts no spermatogenesis.
- AZFc: commonest molecular cause of male infertility (13% of non-obstructive azoospermics and 6% of oligozoospermics). Around 70% will have sperm on testis biopsy.

Post-orgasmic urine analysis: the presence of >10–15 sperm per high powered field confirms the diagnosis of retrograde ejaculation.

Imaging

Scrotal USS: is used to assess for testicular abnormalities and detection of varicocele.

Transrectal USS: is indicated for low ejaculate volumes, to investigate seminal vesicle obstruction (>1.5cm width) or absence and ejaculatory duct obstruction (>2.3mm).

Vasography: the vas deferens is punctured at the level of the scrotum and injected with contrast. A normal test shows the passage of contrast along the vas deferens, seminal vesicles, ejaculatory duct, and into the bladder, which rules out obstruction.

Venography: used to diagnose and guide embolization treatment of varicocele.

Testicular biopsy

Performed for azoospermic patients to help differentiate between obstructive and non-obstructive causes. Simultaneous sperm retrieval can be carried out (testicular sperm extraction, TESE) for use in intracytoplasmic sperm injection (ICSI) treatment, either at the time or at a later date (following freezing and storage). The degree of spermatogenesis can be histologically scored (this is the Johnsen score; Table 12.4). Only mature spermatozoa (score 8 or above) can be used for fertility treatment.

Table 12.1 WHO semen analysis characteristics

Semen analysis parameter	Lower reference limit (95% CI)
Serum volume	1.5mL (1.4–1.7)
pH	≥7.2
Total sperm count	39 x 10^6 per ejaculate (33–46)
Sperm concentration	15 x 10^6 per mL (12–16)
Motility	40% progressive + non-progressive (38–40)
	32% progressive motility (31–34)
	Forward progression >grade 2
Sperm morphology	4% normal forms (3–4)
Vitality	58% live spermatozoa (55–63)
Time to liquefy	5–25min
White blood cells (WBC)	<1 x 10^6 WBC per mL
MAR-test (for antisperm antibody)	<50% motile spermatozoa with bound particles
Zinc	≥2.4μmol per ejaculate
Semen fructose	≥13μmol per ejaculate

Adapted from World Health Organization (WHO) 2010 lower reference limits (5th centile and their 95% CI) for semen characteristics

Table 12.2 Grading of sperm motility

Grade	Type of sperm motility
0	No motility
1	Sluggish; no progressive movement
2	Slow, meandering forward progression
3	Moving in a straight line with moderate speed
4	Moving in a straight line at high speed

Table 12.3 Clinical diagnosis on hormone assay

FSH	LH	Testosterone	Diagnosis
↑	Normal	Normal	Seminiferous tubule damage (defective spermatogenesis)
Normal	Normal	Normal	Normal or bilateral genital tract obstruction
↑	↑	Normal/↓	Testicular failure
↓	↓	↓	Hypogonadotrophism

FSH = follicle-stimulating hormone; LH = luteinizing hormone.

Table 12.4 The Johnsen Score. Histological analysis of testicular biopsy[1]

10	Complete spermatogenesis, many spermatozoa
9	Many spermatozoa, disorganized germinal epithelium
8	Few spermatozoa (<5–10)
7	No spermatozoa but many spermatids
6	No spermatozoa and few spermatids (<5–10)
5	No spermatozoa or spermatids, but many spermatocytes
4	Few spermatocytes (<5), no spermatozoa or spermatids
3	Spermatogonia are the only germ cells
2	Sertoli cells only
1	No cells in tubules

1 Johnsen S (1970) Testicular biopsy score count—a method for registration of spermatogenesis in human testes. Normal values and results in 335 hypogonadal males. *Hormones* **1**:2–25.

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Oligozoospermia and azoospermia

Oligozoospermia

Defined as a sperm concentration of <15 million per mL of ejaculate.

Aetiology: varicocele; idiopathic; androgen deficiency. It is identified in ~60% of patients presenting with testicular cancer or lymphoma.

Associated disorders: Often associated with abnormalities of morphology and motility. The combined disorder is called oligoasthenoteratozoospermia (OAT) syndrome. Common causes of OAT include varicocele, undescended testes, idiopathic; drug and toxin exposure, febrile illness.

Investigations

- **Semen analysis:** sperm counts <5–10 million/mL (severe form) require hormone investigation (FSH and testosterone) and genetic analysis. Severe oligozoospermia is associated with seminiferous tubular failure, small soft testes, and ↑ FSH.
- **Hormone assays:** also include prolactin levels if testosterone is low as hyperprolactinaemia can adversely affect spermatogenesis.
- **Scrotal** USS: to identify a varicocele.

Treatment: Lifestyle advice and modification of risk factors. Correct the underlying cause (i.e. varicocele repair or embolization may improve testosterone and sperm production and parameters). Idiopathic cases may respond to empirical medical therapy (clomiphene) or require assisted reproductive techniques (ART) (see 📖 p. 565).

Azoospermia

Defined as an absence of sperm in the ejaculate.

Aetiology

Obstructive causes

- **Vas deferens obstruction:** congenital bilateral absence of vas deferens (CBAVD),[1] post-surgery, or post-vasectomy.
- **Epididymal obstruction:** idiopathic, post-infective or post-surgery, agenesis.
- **Ejaculatory duct obstruction:** post-infective, post-surgery, congenital, Müllerian cyst.

Non-obstructive causes

- **Hormonal abnormality:** hypogonadotrophism (Kallmann's syndrome, pituitary tumour).
- **Abnormalities of spermatogenesis:** commonest cause is idiopathic (60% of non-obstructive azoospermia). Others are secondary to testicular torsion or trauma, viral orchitis or idiopathic, chromosomal anomalies (i.e. Klinefelter's syndrome).

Investigations

- **Hormone assay:** raised FSH suggestive of non-obstructive cause (i.e. reduced spermatogenesis presents with ↑ FSH associated with ↓ inhibin). Normal FSH with normal testes indicates increased likelihood of obstruction.
- **Semen analysis:** ejaculatory duct obstruction is associated with a reduced volume, acidic ejaculate without spermatozoa, or fructose.
- **Chromosomal analysis:** karyotyping to identify Klinefelter's syndrome in patients presenting with azoospermia, small soft testes, gynaecomastia, ↓ FSH/LH and ↓ testosterone. Y chromosome microdeletion assay (see 📖 p. 556).
- **Transrectal** USS: assesses absence or blockage of vas deferens and ejaculatory duct obstruction. Exclude cystic fibrosis in patients with vas deferens defects.
- **Renal tract** USS: for CBAVD as it is associated with unilateral renal agenesis.
- **Vasogram:** to assess for vas deferens obstruction.
- **Testicular biopsy:** to help distinguish between obstructed and non-obstructed cases where the aetiology is not clear clinically and for sperm retrieval (for therapeutic use).

Management

Treatment will depend on the underlying aetiology (see also 📖 p. 554).

Obstructive aetiology

- **Bilateral absence or agenesis of vas deferens:*** ART are required. Options include percutaneous epididymal sperm aspiration (PESA), microsurgical epididymal sperm aspiration (MESA), or testicular exploration and sperm extraction (TESE).
- **Obstructive cause with normal testis:** if an isolated obstruction of the epididymis is identified, vasoepididymostomy can be performed. A vaso-vasostomy can be performed in the case of previous vasectomy with good results and there is a trend to offer simultaneous TESE, particularly if there has been a long interval since the vasectomy. If reconstruction is not possible, TESE alone may be needed.

Non-obstructive aetiology

- **Primary testicular failure with testicular atrophy:** microsurgical testicular exploration and sperm extraction (micro-TESE) with ICSI and *in vitro* fertilization (IVF). Consider artificial insemination using donor (AID) if this fails
- **Primary testicular failure with normal testis:** TESE with ICSI and IVF; AID.

* Congenital bilateral absence of vas deferens (CBAVD) is associated with mutations in the cystic fibrosis transmembrane conductance regulator gene. Most of these patients are not candidates for reconstruction as they have a defect in sperm transport from mid-epididymis to seminal vesicles.

Varicocele

Definition

Dilatation of veins in the pampiniform plexus of the spermatic cord.

Prevalence

Found in 15% of men in the general population, 20–40% of males presenting with primary infertility and 45–80% of men with secondary infertility. Rare prior to puberty; present in ~10% of adolescents. Bilateral or unilateral (left side affected in 90%).

Aetiology

Incompetent valves in the internal spermatic veins lead to retrograde blood flow, vessel dilatation, and tortuosity of the pampiniform plexus. The left internal spermatic (testicular) vein enters the left renal vein at right angles and is under a higher pressure than the right vein which enters the vena cava obliquely at a lower level. As a consequence, the left side is more likely to develop a varicocele.

Pathophysiology

Testicular venous drainage is via the pampiniform plexus, a meshwork of veins encircling the testicular arteries. This arrangement normally provides a countercurrent heat exchange mechanism which cools arterial blood as it reaches the testis. Varicoceles adversely affect this mechanism, resulting in elevated scrotal temperatures and consequent deleterious effects on spermatogenesis (± loss of testicular volume over time).

Table 12.5 Varicocele grading system

Grade	Size	Definition
0	Subclinical	Detected only on USS
1	Small	Palpable only with Valsalva manoeuvre
2	Moderate	Palpable without Valsalva
3	Large	Visible through the scrotal skin

Presentation

The majority are asymptomatic, although large varicoceles may cause pain or a heavy feeling in the scrotal area. Examine, both lying and standing, and ask the patient to perform the Valsalva manoeuvre (strain down). A varicocele is identified as a mass of dilated and tortuous veins above the testicle ('bag of worms') which decompress on lying supine. Examine for testicular atrophy.

Investigation

- **Scrotal Doppler** USS: is diagnostic (venous diameter >3.5mm with patient supine).
- **Venography:** is the 'gold standard', but is reserved for patients considering embolization or for varicocele recurring after treatment.

- **Semen analysis:** varicoceles are associated with low or absent sperm counts, reduced sperm motility, and abnormal morphology, either alone or in combination (OAT syndrome).

Indications for varicocele repair

Adolescents: Pain, bilateral large varicoceles, varicocele in a solitary testis, persistent delayed testicular growth by >20% (as compared with non-affected side).

Adults: Varicocele repair improves semen parameters and is recommended in the United States.* However, in the UK, the Cochrane review failed to identify any benefit to pregnancy rates and intervention for infertility reasons is not currently recommended by NICE. Patients should be fully counselled on the limitations of varicocele repair for infertility before being booked for treatment.

Management

Embolization: interventional radiological technique where the femoral vein is used to access the spermatic veins for venography and embolization (with coils or other sclerosing agents), with success rates of 83%.

Surgical ligation of spermatic veins

- **High retroperitoneal (Palomo) approach:** a muscle-splitting incision is made near the anterior superior iliac spine and the internal spermatic veins are ligated at that level.
- **Inguinal (Ivanissevich) approach:** the inguinal canal is incised to access the spermatic cord and the external spermatic veins are tied off as they exit the internal ring.
- **Subinguinal (Marmar) approach:** external spermatic veins are accessed and ligated via a small transverse incision below the external ring. With microscopic assistance, this technique is reported to have superior outcomes to other approaches.
- **Laparoscopic:** internal spermatic veins are occluded high in the retroperitoneum.

Surgical complications

Varicocele recurrence; hydrocele formation; testicular atrophy, ilioinguinal nerve damage.

Surgical outcomes

Ninety-five percent success rate of treating the varicocele; 70% of men have improvement of sperm parameters.

* Joint Committee of the American Urological Association and the American Society for Reproductive Medicine recommend intervention for a palpable varicocele associated with abnormal semen analysis.

Treatment options for male infertility

General: aim to identify and treat reversible causes of subfertility and improve semen quality. Advice on modification of lifestyle factors (i.e. reduce alcohol consumption, avoid hot baths).

Medical treatment

Antibiotics

Treat any positive semen, urine, or urethral cultures with the appropriate antibiotics.

Hormonal

- **Secondary hypogonadism** (pituitary intact): may respond to administration of human chorionic gonadotrophin (HCG) which stimulates an increase in testosterone and testicular size. If the patient remains azoospermic after 6 months of treatment, FSH is added (human recombinant FSH or human menopausal gonadotrophin). Alternatively, pulsatile LHRH can be administered subcutaneously via a minipump (used for treating Kallman's syndrome).
- **Hyperprolactinaemia:** is treated with dopamine agonists. Arrange an MRI to rule out a pituitary tumour.
- **Antioestrogens** (clomiphene citrate 25mg od): are used empirically to increase LHRH which stimulates endogenous gonadotrophin secretion. Used for idiopathic oligospermia.

Antioxidants

Vitamin E supplements have been shown to improve sperm function and IVF success rates; zinc and folic acid may increase sperm concentrations.

Erectile and ejaculatory dysfunction

Erectile dysfunction may be treated conventionally (oral, intraurethral, intracavernosal drugs; vacuum devices or prostheses). Ejaculatory failure may respond to sympathomimetic drugs (desipramine) or electroejaculation or vibro-ejaculation (used in SCI), where an electrical stimulus is used to produce ejaculation. It is delivered via a rectal probe to the post-ganglionic sympathetic nerves that innervate the prostate and seminal vesicles.

Surgical treatment

Genital tract obstruction

- **Epididymal obstruction:** can be overcome by microsurgical anastomosis between the epididymal tubule and vas (vasoepididymostomy).
- **Vas deferens obstruction:** is treated by microsurgical reanastomosis of ends of the vas (vasovasotomy) and is used for vasectomy reversal. Highest success rates for finding viable sperm occur in the first 8y post-vasectomy (80–90%); overall pregnancy rates are ~50%. Patency rates are better than pregnancy rates; success rates drop to 30% if >15y post-vasectomy.[1]
- **Ejaculatory duct obstruction:** requires transurethral resection of the ejaculatory ducts (TURED).
- **Varicocele:** can be treated by embolization or open or laparoscopic surgical ligation.

Assisted reproductive techniques (ART)

Sperm extraction: sperm are removed directly from the epididymis by ***PESA*** or ***MESA***. If these methods fail, ***TESE*** by conventional biopsy or microsurgical techniques, or aspiration (***TESA***) may be tried. Sperm undergo cryopreservation until required. Later, they are separated from seminal fluid by dilution and centrifuge methods, with further selection of motile sperm and normal forms using Percoll gradient techniques.

Assisted conception

- **Intrauterine insemination** (IUI)**:** following ovarian stimulation, sperm are placed directly into the uterus.
- IVF**:** controlled ovarian stimulation with gonadotrophins produces oocytes which are then retrieved by transvaginal USS-guided needle aspiration. Oocytes and sperm are placed in a petri dish for fertilization to occur. Embryos are incubated and cultured for 2–3 days and then transferred to the uterine cavity. Pregnancy rates are 20–30% per cycle.
- **Gamete intrafallopian transfer** (GIFT)**:** oocytes and sperm are mixed and deposited into the Fallopian tubes via laparoscopy. Variations include zygote intrafallopian transfer (ZIFT) and tubal embryo transfer (TET).
- ICSI**:** A single spermatozoa is injected directly into the oocyte cytoplasm (through the intact zona pellucida). The advantage is that fewer sperm are needed. ICSI is always combined with IVF and the clinical pregnancy rate is 28–40% per cycle.

1 Belker AM, Thomas AJ Jr, Fuchs EF, Konnak JW, Sharlip ID (1991) Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. *J Urol* **145**:505–11.

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Chapter 13

Sexual health

Physiology of erection and ejaculation

Innervation

Autonomic: sympathetic nerves originating from T11–L2 and parasympathetic nerves originating from S2–4 join to form the pelvic plexus. The cavernosal nerves are branches of the pelvic plexus (i.e. parasympathetic) that innervate the penis. Parasympathetic stimulation causes erection; sympathetic activity causes ejaculation and detumescence (loss of erection).

Somatic: somatosensory (afferent) information travels via the dorsal penile and pudendal nerves and enters the spinal cord at S2–4. Onuf's nucleus (segments S2–4) is the somatic centre for efferent (i.e. somatomotor) innervation of the ischiocavernosus and bulbocavernosus muscles of the penis.

Central: medial preoptic area (MPOA) and paraventricular nucleus (PVN) in the hypothalamus are important centres for sexual function and penile erection.

Mechanism of erection

Neuroendocrine signals from the brain, created by audiovisual or tactile stimuli, activate the autonomic nuclei of the spinal erection centre (T11–L2 and S2–4). Signals are relayed via the cavernosal nerve to the erectile tissue of the corpora cavernosa, activating the ***veno-occlusive mechanism*** (Table 13.1). This triggers increased arterial blood flow into sinusoidal spaces (secondary to arterial and arteriolar dilatation), relaxation of cavernosal smooth muscle, and opening of the vascular space. The result is expansion of the sinusoidal spaces against the tunica albuginea which compresses the subtunical venous plexuses, decreasing venous outflow. Maximal stretching of the tunica albuginea, which acts to compress the emissary veins that lie within its inner circular and outer longitudinal layers, reduces venous flow even further. Rising intracavernosal pressure and contraction of the ischiocavernosus muscles produce a rigid erection. Following orgasm and ejaculation, vasoconstriction (due to increased sympathetic activity, endothelin, PGF2, and breakdown of cGMP) produces detumescence. Noradrenaline (NA) released from sympathetic nerve terminals in the corpora acts on smooth muscle cell α_1-adrenoceptors, leading to raised intracellular calcium which helps maintain penile flaccidity (Figs. 13.1 and 13.2).

Ejaculation

Tactile stimulation of the glans penis sends sensory information (via the pudendal nerve) to the lumbar spinal sympathetic nuclei. Sympathetic efferent signals (travelling in the hypogastric nerve) cause contraction of smooth muscle of the epididymis, vas deferens, and secretory glands, propelling spermatozoa and glandular secretions into the prostatic urethra (emission). There is simultaneous closure of the internal urethral sphincter and relaxation of the extrinsic sphincter, directing sperm into the bulbourethra, but preventing sperm from entering the bladder. Rhythmic

contraction of the bulbocavernosus muscle (somatomotor innervation) leads to the pulsatile emission of the ejaculate from the urethra. During ejaculation, the alkaline prostatic secretion is discharged first, followed by spermatozoa and finally, seminal vesicle secretions (ejaculate volume 2–5mL). The seminal vesicles contribute 2mL, prostate 0.5mL, and Cowper's glands 0.1mL of the ejaculate. There is an additional vasal and testicular contribution (accounting for around 5–10% of the total ejaculate volume).

Table 13.1 Phases of erectile process

Phase	Term	Description
0	Flaccid phase	Cavernosal smooth muscle contracted; sinusoids empty; minimal arterial flow
1	Latent (filling) phase	Increased pudendal artery flow; penile elongation
2	Tumescent phase	Rising intracavernosal pressure; erection forming
3	Full erection phase	Increased cavernosal pressure causes penis to become fully erect
4	Rigid erection phase	Further increases in pressure + ischiocavernosal muscle contraction
5	Detumescence phase (initial, slow and fast phases)	Following ejaculation, sympathetic discharge resumes; there is smooth muscle contraction and vasoconstriction; reduced arterial flow; blood is expelled from sinusoidal spaces

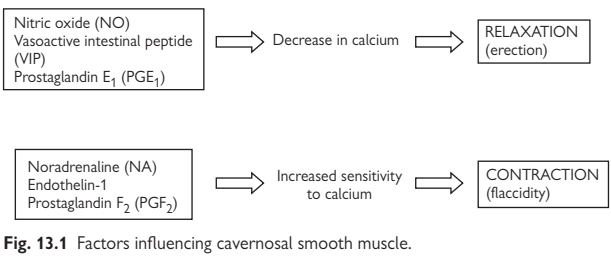

Fig. 13.1 Factors influencing cavernosal smooth muscle.

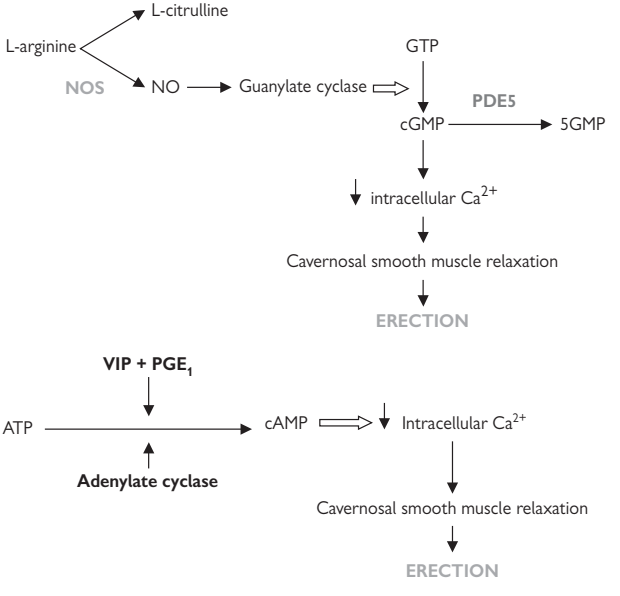

Fig. 13.2 Secondary messenger pathways involved in erection (ATP, adenosine triphosphate; Ca^{2+},calcium; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NA, noradrenaline; NO, nitric oxide; NOS, nitric oxide synthase enzyme; PDE5, phosphodiesterase type 5; PGE1, prostaglandin E1; PGF2, prostaglandin F2; VIP, vasoactive intestinal polypeptide).

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Erectile dysfunction: evaluation

Definition

Erectile dysfunction (ED) (also called impotence) describes the 'consistent or recurrent inability to attain and/or maintain a penile erection sufficient for sexual intercourse'.[1]

Epidemiology

In men aged 40–70y, mild ED is found in 17%, moderate ED in 25%, and complete ED in 10%.[2] Incidence increases with age, with complete ED affecting ~15% of men in their 70's and 30–40% in their 80's.

Aetiology

ED is generally divided into psychogenic and organic causes (Table 13.2). It is often multifactorial.

History

Sexual: onset of ED (sudden or gradual); duration of problem; presence of erections (nocturnal, early morning, spontaneous); ability to maintain erections (early collapse, not fully rigid); loss of libido; relationship issues (frequency of intercourse and sexual desire).

Sexual function symptom questionnaires: International Index of Erectile Function (IIEF)—full and short version (IIEF 5) (see 📖 p. 575; Table 13.3); Brief Male Sexual Function Inventory (BMSFI); quality of life questionnaire (QoL-MED).

Medical and surgical: enquire about risk factors, including diabetes mellitus (ED affects 50% overall and 30% of treated diabetics);[2] cardiovascular disease; hypertension; peripheral vascular disease; endocrine or neurological disorders; pelvic and penile surgery, radiotherapy, or trauma (which damage innervation and blood supply to the pelvis and penis). Intermediate or high risk cardiovascular disease requires further specialist assessment and treatment prior to ED treatment.

Psychosocial: assess for social stresses, anxiety, depression, coping problems, patient expectations, and relationship details.

Drugs: enquire about current medications and ED treatments already tried and their outcome.

Social: smoking, alcohol consumption.

An **organic cause** is more likely with gradual onset (unless associated with an obvious cause such as surgery where onset is acute); loss of spontaneous erections; intact libido and ejaculatory function; existing medical risk factors and older age groups.

Examination

Full physical examination (cardiovascular, abdomen, neurological); BP; DRE to assess the prostate; assess secondary sexual characteristics; external genitalia assessment to document foreskin phimosis, penile deformities and lesions (Peyronie's plaques); confirm presence, size, and location of

testicles. The bulbocavernosus reflex can be performed to test integrity of spinal segments S2–4 (squeezing the glans causes anal sphincter and bulbocavernosal muscle contraction).

Investigation

- **Blood tests:** fasting glucose; serum (free) testosterone (taken 8.00–11.00 a.m.); fasting lipid profile are basic work-up tests.[3] SHBG; U&E; LH/FSH; prolactin; PSA; thyroid function test should be selected according to patient's history and risk factor profile.
- **Nocturnal penile tumescence and rigidity testing:** the Rigiscan device contains two rings that are placed around the base and distal penile shaft to measure tumescence and number, duration, and rigidity of nocturnal erections. Useful for diagnosing psychogenic ED and for illustrating this diagnosis to patients.
- **Penile colour Doppler USS:** measures arterial peak systolic and end diastolic velocities,* pre- and post-intracavernosal injection of PGE1.
- **Cavernosography:** imaging and measurement of penile blood flow after intracavernosal injection of contrast and induction of artificial erection, used to identify venous leaks.
- **Penile arteriography:** reserved for trauma-related ED in younger men. Pudendal arteriography is performed before and after drug-induced erection to identify those requiring arterial bypass surgery (although this is less commonly indicated now with the advent of modern penile prostheses).
- **MRI:** useful for assessing penile fibrosis and severe cases of Peyronie's disease.

* Normal values: peak systolic velocity >35cm/s; end diastolic velocity <5cm/s.

1 Montorsi F, AdaikanG, Becher E, *et al.* (2010) Summary of the recommendations on sexual dysfunction in men. *J Sex Med* **7**:3572-88.

2 Feldman HA, Goldstein I, Hatzichristou D, *et al.* (1994) Impotence and its medical and psychological correlates: results of the Massachusetts Male Aging Study. *J Urol* **151**:54–61.

3 Hackett G, Kell P, Ralph D, *et al.* (2008) British Society for Sexual Medicine guidelines on the management of sexual dysfunction. *J Sex Med* **5**:1841–65.

4 Catalona WJ, Carvalhal GF, Mager DE, *et al.* (1999) Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. *J Urol* **162**:433–8.

Table 13.2 Causes of erectile dysfunction or 'impotence'

Inflammatory	Prostatitis
Mechanical	Peyronie's disease
Psychological	Depression; anxiety; relationship difficulties; lack of attraction; stress
Occlusive vascular factors	***Arteriogenic:*** hypertension; smoking; hyperlipidaemia; diabetes mellitus; peripheral vascular disease
	Venogenic: impairment of veno-occlusive mechanism (due to anatomical or degenerative changes)
Trauma	Pelvic fracture; spinal cord injury; penile fracture/trauma
Extra factors	***Iatrogenic:*** pelvic surgery; prostatectomy*
	Other: increasing age (secondary to atherosclerosis in penile arteries, leading to corporeal ischaemia and fibrosis); chronic renal failure; cirrhosis, low flow priapism (i.e. corporeal fibrosis); smoking
Neurogenic	***CNS:*** multiple sclerosis (MS); Parkinson's disease; multisystem atrophy; tumour
	Spinal cord: spina bifida; MS; spinal cord injury; tumour
	PNS: pelvic surgery or radiotherapy; peripheral neuropathy (diabetes, alcohol-related)
Chemical	Antihypertensives (β-blockers, thiazides, ACE inhibitors)
	Antiarrhythmics (amiodarone)
	Antidepressants (tricyclics, MAOIs, SSRIs)
	Anxiolytics (benzodiazepine)
	Antiandrogens (finasteride, cyproterone acetate)
	GNRH analogues
	Anticonvulsants (phenytoin, carbamazepine)
	Anti-Parkinson drugs (levodopa)
	Statins (atorvastatin)
	Alcohol (Refer to BNF)
Endocrine	**Diabetes mellitus****; hypogonadism; hyperprolactinaemia; hypo and hyperthyroidism

* Of note, nerve sparing techniques for radical prostatectomy have improved post-operative potency rates to around 50–70%.[4]

** Note that this list of causes is not in the order of frequency, i.e. diabetes mellitus is one of the most important causes.

MAOIs = monoamine oxidase inhibitors; SSRIs = serotonin reuptake inhibitors; BNF = British National Formulary (bnf.org).

Table 13.3 International Index of Erectile Function short form (IIEF 5). Also known as the Sexual Health Inventory for Men (SHIM)

1. How do you rate your confidence that you could get and keep an erection?		Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	No sexual activity 0	Almost never or never 1	A few times 2	Sometimes 2	Most times 4	Almost always or always 5
3. During sexual intercourse, how often were your erections hard enough for penetration?	Did not attempt intercourse 0	Almost never or never 1	A few times 2	Sometimes 2	Most times 4	Almost always or always 5
4. during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourse 0	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory to you?	Did not attempt intercourse 0	Almost never or never 1	A few times 2	Sometimes 2	Most times 4	Almost always or always 5

IIEF 5 is scored from 1–25. Scores 1–7 = severe ED; 8–11 = moderate ED; 12–16 = mild to moderate ED; 17–21 = mild ED; 22–25 = no ED.

Erectile dysfunction: treatment

Correct any reversible causes (i.e. alter lifestyle, stop smoking, change medication, etc.) (Table 13.2).

Psychosexual therapy

Aims to understand and address underlying psychological issues and provides information and treatment in the form of sex education, psychosexual counselling, instruction on improving partner communication skills, cognitive therapy, and behavioural therapy (programmed relearning of couple's sexual relationship). Pharmacotherapy may be a useful adjuvant.

Drug therapy

Phosphodiesterase type-5 (PDE5) inhibitors: **first-line** therapies which include sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®) (Table 13.4). PDE5 inhibitors enhance cavernosal smooth muscle relaxation and erection by blocking the breakdown of cGMP by phosphodiesterase. Sexual stimulus is still required to initiate events. Success is reported in up to 80%. Early use of PDE5 inhibitors following radical prostatectomy can help optimize the return of spontaneous erections (penile rehabilitation).

Contraindications: patients taking nitrates, recent myocardial infarction, recent stroke, hypotension, unstable angina, non-arteritic anterior ischaemic optic nerve neuropathy (NAION). *Cautions:* intermediate and high risk cardiovascular disease requires cardiac review prior to treatment, use with α-blockers, groups with predisposition to priapism.

Dopamine receptor agonist: apomorphine (Uprima®), taken sublingually, acts centrally on dopaminergic receptors in the paraventricular nucleus of the hypothalamus to enhance and coordinate the effect of sexual stimuli. *Side effects:* nausea, headache, dizziness. Not commonly used.

Intraurethral therapy: second-line therapy when oral therapies have been ineffective. A synthetic prostaglandin E1 (PGE1) pellet (alprostadil) is placed into the urethra via a specialized applicator (Medicated Urethral System for Erection (MUSE)™ device). Once inserted, the penis is gently rolled to encourage the pellet to dissolve into the urethral mucosa from where it enters the corpora. PGE1 acts to increase cAMP within the corporal smooth muscle, resulting in muscle relaxation. *Side effects:* penile and urethral pain, priapism, local reactions.

Intracavernosal injection therapy

- Alprostadil (Caverjet™).
- Papaverine (PDE inhibitor). Usually given in combination with either phentolamine (α-adrenoceptor antagonist) or PGE1 in patients who have failed oral or single-agent injectable therapies.

Training of technique and first dose is given by a health professional. Needle is inserted at right angles into the corpus cavernosum on the lateral aspects of mid-penile shaft. Discontinuation rates from penile injection techniques are high. *Contraindications:* sickle cell disease or high-risk candidate for priapism. *Adverse effects:* pain, priapism, haematoma.

Vacuum erection device

Used when pharmacotherapies have failed. It contains three components: a vacuum chamber, pump, and constriction band. The penis is placed in the chamber and the vacuum created by the pump increases blood flow to the corpora cavernosa to induce an erection. The constriction band is placed onto the base of the penis to retain blood in the corpora and maintain rigidity. *Relative contraindication:* anticoagulation therapy. *Side effects:* penile coldness, bruising.

Microvascular arterial bypass and venous ligation surgery

Used in: specialist centres where there is a clear-cut diagnosis of a vascular disorder. Acts to increase arterial inflow and decrease venous outflow. Rarely used now as it is uncommon for success rates to exceed 50%.

Penile prosthesis

Semi-rigid, malleable, and inflatable penile prostheses are available when other therapies have failed or are unsuitable. Also indicated for Peyronie's disease, trauma, and penile fibrosis (i.e. secondary to priapism). The device is surgically implanted into the corpora to provide penile rigidity and generally has high satisfaction rates, up to 90% (Fig. 13.3). *Side effects:* infection, erosion, mechanical failure, penile shortening, glans may not fully engorge.

Testosterone replacement therapy

Indicated for hypogonadism and is available in oral, buccal, intramuscular, pellet, transdermal patch, and gel forms. Most guidelines recommend PSA, Hb, and LFT checks before and after starting treatment (see 🕮 pp. 596–7). It can improve the results of PDE5 inhibitors in hypogonadal men.

Table 13.4 A comparison of PDE5 inhibitors

PDE5I	Doses (mg)	Half-life	Effective within	Duration of action	Common side effects
Sildenafil (Viagra)	25/50/100	3.7h	30–60min	Up to 4–5h	Headache, dizzy, GI upset, flushing, nasal congestion, blurred vision
Vardenafil (Levitra)	5/10/20	3.9h	25–60min	Up to 4–5h	As above
Tadalafil (Cialis)	2.5/5/10/20	17.5h	30min to 2h	Up to 36h	As above

Free NHS prescription (SLS Schedule 11) applies for certain conditions including: diabetes, spinal cord injury, multiple sclerosis, Parkinson's disease, polio, spina bifida, one gene neurological disease, severe pelvic injury, prostate cancer, prostatectomy, radical pelvic surgery, renal failure (treated by dialysis or transplant), for 'severe distress' and patients already receiving NHS ED treatment on 14th September, 1998.

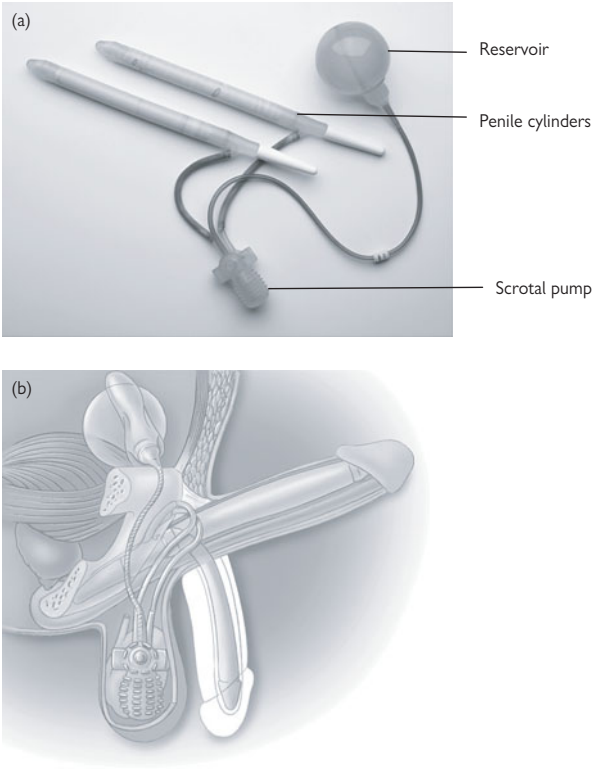

Fig. 13.3 (a) AMS 700 TM Series Tactile Pump penile prosthesis. (b) Inflated prosthesis *in situ*. (Reproduced with permission, courtesy of American Medical Systems Inc., Minnesota.)

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Peyronie's disease

Definition

An acquired benign penile condition characterized by deformity of the penile shaft secondary to the formation of a fibrous inelastic scar on the tunica albuginea.[1]

Epidemiology

Prevalence is 3–9%,[1] predominantly affecting men aged 40–60y.

Pathophysiology

Histologically, plaques have excessive connective tissue (fibrosis) and increased cellularity with random orientation of collagen fibres. Dorsal penile plaques are most common (66%). The corpus cavernosus underlying the lesion cannot lengthen fully on erection, resulting in penile curvature. The disorder has two phases:

- **Active phase** (1–6 months): early inflammatory phase with painful erections and changing penile deformity.
- **Quiescent (stable) phase** (9–12 months): disease 'burns out'. Pain disappears with resolution of inflammation and there is stabilization of the penile deformity.

The natural history of Peyronie's plaques over 18 months is that 40% will progress, 47% will remain stable, and 13% will improve.[2]

Aetiology

The exact cause is unknown, but it is currently considered to be a wound healing disorder which occurs after penile trauma in genetically predisposed men.[1] It is likely that repeated minor trauma during intercourse causes microvascular injury and bleeding into the tunica, resulting in inflammation and fibrosis (exacerbated by transforming growth factor-β (TGF-β).

Presentation

Peyronie's disease may present with penile pain, a palpable lump (plaque), penile curvature, ED (in 40%), a more complex deformity (shortening, indentation, hourglass deformity), or a combination of these features.

Common comorbidities

Diabetes mellitus (in 30%); ED; arterial disease; Dupuytren's contractures (25%); plantar fascial contracture; tympanosclerosis; raised cholesterol or triglycerides; hypertension; low testosterone.

Evaluation

A full medical and sexual history (including erectile function) are taken. Patient photographs or outpatient injection of intracavernosal PGE1 can be used to assess the degree of curvature. Assess the location and size of the plaque (is it tender?). Record stretched penile length preoperatively to help advise patients that loss of penile length is partly due to the disease and not all due to the surgical correction. ***Colour Doppler USS*** is useful in assessing the plaque and any vascular abnormalities whereas contrast-enhanced ***MRI*** is indicated for complex and extensive cavernosal fibrosis.

Management

Early disease with active inflammation (<3 months, penile pain, changing deformity) may benefit from medical therapy. Surgery is indicated for stable, mature disease (present for 12 months; stable for 3 months), with significant deformity preventing intercourse. Non-mechanical components of ED can be treated conventionally (e.g. oral PDE5 inhibitors or intracavernosal pharmacotherapy).

Conservative treatment

Medical treatment

- **Oral therapy:** pentoxifylline, a non-specific PDE, and TGF- 1 inhibitor have been shown to improve curvature, ED, and reduce plaque size. Colchine combined with vitamin E significantly improves pain, plaque size, and curvature. Other treatments, including vitamin E, tamoxifen, POTABA (para-aminobenzoate), and colchicines, have not shown significant effects on penile deformity.
- **Intralesional injection:** verapamil (10mg in 10mL saline) injected into lesion every 2 weeks for 24 weeks.[3] Alternatives are collagenase and interferon α2-β injection.
- **Iontophoresis:** small amounts of electric current are used to transfer drugs (verapamil ± dexamethasone and lidocaine) transdermally to act on the plaque.[4]

ESWL: has little effect on penile deformity, but may help reduce pain.

Peyronie's vacuum therapy: exercises using mechanical stretching.

Surgery (Box 13.1)

- **Nesbit procedure:** the penis is degloved via a circumglanular incision. An artificial erection is induced by intracavernosal saline injection. On the opposite side of maximal deformity, an ellipse is excised (a width of 1mm is taken for every 10° of penile curvature) and the defect closed with sutures. Success rates are 88–94%. A circumcision is recommended for those with phimosis or previous surgery. *Risks:* all will have penile shortening (often 2–3cm), bleeding, infection, residual deformity, recurrence, ED (~1%).
- **Simple plication technique:** sutures are placed on the opposite side of maximal deformity to straighten the penis. Success rates tend to be lower (~40%).
- **Plaque incision and grafting (Lue procedure):** incision of plaque with insertion of a venous patch to lengthen the affected side (and minimize penile shortening). Success rates 75–96%. Alternative graft materials: temporalis fascia, Surgisis (porcine small intestinal submucosa), and bovine pericardium. *Risks:* ED 5–12%, bleeding, infection, residual deformity, penile shortening (0–20%).
- **Penile prosthesis:** reserved for patients with moderate to severe ED, cavernosal fibrosis, and complex deformities (see 🕮 p. 578). Residual curvature after prosthesis placement will require correction with manual modelling or if this fails, incision ± graft insertion.

Box 13.1 Choice of surgical intervention for Peyronie's disease

Patients with adequate erectile function preoperatively (with or without the use of pharmacotherapy)

- **Nesbit procedure**: deformity <60°, no complex deformity, predicted loss of erectile length <20%.
- **Lue procedure**: deformity >60°, hinge deformity, aim for minimal loss of penile length.

Patients with poor erectile function preoperatively (and/or poor response to pharmacotherapy)

- **Penile prosthesis**: deformity >60°, complex deformity, cavernosal fibrosis.

1 Ralph D, Gonzalez-Cadavid N, Mirone V, *et al.* (2010)The management of Peyronie's disease: evidence based 2010 guidelines. *J Sex Med* **7**:2359–74.

2 Gelbard MK, Dorey F, James K, *et al.* (1990) The natural history of Peyronie's disease. *J Urol* **144**:1376–9.

3 Levine LA, Goldman KE, Greenfield JM (2002) Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol* **168**:621–5.

4 Riedl CR, Plas E, Engelhardt P, Daha K, Pflüger H (2000) Iontophoresis for treatment of Peyronie's disease. *J Urol* **163**:95–9.

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Priapism

Definition: prolonged, unwanted erection, in the absence of sexual desire or stimulus, lasting >4h.

Epidemiology: incidence of 1.5 per 100 000,[1] with peaks at ages 5–10 and 20–50.

Classification

- **Low-flow (ischaemic) priapism:** due to veno-occlusion (intracavernosal pressures of 80–120mmHg). Most common form which manifests as a painful, rigid erection, with absent or low cavernosal blood flow. Ischaemic priapism >4h requires emergency intervention. Blood gas analysis shows hypoxia and acidosis.
- **High-flow (non-ischaemic) priapism:** due to unregulated arterial blood flow, presenting with a semi-rigid, painless erection. Usually due to trauma and subsequent fistula development and usually self-limiting. Blood gas analysis shows similar results to arterial blood.
- **Recurrent (or stuttering) priapism:** most commonly seen in sickle cell disease. Usually high flow, but may change to low flow with anoxia.

Aetiology (Tables 13.5, 13.6)

Causes are primary (idiopathic) or secondary, including:

- **Intracavernosal injection therapy:** papaverine; PGE1.
- **Drugs:** α-blockers; antidepressants; antipsychotics; psychotrophics; tranquilizers; anxiolytics; anticoagulants; recreational drugs; alcohol excess; total parenteral nutrition.
- **Thromboembolic:** sickle cell disease; leukaemia; thalassaemia; fat emboli.
- **Neurogenic:** spinal cord lesion; autonomic neuropathy; anaesthesia.
- **Trauma:** penile or perineal injury, resulting in cavernosal artery laceration or arteriovenous fistula formation.
- **Infection:** malaria; rabies; scorpion sting, genitourinary sepsis.
- **Other:** prostate or bladder cancer extending into penis; amyloidosis.

Pathophysiology

Priapism lasting for 12h causes trabecular interstitial oedema, followed by destruction of sinusoidal endothelium and exposure of the basement membrane at 24h and sinusoidal thrombi, smooth muscle cell necrosis, and fibrosis at 48h.

Evaluation

- **Serum testing:** to exclude sickle cell, leukaemia, and thalassaemia.
- **Cavernous blood samples:** to determine type of priapism.
- **Colour Doppler USS:** of cavernosus artery and corpora cavernosa. Reduced blood flow in ischaemic priapism; ruptured artery with pooling of blood around injured area in non-ischaemic priapism.

Management in adults (Fig.13.4)

Ice packs, cold showers, and exercise may be beneficial in early stages.

Low-flow priapism

Decompress urgently with aspiration of blood from the corpora (5mL portions using a 18–20 gauge butterfly needle until oxygenated red blood is obtained). If no change after 10min, proceed to intracavernosal injection of α1-adrenergic agonist (phenylephrine 100–200mcg (0.5–1mL of a 200mcg/mL solution to a maximum of 1mg)) every 5–10min until detumescence (loss of erection) occurs; see www.bnf.org). Monitor BP and pulse during drug administration. Oral terbutaline may be effective treatment for intracavernosal injection-related cases. Sickle cell disease requires, in addition, aggressive rehydration, oxygenation, analgesia, and haematological input (consider exchange transfusion).

If aspiration and phenylephrine fails after 1h, surgical intervention is attempted with shunt and biopsy. Following a penile block, the Winter technique places a Trucut biopsy needle through the glans into the corpora cavernosa to remove small pieces of tunica albuginea and allow evacuation of hypoxic blood. Alternatively, a small blade stab incision is made via the glans into the corpora, avoiding the urethra. If there is no response, corporosaphenous shunting can be considered where the long saphenous vein is tunnelled and anastomosed onto the corpora cavernosum.

If this fails or patients present late (after 48–72h), discuss the insertion of a penile prosthesis. This will treat both the priapism and inevitable ED and avoids the difficulty and high complication rates of delayed insertion into a fibrotic penis.

High-flow priapism

Conservative treatment is recommended in most cases. Traumatic or delayed presentations require arteriography and either selective or internal pudendal artery embolization with autologous blood clot or fat. Ligation of fistula may be required.

Recurrent priapism

Optimize haematological management of sickle cell disease to reduce frequency of attacks. Regular oral alpha agonists such as etylephrine can be helpful and/or androgen suppression (i.e. cyproterone acetate).

Complications: 90% of priapism lasting >24h develop complete ED.

Table 13.5 Causes of low- and high-flow priapism

Low-flow priapism	High-flow priapism
Intracavernosal drug injection	Arteriovenous fistula (secondary to penile or perineal trauma or surgery)
Oral medications	
Haematological disease: sickle cell disease, leukaemia, thalassaemia	
Fat embolus	
Spinal cord lesion	
Autonomic neuropathy	
Malignancy	

Table 13.6 Examples of drugs which may cause priapism

Class of drug	Examples
Antihypertensives/alpha blockers	Prazosin, hydralazine
Antidepressants	Sertraline, fluoxetine, lithium
Antipsychotics	Clozapine
Psychotrophics	Chlorpromazine
Tranquilizers	Mesoridazine
Anxiolytics	Hydroxyzine
Anticoagulants	Warfarin, heparin
Recreational drugs	Cocaine

1 Eland IA, van der Lei, Strickler BH, *et al.* (2001) Incidence of priapism in the general population. *Urology* **57**:970–4.

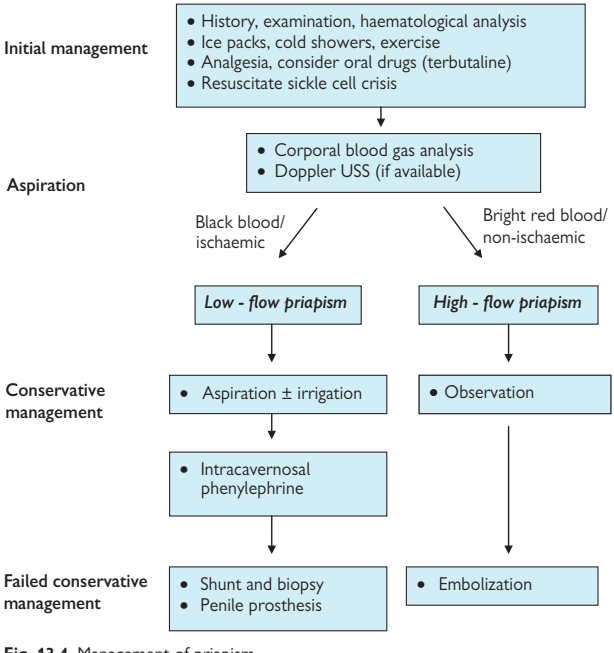

Fig. 13.4 Management of priapism.

Retrograde ejaculation

Definition

Failure of adequate bladder neck contraction results in the propulsion of sperm back into the bladder on ejaculation.

Aetiology

Acquired causes are due to damage or dysfunction of the bladder neck sphincter mechanism. These include ***neurological*** disease (SCI; neuropathy associated with diabetes mellitus; nerve damage after retroperitoneal surgery) or ***anatomical disruption*** following transurethral resection of ejaculatory ducts (for obstruction), bladder neck incision (BNI), TURP, or open prostatectomy. Drugs to treat BOO (α-blockers) causes reversible retrograde ejaculation in 5% of men. ***Congenital*** causes include bladder exstrophy, ectopic ejaculatory ducts, and spina bifida.

Incidence

Retrograde ejaculation following TURP or open prostatectomy occurs in 9 out of 10 men and after BNI, in 1–5 in 10.

Presentation

'Dry' ejaculation (failure to expel ejaculate fluid from the urethral meatus) or low ejaculate volume (<1mL) and cloudy urine (containing sperm) in the first void after intercourse.

Investigation

The presence of >10–15 sperm per high powered field in post-orgasmic urine specimens confirms the diagnosis of retrograde ejaculation.

Treatment

Medical therapy: is initiated in men wishing to preserve fertility and is only effective in patients who have not had bladder neck surgery. Therapy is often given for 7–10 days prior to a planned ejaculation (coordinated with the partner's ovulation).

- Oral α-adrenergic receptor agonist drugs (ephedrine sulphate, pseudoephedrine) may be used to increase the sympathetic tone of the bladder neck smooth muscle sphincter mechanism.
- Imipramine, a tricyclic antidepressant drug with anticholinergic and sympathomimetic effect, may also be used (25mg bd to tds).

Sperm retrieval from urine for assisted fertility techniques

Oral sodium bicarbonate and adjustment of fluid intake is initiated to optimize urine osmolarity and pH and enhance sperm survival. Sperm are collected by gentle urine centrifuge and washed in insemination media in preparation for IUI or IVF treatments.

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Premature ejaculation

Definition

Premature ejaculation (PE) is classified as lifelong or acquired. The ***International Society for Sexual Medicine*** (ISSM) defines lifelong PE as 'ejaculation which always or nearly always occurs prior to or within one minute of vaginal penetration and the inability to delay ejaculation on all or nearly all vaginal penetrations and negative consequences such as distress, bother, frustration, or avoidance of sexual intimacy'.[1] Related conditions include natural variable PE and PE-like dysfunction.

Aetiology

Psychological

- Early sexual experience.
- Anxiety.
- Reduced frequency of sexual intercourse.

Biological

- Penile hypersensitivity.
- 5-Hydroxytryptamine (5-HT) receptor sensitivity (involved in the central control of ejaculation).
- Hyperexcitable ejaculatory reflex.

Evaluation

Detailed medical, sexual, and psychosocial history and physical examination. Establish perceived degree of ejaculatory control, onset, and duration of the problem. Quantitative measures of sexual intercourse include:

- Intravaginal ejaculatory latency time (IELT)—the time between vaginal penetration and ejaculation averaged over several performances. IELT <1–2min suggests a diagnosis of PE.*
- Score of partner's sexual satisfaction.
- Patient's assessment of his voluntary control over ejaculation.

Treatment

Behavioural

- Counselling.
- Seman's stop–start manoeuvre (inhibiting the urge to ejaculate by repeatedly stopping sexual stimulation).
- Masters's and Johnson's squeeze technique (inhibiting the urge to ejaculate by squeezing the glans penis).
- Sensate focus.

Pharmacological

- Selective serotonin reuptake inhibitors (SSRIs). Paroxetine 20mg daily (unlicensed) is the most effective and can also be used on demand 4–6h before intercourse. Dapoxetine is licensed for on demand use and has a more rapid onset of action and shorter half-life. Alternatives taken daily are sertraline, fluoxetine, and citalopram (not licensed). Side effects include gastrointestinal effects, anorexia, and rash.

- Clomipramine (tricyclic antidepressant) given daily or as required 4–6h before intercourse. Side effects include dry mouth, sedation, blurred vision, difficulty voiding.
- Topical local anaesthetics such as lidocaine and/or prilocaine cream, gel, or spray (with condom to prevent transvaginal absorption with resultant vaginal numbness).
- PDE5 inhibitors (sildenafil): limited role for acquired premature ejaculation associated with ED.

Gradual withdrawal of drug therapy can be attempted after 6–8 weeks.

* In comparison, natural variable PE has an IELT of 3–8min; PE-like dysfunction has an IELT of 3–30min. Both conditions respond to reassurance, education, and behavioural therapy.

1 Montorsi F, Adaikan G, Becher E, *et al.* (2010) Summary of the recommendations on sexual dysfunction in men. *J Sex Med* **7**:3572–88.

Other disorders of ejaculation and orgasm

Definition

The ISSM defines orgasmic dysfunction as: 'inability to achieve an orgasm or markedly diminished intensity of orgasmic sensation' or 'marked delay of orgasm during any kind of sexual stimulation'.[1] Under this category, they include delayed ejaculation, inhibited ejaculation, retarded (and partially retarded) ejaculation, anejaculation, and anorgasmia.[1]

Delayed ejaculation (DE): is 'the persistent or recurrent difficulty, delay in, or absence of attaining orgasm after sexual sufficient stimulation, which causes personal distress'.[2] It may be lifelong or acquired, global or situational, and the prevalence increases with age (Table 13.7).[3]

Anejaculation: is the complete absence of an antegrade or retrograde ejaculation. There is failure of emission from the seminal vesicles, prostate, and ejaculatory ducts into the urethra. True anejaculation is associated with normal orgasm and is most often due to drug-related causes or central or peripheral nervous system dysfunction (Table 13.7).

Anorgasmia: is the inability to reach orgasm (which may give rise to anejaculation in men). This is rare. Primary conditions are usually attributed to psychological causes. Secondary causes may be related to drugs or decreased penile sensation (secondary to pudendal nerve dysfunction, seen in peripheral neuropathy associated with diabetes mellitus) (Table 13.7).

Evaluation

A detailed sexual history, including the exact symptoms, duration, related arousal or desire problems, and precipitating factors should be taken. A full medical and drug history identifies any underlying or reversible causes. A focused physical (including external genitalia and palpation for bilateral vasa) and neurological examination (including bulbocavernosus reflex, anal sphincter tone, and perineal sensitivity where appropriate) should be performed. Urine microscopy and culture may identify infection. Post-ejaculatory urinalysis can be performed to exclude retrograde ejaculation. If there is clinical suspicion of possible ejaculatory duct obstruction, consider transrectal USS, vasography, or percutaneous puncture of the seminal vesicles. Cystourethroscopy can be used to assess the ejaculatory ducts and exclude urethral obstruction (urethral stensosis).

Management

General: aim to identify and treat the underlying aetiology and address any infertility issues in men of reproductive age. Patient education and counselling on lifestyle change (i.e. reducing alcohol consumption, attempting sexual intercourse when not tired) are helpful adjuvants. If an organic cause has been excluded, psychosexual therapy is recommended.

Drugs: that facilitate ejaculation by central dopaminergic or antiserotonergic action have been tried, especially in drug-induced anejaculation,

Table 13.7 Causes of delayed ejaculation, anejaculation, and anorgasmia[3]

Drugs	Antihypertensive drugs (thiazides)
	Antidepressants (tricyclics, SSRIs)
	Antipsychotic drugs (phenothiazines)
	Alcohol excess
Neurological	Diabetic autonomic neuropathy
	Spinal cord injury
	Multiple sclerosis
	Parkinson's disease
	Pelvic surgery (2° to proctocolectomy)
	Para-aortic lymphadenectomy
Psychological	
Surgical	Prostate surgery (TURP, BNI)
Congenital	Mullerian duct obstruction
Infection	Urethritis
Endocrine	Hypogonadism, hypothyroidism

although no randomized trials have been carried out for this condition. Examples include: 5-HT receptor antagonists (cyproheptadine); dopaminergic drugs (amantadine, yohimbine); dopamine reuptake inhibitors (bupropion); 5-HT1A receptor agonists (buspirone). The treatment of delayed ejaculation is similar to anejaculation.

Anejaculation: where the aim is to retrieve sperm for ART methods include:

- **Vibrostimulation** (first-line therapy): a vibrator is applied to the penis, evoking the ejaculation reflex. It requires an intact lumbosacral spinal cord segment.
- **Electroejaculation:** involves the electrical stimulation of periprostatic nerves via a rectal probe, usually under anaesthesia.
  Can also be used for anorgasmia.

1 Montorsi F, Adaikan G, Becher E, *et al.* (2010) Summary of the recommendations on sexual dysfunction in men. *J Sex Med* **7**:3572–88.

2 McMahon CG, Althof SE, Waldinger MD, *et al.* (2008) An evidence-based definition of lifelong premature ejaculation: Report of the International Society of Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. *J Sex Med* **5**:1590–606.

3 Rowland D, McMahon CG, Abdo C, *et al.* (2010) Disorders of ejaculation and orgasm in men. *J Sex Med* **7**:1668–86.

Late-onset hypogonadism (LOH)

Late-onset hypogonadism (LOH): is defined as 'a clinical and biochemical syndrome associated with advancing age and characterized 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 quality of life and adversely affect the function of multiple organ systems'.[1] It is also known as age-associated testosterone deficiency (TDS).[1]

Pathophysiology

LOH involves components of both primary and secondary hypogonadism (see 📖 p. 596) and a degree of reduced responsiveness of target organs to testosterone and its adrogenic mediators. Ageing decreases the production of LHRH and LH due to effects on the hypothalamus and pituitary. This causes a decline in the both the number of Leydig cells in the testes and their sensitivity to LH so reducing testosterone levels. SHBG binds testosterone and renders it unavailable to most tissues and levels of SHBG increase with age. Along with age-related changes in androgen receptors and altered androgen metabolism, the result is less bioavailable testosterone.

Presentation

- ED.
- Reduced libido.
- Reduced concentration.
- Hot flushes.
- Changes in mood (depression).
- Lethargy/fatigue.
- Sleep disturbance.
- Hair/skin changes.
- Osteoporosis.
- Decreased muscle mass and strength.
- Infertility.

Evaluation (see Fig. 13.5)

- History to elicit symptoms related to low testosterone levels.
- Examination, including DRE (with PSA to exclude prostate cancer prior to giving testosterone and to assess prostate size).
- Flow rate and post-void residual volume to assess for BOO.
- Serum bloods: early morning total testosterone, LH, PSA, FBC, LFT, and fasting lipid profile.
- Further blood tests: prolactin (if total testosterone <5.2nmol/L); SHBG (if borderline testosterone or if suspect secondary hypogonadism).
- DEXA scan to check bone mineral density.

Testosterone assessment

In a normal adult male, the serum testosterone reference range is around 10.4–34.7nmol/L. Testosterone levels show diurnal variation, peaking in early morning and recommendations for testing are:

- Early morning serum total testosterone (taken 8:00–11:00 a.m.).
- If low or borderline total testosterone level, perform repeat testosterone level with LH, FSH, and prolactin.

Treatment of LOH

Symptoms and biochemical evidence of testosterone deficiency indicate the need for testosterone replacement therapy (Fig. 13.5). Where testosterone levels are borderline/normal, but symptoms are present, consider an initial 3-month trial of testosterone and then review (see 📖 p. 597). Residual symptoms may need specific treatment such as PDE5 inhibitors for ED.

For normal testosterone physiology, refer to 📖 p. 552; for normal androgen metabolic pathways, see 📖 p. 684.

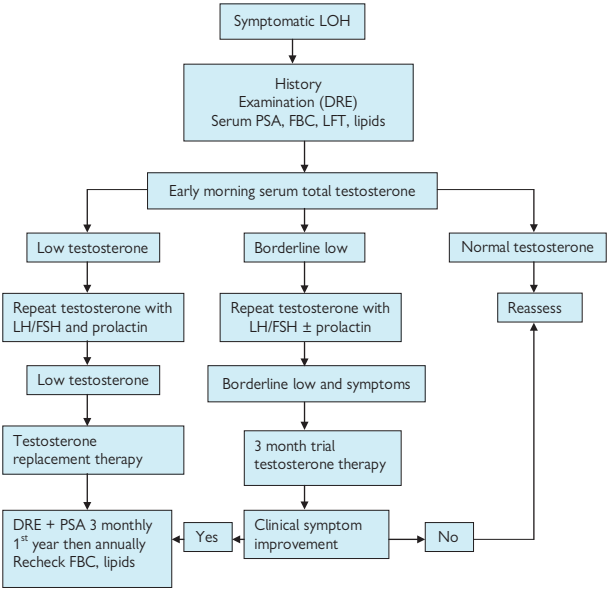

Fig. 13.5 Management pathway for symptomatic LOH.

1 Wang C, Nieschlag E, Swerdloff R, *et al.* (2009) Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *Eur Urol* **55**:121–30.

Hypogonadism and male hormone replacement therapy

Male hypogonadism has been defined as inadequate gonadal function due to deficiencies in gametogenesis and/or the secretion of gonadal hormones. Hypogonadism may be ***primary*** (due to abnormal testicular function or testicular response to gonadotrophins) or ***secondary*** (due to failure of the hypothalamic–pituitary axis, leading to inadequate gonadotrophic stimulation and reduced testicular testosterone production (Table 13.8). The result is testosterone deficiency.

Indications for testosterone treatment

Hypogonadism and related symptoms caused by low testosterone levels. Symptomatic LOH and primary hypogonadism should be treated with androgens. Patients with secondary hypogonadism may be given LH and FSH or pulsatile LHRH if fertility is required, otherwise they should receive androgen replacement (see 📖 p. 598). The aim is to achieve normal serum testosterone levels.

Contraindications to testosterone treatment

- Male breast cancer.
- Prostate cancer (current recommendation, but is controversial).
- History of primary liver tumour.
- Hypercalcaemia.
- Clinically significant obstructive benign prostatic enlargement.
- Pre-existing polycythaemia.
- Avoid if untreated severe liver, renal, or heart failure.
- Untreated sleep apnoea.

Assessment prior to testosterone treatment

- In men >45y, DRE and serum PSA are mandatory to assess prostate health.
- Fasting lipid profile.
- LFT.
- FBC.
- Flow rate, residual volume, IPSS to assess for BOO.
- Assess bone density prior to and during treatment (DEXA scan).

Assessment during testosterone treatment

- DRE and PSA every 3–6 months for the first 12 months, then yearly (for prostate cancer).
- FBC every 3–6 months for the first year and then yearly (to assess for new onset polycythaemia).
- Fasting lipid profile (testosterone can alter total and low-density lipoprotein cholesterol).

Side effects of testosterone treatment

- Headache.
- Oedema due to sodium retention.
- Depression.
- Gastrointestinal bleeding.
- Nausea.
- Cholestatic jaundice.
- Liver toxicity.
- Gynaecomastia.
- Androgenic effects (hirsutism, male pattern baldness).
- Polycythaemia.

Testosterone treatment

Testosterone replacement can be given by transdermal patch or gel, intramuscular injection, subdermal implant, buccal, and oral administrations (Table 13.9). Transdermal preparations produce a normal testosterone level with physiological diurnal profile, but they can produce local skin reaction. Intramuscular injections are long-acting, but do not provide normal hormonal circadian rhythm. Oral preparations tend to be less used due to variable pharmacokinetics. Buccal mucoadhesive tablets (Striant®) produce more reliable testosterone levels, but require twice daily application.

Metabolic syndrome

This is characterized by central obesity, insulin resistance, dyslipidaemia, and hypertension, resulting in increased risk of cardiovascular disease and progression to diabetes mellitus. ***Hypogonadism*** is frequently associated with metabolic syndrome. There is evidence that testosterone treatment may help some conditions associated with the syndrome and reduce the risk of cardiovascular complications.

Table 13.8 Causes of primary and secondary hypogonadism

Primary hypogonadism (hypergonadotrophic hypogonadism)	Secondary hypogonadism (hypogonadotrophic hypogonadism)
Congenital	***Congenital***
Chromosomal (Klinefelter's syndrome)	Kallmann's syndrome*
Undescended testes	
Acquired	***Acquired***
Surgery (bilateral orchidectomy)	Hypopituitarism (pituitary lesion; surgery or radiation to the cranium)
Bilateral testicular torsion	
Radiotherapy/chemotherapy	
Infection (bilateral orchitis)	
Cirrhosis	

* Kallman's syndrome is an isolated gonadotrophin (GnRH) deficiency which leads to hypogonadism.

Table 13.9 Testosterone preparations

Route of administration	Examples of preparations	Dosing regimen
Intramuscular injection	Testosterone enantate	Initial: 250mg every 2–3 weeks Maintenance: 250mg every 3–6 weeks
	Sustanon 250®	1mL every 3 weeks
	Nebido®	1g every 6 weeks for 12 weeks Maintenance: 1g every 3 months
Implant	Testosterone	100–600mg; 600mg maintains plasma testosterone in normal range for 4–5 months
Transdermal patch	Andropatch®	2.5–7.5mg/24h: dose according to plasma testosterone concentration
Transdermal gel	Testim®	5g gel (50mg testosterone) apply daily; adjust according to response (max 10g gel/24h)
	Testogel®	5g gel (50mg testosterone), apply daily Can be increased to 10g daily
Buccal	Striant®	30mg 12-hourly
Oral	Restandol® (testosterone undecanoate)	40mg 3–4 times per day (120–160mg daily) for 2–3 weeks Maintenance: 40–120mg daily

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Urethritis

Urethritis is inflammation of the urethra. Infective urethritis may present with clear, mucopurulent, or purulent urethral discharge, coloured white, yellow, green, or brown. It can be associated with dysuria and pain at the external urethral meatus or in the penile shaft, which persist between voiding. There may be urinary frequency and urgency. Some infections are asymptomatic.

Infective causes

- *Chlamydia (C.) trachomatis.*
- *Neisseria (N.) gonorrhoeae.*
- *Trichomonas vaginalis.*
- *Ureaplasma urealyticum.*
- *Mycoplasma genitalium.*
- *Herpes simplex* virus.

Evaluation

Assess symptoms, sexual history, and sexual contacts. Examine external genitalia for testicular or epididymal tenderness, discharge at the meatus, lymphadenopathy, or skin lesions. Refer to genitourinary medicine for management and to trace and treat contacts.

Investigation

The diagnosis of urethritis on urethral smear is defined as ≥5 polymorphonuclear leucocytes (PMNL) per high powered field (1000 magnification) or ≥10 PMNL per high powered field (400 times magnification) in the first voiding urine specimen.

Specific tests

- Urethral swabs (with endocervical swabs in women) transported in charcoal transport medium. Used for culture and Gram stain to identify *N. gonorrhoeae*. Also used for nucleic acid amplification test (NAAT) or enzyme immunoassay (EIA) to detect *N. gonorrhoeae* and *C. trachomatis.*
- First 20mL void of urine (after holding urine ≥1h). Used for EIA to identify *C. trachomatis.*
- MSU: dipstick testing ± microscopy to investigate UTI.
- In selected cases, consider HIV and syphilis testing with serum rapid plasma regain (RPR) test.

Gonococcal urethritis (GU): is caused by the Gram-negative dipplococcus *N. gonorrhoea*. Complications include genitourinary tract involvement causing epididymitis. Haematogenous spread of infection to other sites (71%) can cause disseminated gonococcal infection (DGI), manifest initially as tendon or joint pain (see Table 13.10).

Non-gonococcal urethritis (NGU): is mainly caused by *C. trachomatis* infection and may be asymptomatic (particularly in women). Specific complications include oculogenital syndrome (NGU and conjunctivitis). Transmission to females results in increased risk of pelvic

inflammatory disease, abdominal pain, ectopic pregnancy, infertility, and perinatal infection (see Table 13.10).

Genitourinary tract complications

- Epididymitis.
- Prostatitis.
- Urethral stricture.

Post-gonococcal urethritits

Recurrence of symptoms and signs 4–7 days after successful single-dose therapy for GU, caused by a dual urethral infection for which the NGU element was untreated. The most common cause is *C. trachomatis*. It is recommended an active antichlamydial treatment should be added in to the original gonorrhoea treatment because of this.

Table 13.10 Comparison and treatment of non-gonococcal and gonoccocal urethritis

	Non-gonococcal urethritis	Gonococcal urethritis
Main causative organism	*C. trachomatis*	*N. gonorrhoea*
Incubation time (days)	7–21	2–7
Onset	Gradual	Sudden
Discharge	Watery and clear	Larger volume and yellow
Dysuria	Mild	Moderate
Treatment	Azithromycin 1g single oral dose or Doxycycline 100mg bd oral for 7 days	Cefixime 400mg single oral dose or Ceftriaxone 250mg single deep intramuscular dose or Ciprofloxacin 500mg single oral dose

Non-specific urethritis and urethral syndrome

Non-specific urethritis (NSU): is described as the presence of PMNL (≥5 per high powered field at 1000 magnification) in a male urethral smear, in the absence of any proven specific infection.

Causes of NSU

Infective causes of urethritis with false-negative laboratory results (i.e. missed sexually transmitted infection (STI)).

Non-infective causes of urethritis

- Urethral trauma/foreign object.
- Contact urethritis (spermicides, shower gel).
- Reiter's syndrome (urethritis, seronegative arthritis, and conjunctivitis).
- Wegener's granulomatosis (vasculitis of unknown aetiology).

Management

Urethral swab: culture, Gram stain, and NAAT to exclude STI. Bearing in mind that some cases of NSU may be due to STI with false-negative results, sexual contacts should be traced and antibiotics can often alleviate symptoms. Standard *C. trachomatis* treatments are usually recommended (azithromycin 1g single oral dose or oral doxycycline 100mg bd 7 days) and are often effective.

Urethral syndrome

This is a condition of uncertain aetiology that only affects women. It manifests as dysuria, frequency, urgency, and suprapubic discomfort without any evidence of infection or urological abnormality to account for the symptoms.

Differential diagnosis

Infection, painful bladder syndrome/interstitial cystitis, urethral diverticulum.

Management

It is a diagnosis of exclusion. Urethral and endocervical swabs should be taken for culture, Gram stain, and NAAT to exclude an STI cause and MSU specimen to examine for UTI. Where indicated, consider cystoscopy to exclude BPS/IC or MRI to investigate for urethral diverticulum.

Treatment

A course of antibiotics (covering *C. trachomatis* and anaerobes) can provide symptom relief in some cases, even in the absence of positive cultures. Alkalinization of the urine (potassium citrate, sodium bicarbonate) may help alleviate symptoms.

Chapter 14

Neuropathic bladder

Innervation of the lower urinary tract (LUT)

Motor innervation of the bladder

Parasympathetic motor innervation of the bladder

Preganglionic, parasympathetic nerve cell bodies are located in the intermediolateral column of spinal segments S2–4. These preganglionic, parasympathetic fibres pass out of the spinal cord through the anterior primary rami of S2, S3, and S4 and contained within nerves called the nervi erigentes, they head towards the pelvic plexus. In the pelvic plexus (in front of the piriformis muscle), the preganglionic, parasympathetic fibres synapse within ganglia with the cell bodies of the post-ganglionic parasympathetic nerves which then run to the bladder and urethra. Fifty percent of the ganglia of the pelvic plexus lie in the adventitia of the bladder and bladder base (the connective tissue surrounding the bladder) and 50% are within the bladder wall. The post-ganglionic axons provide cholinergic excitatory input to the smooth muscle of the bladder.

Sympathetic motor innervation of the bladder

In the male, preganglionic sympathetic nerve fibres arise from the intermediolateral column of T10–12 and L1–2. These preganglionic neurons synapse in the sympathetic chain and post-ganglionic sympathetic nerve fibres travel as the hypogastric nerves to innervate the trigone, blood vessels of the bladder, and the smooth muscle of the prostate and preprostatic sphincter (i.e. the bladder neck). In the female, there is sparse sympathetic innervation of the bladder neck and urethra.

In both sexes, some post-ganglionic sympathetic nerves also terminate in parasympathetic ganglia (in the adventitia surrounding the bladder and within the bladder wall) and exert an inhibitory effect on bladder smooth muscle contraction.

Afferent innervation of the bladder

Afferent nerves from receptors throughout the bladder ascend with parasympathetic neurons back to the cord and from there, up to the pontine storage and micturition centres or to the cerebral cortex. They sense bladder filling.

Other receptors are located in the trigone and afferent neurons from these neurons ascend with sympathetic neurons up to the thoracolumbar cord and thence to the pons and cerebral cortex.

Other receptors are located in the urethra. The afferent neurons pass through the pudendal nerve and again ascend to the pons and cerebral cortex. All these neurons have local relays in the cord.

Somatic motor innervation of the urethral sphincter: the distal urethral sphincter mechanism

Anatomically, this is located slightly distal to the apex of the prostate in the male (between the verumontanum and proximal bulbar urethra) and in the mid-urethra in the female. It has three components:

- **Extrinsic skeletal muscle:** this is the outermost layer, the pubourethral sling (part of levator ani). Composed of striated muscle and

innervated by the pudendal nerve (spinal segments S2–4, somatic nerve fibres). It is activated under conditions of stress and augments urethral occlusion pressure.

- **Smooth muscle within the wall of the urethra:** cholinergic innervation. Tonically active. Relaxed by nitric oxide (NO).
- **Intrinsic striated muscle** (i.e. skeletal muscle *within* the wall of the urethra, hence known as the 'intrinsic rhabdosphincter'): it forms a 'U' shape around the urethra and around the anterior and lateral aspects of the membranous urethra and is absent posteriorly (i.e. it does not completely encircle the membranous urethra). It may produce urethral occlusion by kinking the urethra rather than by circumferential compression.

Preganglionic ***somatic*** nerve fibres (i.e. neurons which innervate ***striated*** muscle) are, along with ***parasympathetic*** nerve fibres (which innervate the bladder), derived from spinal segments S2–4, specifically from Onuf's nucleus (also known as spinal nucleus X) which lies in the medial part of the anterior horn of the spinal cord. (Onuf's nucleus is the location of the cell bodies of somatic motoneurons that provide motor input to the striated muscle of the pelvic floor—the external urethral and anal sphincters.) These somatomotor nerves travel to the rhabdosphincter via the perineal branch of the pudendal nerve (documented by direct stimulation studies and horseradish peroxidase (HRP) tracing—accumulates in Onuf's nucleus following injection into either the pudendal or pelvic nerves). There also seems to be some innervation to the rhabdosphincter from branches of the pelvic plexus (specifically the inferior hypogastric plexus) via pelvic nerves. In dogs, complete silence of the rhabdosphincter is seen only if both the pudendal and pelvic efferents are sectioned. Thus, pudendal nerve block or pudendal neurectomy does not cause incontinence.

The nerve fibres that pass distally to the distal sphincter mechanism are located in a dorsolateral position (5 and 7 o'clock). More distally, they adopt a more lateral position.

Sensory innervation of the urethra

Afferent neurons from the urethra travel in the pudendal nerve. Their cell bodies lie in the dorsal root ganglia and they terminate in the dorsal horn of the spinal cord at S2–4, connecting with neurons that relay sensory information to the brainstem and cerebral cortex.

The pudendal nerve (a somatic nerve derived from spinal segments S2–4) innervates striated muscle of the pelvic floor (levator ani, i.e. the pubo-urethral sling). Bilateral pudendal nerve block[1] does not lead to incontinence because of maintenance of internal (sympathetic innervation) and external sphincter function (somatic innervation, S2–4, nerve fibres travelling to the external sphincter alongside parasympathetic neurons in the nervi erigentes).

Clinical consequences of damage to the nerves innervating the LUT

Bladder neck function in the female

About 75% of continent young women and 50% of perimenopausal continent women have a closed bladder neck during the bladder filling phase. Twenty-five percent of continent young women and 50% of perimenopausal continent women have an open bladder neck and yet they remain continent (because of their functioning distal sphincter mechanism, the external sphincter).[2,3] Presacral neurectomy (to destroy afferent pain pathways) does not lead to incontinence because of maintenance of the somatic innervation of the external sphincter.

Sympathetic motor innervation of the bladder

Division of the hypogastric plexus of nerves during a retroperitoneal lymph node dissection for metastatic testis tumours results in paralysis of the bladder neck. This is of significance during ejaculation where normally sympathetic activity results in closure of the bladder neck so that the ejaculate is directed distally into the posterior and then anterior urethra. If the bladder neck is incompetent, the patient develops retrograde ejaculation; they remain continent of urine because the distal urethral sphincter remains functional, being innervated by somatic neurons from S2–4.

During pelvic fracture, the external sphincter and/or its somatic motor innervation may be damaged such that it is incompetent and unable to maintain continence of urine. Preservation of bladder neck function (the sympathetic innervation of the bladder neck usually remains intact) can preserve continence. However, if in later life, the patient undergoes a TURP or bladder neck incision for symptomatic prostatic obstruction, they may well be rendered incontinent because their one remaining sphincter mechanism (the bladder neck) will be divided during these operations.

1 Brindley GS (1974) The pressure exerted by the external sphincter of the urethra when its motor nerve fibres are stimulated electrically. *Br J Urol* **46**:453–62.

2 Chapple CR, Helm CW, Blease S, Milroy EJ, Rickards D, Osborne JL (1989) Asymptomatic bladder neck incompetence in nulliparous females. *Br J Urol* **64**:357–9.

3 Versi E, *et al.* (1990) Distal urethral compensatory mechanisms in women with an incompetent bladder neck who remain continent and the effect of the menopause. *Neurourol Urodyn* **9**:579–90.

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The physiology of urine storage and micturition

Urine storage

During bladder filling, bladder pressure remains low despite a substantial increase in volume. The bladder is thus highly compliant. Its high compliance is partly due to the elastic properties (viscoelasticity) of the connective tissues of the bladder and partly due to the ability of detrusor smooth muscle cells to increase their length without any change in tension. The detrusor is able to do this as a consequence of prevention of transmission of activity from preganglionic parasympathetic neurons to post-ganglionic efferent neurons—a so-called 'gating' mechanism within the parasympathetic ganglia. In addition, inhibitory interneuron activity in the spinal cord prevents transmission of afferent activity from sensors of bladder filling.

Micturition

A spino-bulbar-spinal reflex, coordinated in the pontine micturition centre in the brainstem (also known as Barrington's nucleus or the M region), results in simultaneous detrusor contraction, urethral relaxation, and subsequent micturition. Receptors located in the bladder wall sense increasing *tension* as the bladder fills (rather than stretch). This information is relayed, by afferent neurons to the dorsal horn of the sacral cord. Neurons project from here to the periaqueductal grey (PAG) matter in the pons. The PAG is thus informed about the state of bladder filling. The PAG and other areas of the brain (limbic system orbitofrontal cortex) input into the pontine micturition centre (PMC) and determine whether it is appropriate to start micturition.

At times when it is appropriate to void, micturition is initiated by relaxation of the external urethral sphincter and pelvic floor. Urine enters the posterior urethra and this, combined with pelvic floor relaxation, activates afferent neurons, which results in stimulation of the PMC (located in the brainstem). Activation of the PMC switches on a detrusor contraction via a direct communication between neurons of the PMC and the cell bodies of parasympathetic, preganglionic motoneurons located in the sacral intermediolateral cell column of S2–4. At the same time that the detrusor contracts, the urethra (the external sphincter) relaxes. The PMC inhibits the somatic motoneurons located in Onuf's nucleus (the activation of which causes external sphincter contraction) by exciting GABA and glycine-containing inhibitory neurons in the intermediolateral cell column of the sacral cord, which in turn project to the motoneurons in Onuf's nucleus. In this way, the PMC relaxes the external sphincter.

Micturition is an example of a positive feedback loop, the aim being to maintain bladder contraction until the bladder is empty. As the detrusor contracts, tension in the bladder wall rises. The bladder wall tension receptors are stimulated and the detrusor contraction is driven harder. One of the problems of positive feedback loops is their instability. Several inhibitory pathways exist to stabilize the storage–micturition 'loop'.

- Tension receptors activate bladder afferents, which via the pudendal and hypogastric nerves, inhibit S2–4 parasympathetic motor nerve output. An ongoing detrusor contraction cannot be overridden.
- Afferents in the anal and genital regions and in the distribution of the posterior tibial nerve stimulate inhibitory neurons in the sacral cord and these neurons inhibit S2–4 parasympathetic motor nerve output. This pathway can override an ongoing detrusor contraction. It is hypothesized that this system prevents involuntary detrusor contraction during sexual activity, defaecation, and while walking, running, and jumping.

Excitatory neurotransmission in the normal detrusor is exclusively cholinergic and reciprocal relaxation of the urethral sphincter and bladder neck is mediated by NO released from post-ganglionic parasympathetic neurons.

Further reading

De Groat WC (1993) Anatomy and physiology of the lower urinary tract. *Urol Clin NA* **20**: 383–401.

Bladder and sphincter behaviour in the patient with neurological disease

A variety of neurological conditions are associated with abnormal bladder and sphincter function (e.g. SCI, spina bifida (myelomeningocele), MS). The bladder and sphincters of such patients are described as 'neuropathic'.

They may have abnormal bladder function or abnormal sphincter function or, more usually, both. The bladder may be over- or underactive, as may the sphincter and any combination of bladder and sphincter over- or underactivity may coexist. 'Activity' here means bladder and sphincter pressure.

In the normal LUT during bladder filling, the detrusor muscle is inactive and the sphincter pressure is high. Bladder pressure is, therefore, low and the high sphincter pressure maintains continence. During voiding, the sphincter relaxes and the detrusor contracts. This leads to a short-lived increase in bladder pressure, sustained until the bladder is completely empty. The detrusor and sphincter thus function in synergy—when the sphincter is active, the detrusor is relaxed (storage phase) and when the detrusor contracts, the sphincter relaxes (voiding phase).

An overactive bladder is one that intermittently contracts during bladder filling so developing high pressures when normally bladder pressure should be low. In between these waves of contraction, bladder pressure returns to normal or near normal levels. In a patient with an underlying neurological problem, bladder overactivity is called detrusor hyperreflexia (DH). In other patients, the bladder wall is stiffer than normal, a condition known as poor compliance. Bladder pressure rises progressively during filling, such bladders being unable to store urine at low pressures. Some patients have a combination of DH and poor compliance. The other end of the spectrum of bladder behaviour is the underactive bladder which is low pressure during filling and voiding. This is called detrusor areflexia.

An overactive sphincter generates high pressure during bladder filling, but it also does so during voiding when normally it should relax. This is known as detrusor–external sphincter dyssynergia (DESD or DSD; Fig. 14.1). During EMG recording, activity in the external sphincter increases during attempted voiding (the external sphincter should normally be 'quiet' during voiding; see Fig. 3.16). An underactive sphincter is unable to maintain enough pressure in the face of normal bladder pressures to prevent leakage of urine.

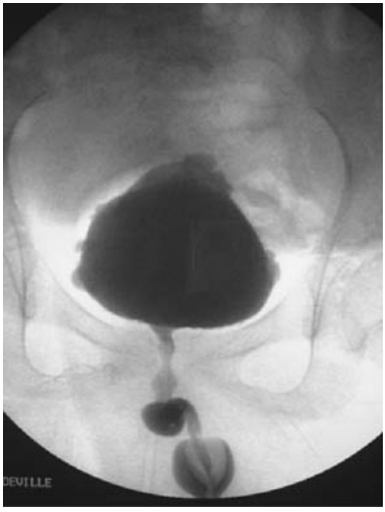

Fig. 14.1 Detrusor–external sphincter dyssynergia (DESD) seen during video cystourethrography.

The neuropathic lower urinary tract: clinical consequences of storage and emptying problems

Neuropathic patients experience two broad categories of problems—bladder filling and emptying—depending on the *balance* between bladder and sphincter pressures during filling and emptying. The effects of these bladder filling and emptying problems include incontinence, retention, recurrent UTIs, and renal failure.

High-pressure sphincter

High-pressure bladder

If the bladder is overactive (detrusor hyperreflexia) or poorly compliant, bladder pressures during filling are high. The kidneys have to function against these chronically high pressures. Hydronephrosis develops and ultimately, the kidneys fail (***renal failure***). At times, the bladder pressure overcomes the sphincter pressure and the patient leaks urine (***incontinence***). If the sphincter pressure is higher than the bladder pressure during voiding (DSD), bladder emptying is inefficient (***retention, recurrent UTIs***).

Low-pressure bladder

If the bladder is underactive (detrusor areflexia), pressure during filling is low. The bladder simply fills up—it is unable to generate enough pressure to empty (retention, recurrent UTIs). Urine leaks at times if the bladder pressure becomes higher than the sphincter pressure (incontinence), but this may occur only at very high bladder volumes or not at all.

Low-pressure sphincter

High-pressure bladder

If the detrusor is hyperreflexic or poorly compliant, the bladder will only be able to hold low volumes of urine before leaking (incontinence).

Low-pressure bladder

If the detrusor is areflexic such that it cannot develop high pressures, the patient may be dry for much of the time. They may, however, leak urine (incontinence) when abdominal pressure rises (e.g. when coughing, rising from a seated position, or when transferring to or from a wheelchair). Their low bladder pressure may compromise bladder emptying (recurrent UTIs).

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Bladder management techniques for the neuropathic patient

A variety of techniques and procedures are used to treat retention, incontinence, recurrent UTIs, and hydronephrosis in the patient with a neuropathic bladder. Each of the techniques described here can be used for a variety of clinical problems. Thus, a patient with a high-pressure, hyperreflexic bladder that is causing incontinence can be managed with an ISC (with intravesical botox injections, if necessary) or an SPC or by sphincterotomy with condom sheath drainage or by deafferentation combined with a sacral anterior root stimulator (SARS). Precisely which option to choose will depend on the individual patient's clinical problem, their hand function, their lifestyle, and other 'personal' factors such as body image, sexual function, etc. Some patients will opt for an SPC as a simple, generally safe, generally very convenient, and effective form of bladder drainage. Others wish to be free of external appliances and devices because of an understandable desire to look and 'feel' normal. They might opt for deafferentation with a SARS.

Intermittent self-catheterization (ISC)

See 🕮 p. 622.

Indwelling catheters

See 🕮 p. 622.

External sphincterotomy

Deliberate division of the external sphincter to convert the high-pressure, poorly emptying bladder due to DSD to a low-pressure, efficiently emptying bladder. *Indications:* retention, recurrent UTIs, hydronephrosis.

Techniques

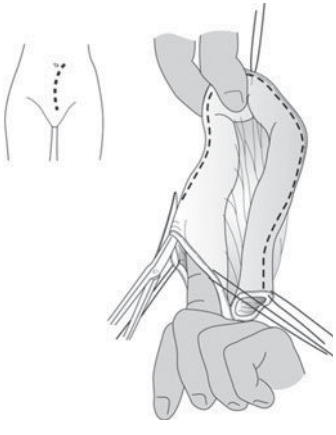
- Surgical (with an electrically heated 'knife' or laser). *Disadvantages:* irreversible, post-operative bleeding, septicaemia, and stricture formation.[1]
- Intra-sphincteric botox (botulinum toxin). A minimally invasive and reversible alternative to surgical sphincterotomy. *Disadvantage:* repeat injection required every 6–12 months; in the authors opinion (based on years of experience of botox and surgical sphincterotomies), probably not as effective at lowering bladder pressure and improving bladder emptying as surgical sphincterotomy (but no trials have compared the two techniques).
- A third potential option is an oral or sublingual NO donor (e.g. nifedipine, GTN). NO is a neurotransmitter which relaxes the external sphincter. Hypothesized as a treatment for DSD and preliminary studies support this hypothesis.[2,3]

Augmentation

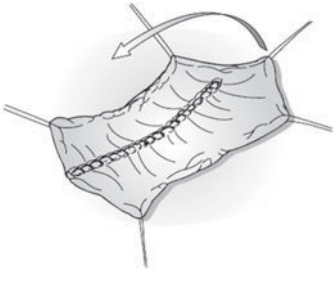
Technique of increasing bladder volume to lower pressure by implanting detubularized small bowel into the bivalved bladder ('clam' ileocystoplasty) (Fig. 14.2) or by removing a disc of muscle from the dome of the bladder

(a) Midline incision

(b) The isolated small bowel segment is detubularized.



(c) The ileal patch has been configured into a 'U' shape ready for anastomosis onto the bladder.



(d) The patch of ileum is anastomosed to the bladder.

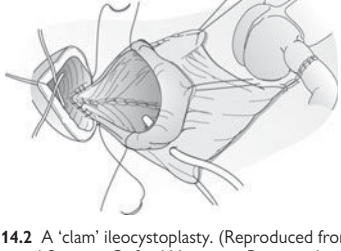


Fig. 14.2 A 'clam' ileocystoplasty. (Reproduced from Reynard, J, Mark, S. *et al.*, Urological Surgery. Oxford University Press, with permission from OUP.)

(auto-augmentation or detrusor myectomy). In the botox era, augmentation is becoming less and less frequently used because repeat (every 6–12 months) botox injections are often all that is required to achieve an acceptable level of continence, but also because of the short- and long-term morbidity of augmentation (bladder stones in 15%, bladder perforation, high grade invasive bladder cancers).[4] *Indications:* incontinence unacceptable to the patient or hydronephrosis despite full conservative therapy (regular ISC combined with anticholinergics and a trial of bladder botox injections).

Intravesical botlinum toxin injections

Recently, intravesical botulinum toxin type A injections at multiple sites in the bladder every 6–12 months have produced impressive reductions in bladder pressure and increases in volume (bladder capacity), with a low risk of side effects. As a consequence, surgical augmentation is nowadays only rarely done, being reserved for cases where botox has failed to work (where the patient is still wet between passing ISC catheters or where there is persistent hydronephrosis).

Botulinum toxin is a potent neurotoxin produced by the Gram-negative anaerobic bacterium *Clostridium botulinum*. Of the seven serotypes, only types A (BoNT-A) ('Botox®', Allergan, CA in the United States; 'Dysport®', Ipsen, Slough, UK) and B ('Myobloc®', Elan Pharmaceuticals, NJ, United States) are used clinically. BoNT-A is synthesized as an inactive single chain of 1285 amino acid polypeptide and is activated when cleaved by Clostridial protease into a two-chain polypeptide (50kDa light chain, 100kDa heavy chain).

Botulinum toxin type A ('Botox®' or 'Dysport®') binds to the SV2 receptor (synaptic vesicle protein) on the presynaptic nerve terminal where it is internalized by endocytosis. It causes proteolysis of the synaptosomal associated protein, SNAP-25, which is one of a group of SNARE proteins—with neuronal cell membranes (BoNT-B cleaves synaptobrevin). Thus, botulinum toxin inhibits neurotransmission at motor cholinergic, noradrenergic, and other (sensory) nerve terminals. It also reduces the expression of the vanilloid receptor, TPRV1, and the purinoreceptor, P2X3, both of which are sensory neuron receptors.

Thus, while we tend to think of botulinum toxin type A as inhibiting *neuromuscular* nerve transmission and, therefore, as a muscle *paralysing* agent, it is likely that it also has effects on sensory nerve transmission. BoNT-A inhibits the release of calcitonin gene-related peptide, substance P, glutamate, nerve growth factor, and ATP, which are neurotransmitters involved in pain pathways. In rat pain models, BoNT-A reduces pain behaviour.[5,6] How this effect on sensory nerve function translates into a role, if any, in the management of sensory urological conditions (sensory urgency, interstitial cystitis) remains to be established.

Recovery of neurotransmission requires removal of BoNT and restoration of intact SNARE proteins.

Intravesical botox injections can be administered using a flexible cystoscope (with a flexible injection needle) or a rigid scope. Multiple techniques of injection have been described and all seem to be effective. Some surgeons dilute the botox in 5mL of saline whereas others use the same number of units in 10 or 20mL of saline. Some use 'Dysport®' (Ipsen) while

others use 'Botox®' (Allergan). Some inject in ten sites, others in 20 sites, while others make 50 injections. Whether one technique or concentration or formulation of botox is superior to any other remains to be established. Precisely where the botox is actually administered (into the detrusor muscle or into the suburothelium) is debatable (the bladder wall is thin).

For intravesical injection in neuropathic patients (e.g. those with SCI or MS), the author uses a standard dose of 1000 units of Dysport® (though not infrequently between 1000 and 1500 units in those failing to respond for an adequate duration with 1000 units), diluted in 10mL of saline, and injects 0.33mL per site (three doses per 1mL syringe) in approximately 30 sites (roughly 30–35 units per site), using (usually) a flexible cystoscope and flexible injection needle. Some surgeons spare the trigone (i.e. avoid injecting the trigone), the theory (not proven) being that this avoids disrupting the valve mechanism of the VUJ. Other surgeons (the author included) inject in the trigone. Since the trigone has a dense sensory innervation, trigonal injections may (unproven) be more effective for sensory or painful bladder syndromes.

Intravesical botox injections are indicated for hydronephrosis which has failed to respond to increased frequency of ISC combined with oral anticholinergic medication; inter-ISC leakage which has failed to respond to increased frequency of ISC combined with oral anticholinergic medication; urethral leakage in patients with SPC where the leakage is thought to be due to uninhibited bladder contractions.

Outcomes of bladder botulinum toxin injections in the neuropathic patient

Bladder botox injections reduced incontinence episodes by a mean of 50% in patients with SCI when compared with placebo[7] and markedly improve continence in patients with MS where 80% are wet before botox, approximately 80% being dry afterwards, and remaining so for a median of 12–13 months.[8]

Outcomes of bladder botulinum toxin injections in the non-neuropathic patient

In non-neuropathic patients, three randomized placebo-controlled trials have shown that patients treated with 200–300 units of Botox® dissolved in between 2.5 to 20mL of saline and given at 10–20 sites had reduced urinary frequency and on average 3.88 fewer incontinence episodes per day.[9] The botox took effect within 3–14 days and lasted for a median of 307 days.

What dose of bladder botulinum should be used?

There have been few studies to determine the 'correct' dose of botox either in neuropaths or non-neuropaths, e.g. the minimal effective dose or the dose giving an adequate duration of effect (balanced against a low frequency of side effects). For the patient who has to change their clothes several times a day, knowledge of the undoubted efficacy of intravesical botox injections makes it is difficult to decide to enter a placebo-controlled study or one where a low, possibly ineffective, dose might be used.

In the neuropathic patient, there appears to be no significant difference in clinical and urodynamic outcomes in patients (mainly spinal injury or MS and almost all doing ISC) randomized to 500 vs 750 units of Dysport®

(5mL saline, 20 injection sites).[10] Complete continence was achieved in 56% and 74%, respectively (no significant dose difference). Reappearance of incontinence occurred at a median of 168 days (5.5 months). The bladder volume at which a reflex bladder contraction occurred increased by a mean of approximately 150mL and maximum cystometric capacity increased by a median of 192mL (500 units) to 243mL (750 units) (no significant dose difference, but a trend towards a better symptomatic and urodynamic improvement in those receiving 750 units).

In the author's experience, intravesical botox injections are most successful for the neuropathic patient with inter-ISC leakage, but they are also a very effective treatment for the symptoms of frequency, nocturia, urgency, and urge incontinence caused by non-neuropathic detrusor overactivity. They last for somewhere between 6 and 12 months and the efficacy and duration of effect of the botulinum toxin does not appear to diminish with repeat injections in both the neuropath or non-neuropath over, at present, 10y of follow-up, an experience shared by others.[8,11]

Side effects of botulinum toxin type A

The principle side effect is urinary retention, a retention volume of >150–200mL of urine occurring in approximately 40% of individuals (in the non-neuropathic patient); in the neuropathic patient, the deliberate aim is to achieve retention so that the patient becomes completely continent between doing ISC. Up to 41% of patients were said to 'require' ISC for up to 6 months.[9] Committing a patient to ISC for as long as 6 months after botox injections according to a rigid definition of urinary retention based solely on a post-void residual urine volume of >150–200mL, but in the absence of symptoms, is, in the authors' opinion, an unnecessary imposition. The author has a less rigid practice and places a patient on ISC only if they have (a) painful, complete urinary retention (painful inability to pass any urine, the pain being relieved by catheterization), or (b) are able to void only a few mL of urine while retaining the bulk of their urine production, or (c) has complete painless retention (painless inability to pass any urine—very unusual), or (d) develop symptomatic, recurrent UTI in the post-botox period. The author recommends the patient discontinue ISC once they feel comfortable to do so which, empirically, is usually when the balance between voided urine volume and retained urine volume shifts in favour of the former.

There is limited evidence suggesting retention is more likely with higher doses of Botox® at 200 units leading to retention of urine compared with no retention after 100 units.[12]

Haematuria is almost inevitable after making multiple intravesical injections and is almost always self-limiting (very occasionally, admission for a bladder washout of clots and irrigation via a 3-way catheter is required, but this is rare—two cases in 10y in the author's experience). Occasionally, systemic side effects can occur. These are uncommon, but can be disabling, particularly in the patient with pre-existing neurological disease. The author warns patients of the risks of generalized weakness which occurs in approximately 1 in 100 patients (lower risk after bladder injections; higher risk after external sphincter injections) and can impair the ability to transfer on and off a wheelchair and affect daily living and working activities;

blurring of vision (due to intraocular muscle effects—very rare, but very disabling); and difficulty taking a deep breath and/or swallowing (two cases in 10y in the author's experience, both resolving spontaneously within 2–3 weeks and neither required in-hospital observation). All of these side effects are uncommon, will last weeks or a few months, require no specific treatment, and usually do not recur with subsequent repeat injections.

Deafferentation

Division of dorsal spinal nerve roots of S2–4 to convert the hyperreflexic, high-pressure bladder into an areflexic, low-pressure one. Can be used where the hyperreflexic bladder is the cause of incontinence or hydronephrosis. Bladder emptying can subsequently be achieved by ISC or implantation of a nerve stimulator placed on ventral roots (efferent nerves) of S2–4 to 'drive' micturition when the patient wants to void (a pager-sized externally applied radiotransmitter activates micturition (Figs. 14.3 and 14.4). Also useful for DSD/incomplete bladder emptying causing recurrent UTIs and retention.

1 Reynard JM (2003) Sphincterotomy and the treatment of detrusor–sphincter dyssynergia: current status, future prospects. *Spinal Cord* **41**:1–11.

2 Reitz A, Knapp PA, Müntener M, Schurch B (2004) Oral nitric oxide donors: a new pharmacological approach to detrusor-sphincter dyssynergia in spinal cord injured patients. *Eur Urol* **45**:516–20.

3 Mamas MA, Reynard JM, Brading AF (2001) Augmentation of external uretheral sphincter nitric oxide: a potential pharmacological treatment for detrusor-external sphincter dyssynergia in spinal cord injury. *Lancet* **357**:1964–7.

4 Cain MP, Rink RC (2010) Augmentation for neuropathic bladder dysfunction – A thing of the past? *J Urol* **183**:2124–5.

5 Cui M, Khanijou S, Rubino J, Aoki KR (2004) Subcutaneous administration botulinum toxin type A reduces formalin-induced pain. *Pain* **107**:125–33.

6 Chuang YC, Yoshimura N, Huang CC, Chiang PH, Chancellor MB (2004) Intravesical botulinum toxin A administration produces analgesia against acetic acid induced bladder pain responses in rats. *J Urol* **172**:1529–32.

7 Schurch B, de Sèze M, Denys P,*et al.* (2005) Botox detrusor hyper-reflexia study team. Botulinum toxin type A is safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6 month study. *J Urol* **174**:196–200.

8 Khan S, Game X, Kalsi V, *et al.* (2011) Long term effect on quality of life of repeat detrusor injections of botulinum neurotoxin-A for detrusor overactivity in patients with multiple sclerosis. *J Urol* **185**:1344–9.

9 Anger JT, Weinberg A, Suttorp MJ, Litwin MS, Shekelle PG (2010) Outcome of intravesical botulinum toxin for idiopathic overactive bladder symptoms: a systematic review of the literature. *J Urol* **183**:2258–64.

10 Grise P, Ruffion A, Denys P, Egon G, Chartier Kastler E (2010) Efficacy and tolerability of botulinum toxin type A in patients with neurogenic detrusor overactivity and without concomitant anticholinergic therapy: comparison of two doses. *Eur Urol* **58**:759–66.

11 Game X, Khan S, Panicker JN, *et al.* (2010) Comparison of the impact on health related quality of life of repeated detrusor injections of botulinum toxin in patients with idiopathic or neurogenic detrusor overactivity. *BJU Int* **107**:1786–92.

12 Kuo HC (2006) Will suburothelial injection of a small dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity. *Urology* **68**:993–7.

Fig. 14.3 A sacral anterior root stimulator used to 'drive' micturition following a deafferentation (external components).

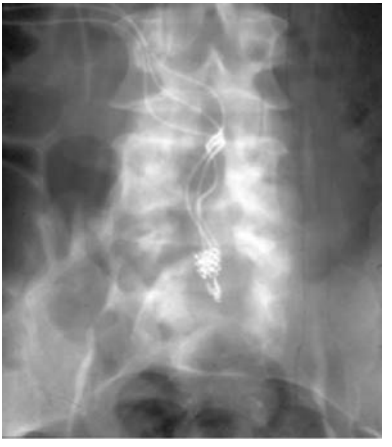


Fig. 14.4 KUB X-ray showing the sacral electrodes positioned on the ventral roots of S2, 3, and 4.

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Catheters and sheaths and the neuropathic patient

Many patients manage their bladders by intermittent catheterization (IC) done by themselves (ISC) or by a carer if their hand function is inadequate, as is the case with most (though remarkably not all) tetraplegics. Many others manage their bladders with an indwelling catheter (urethral or suprapubic). Both methods can be effective for managing incontinence, recurrent UTIs, and BOO causing hydronephrosis.

Intermittent catheterization

Requires adequate hand function. The technique is a 'clean' one (simple handwashing prior to catheterization) rather than 'sterile'. Gel-coated catheters become slippery when in contact with water so providing lubrication. Usually done 3–4 hourly.

Problems

- Recurrent UTIs.
- Recurrent incontinence: check technique (adequate drainage of last few drops of urine). Suggest increasing frequency of ISC to minimize volume of urine in the bladder (reduces bacterial colonization and minimizes bladder pressure). If incontinence persists, consider intravesical botulinum toxin.

Long-term catheterization

Some patients prefer the convenience of a long-term catheter. Others regard it as a last resort when other methods of bladder drainage have failed. The suprapubic route (SPC) is preferred over the urethral because of pressure necrosis of the ventral surface of the distal penile urethra in men (acquired hypospadias—'kippering' of the penis) and pressure necrosis of the bladder neck in women which becomes wider and wider until urine leaks around the catheter ('patulous' urethra) or frequent expulsion of the catheter occurs with the balloon inflated.

Problems and complications of long-term catheters

- **Recurrent UTIs:** colonization with bacteria provides a potential source of recurrent infection.
- **Catheter blockages are common:** due to encrustation of the lumen of the catheter with bacterial biofilms. *Proteus mirabilis, Morganella*, and *Providencia* species secrete a polysaccharide matrix. Within this, urease-producing bacteria generate ammonia from nitrogen in urine, raising urine pH and precipitating magnesium and calcium phosphate crystals. The matrix–crystal complex blocks the catheter. Catheter blockage causes bypassing which soils the patient's clothes. Bladder distension can cause autonomic dysreflexia, leading to extreme rises in BP which can cause stroke and death! Regular bladder washouts and increased catheter size sometimes help. Impregnation of catheters with antibacterials (e.g. triclosan) are under investigation.[1] Intermittent filling and emptying of the bladder using a 'flip-flow' valve may reduce the frequency of catheter blockages.

- **Bladder stones:** develop in 1 in 4 patients over 5y.[2]
- **Bladder cancer:** chronic inflammation (from bladder stones, recurrent UTIs, long-term catheterization) may increase the risk of squamous cell carcinoma in SCI patients. Some studies report a higher incidence of bladder cancer (whether chronically catheterized or not); others do not.[3]

Condom sheaths

These are an externally worn urine collection device, consisting of a tubular sheath applied over the glans and shaft of the penis (just like a contraceptive condom, only without the lubrication to prevent it slipping off). Usually made of silicone rubber with a tube attached to the distal end to allow urine drainage into a leg bag. They are used as a convenient way of preventing leakage of urine, but are obviously only suitable for men. Detachment of the sheath from the penis is prevented by using adhesive gels and tapes. They are used for patients with reflex voiding (where the hyperreflexic bladder spontaneously empties and where bladder pressure between voids never reaches a high enough level to compromise kidney function). They are also used as a urine collection device for patients after external sphincterotomy (for combined detrusor hyperreflexia and sphincter dysynergia where incomplete bladder emptying leads to recurrent UTIs and/or hydronephrosis).

Problems

The principal problem experienced by some patients is sheath detachment. Despite the fact that a man walked on the moon 30y ago, we have been unable to design a condom sheath that will consistently prevent urine leakage in all men. This can be a major problem and in some cases, requires a complete change of bladder management. Skin reactions sometimes occur.

1 Stickler D, Jones GL, Russell AD (2003) Control of encrustation and blocked Foley catheters. *Lancet* **361:**1435–7.

2 Ord J, Lunn D, Reynard J (2003) Bladder management and risk of bladder stone formation in spinal cord injured patients. *J Urol* **170:**1734–7.

3 Subramonian K, Cartwright RA, Harnden P, Harrison SC (2004) Bladder cancer in patients with spinal cord injuries. *BJU Int* **93:**739–43.

Management of incontinence in the neuropathic patient

Causes

High-pressure bladder (detrusor hyperreflexia, reduced bladder compliance); sphincter weakness; UTI; bladder stones; rarely, bladder cancer (enquire for UTI symptoms and haematuria). Hyperreflexic peripheral reflexes suggest bladder may be hyperreflexic (increased ankle jerk reflexes, S1–2, and a positive bulbocavernosus reflex indicating an intact sacral reflex arc, i.e. S2–4 intact). Absent peripheral reflexes suggest the bladder and sphincter may be areflexic (i.e. sphincter unable to generate pressures adequate for maintaining continence).

Initial investigations

Urine culture (for infection); KUB X-ray for bladder stones; bladder and renal USS for residual urine volume and to detect hydronephrosis; cytology and cystoscopy if bladder cancer suspected.

Empirical treatment

Start with simple treatments. If the bladder residual volume is large, regular ISC may lower bladder pressure and achieve continence. Try an anticholinergic drug (e.g. oxybutynin, tolterodine). Many SCI patients are already doing ISC and simply increasing ISC frequency to 3–4 hourly may achieve continence. ISC more frequently than 3-hourly is usually impractical, particularly for paraplegic women who usually have to transfer from their wheelchair onto a toilet and then back onto their wheelchair (Table 14.1).

Management of failed empirical treatment

Determined by videocystourethrography (VCUG) to assess bladder and sphincter behaviour.

Detrusor hyperreflexia or poor compliance

High-pressure sphincter (i.e. DSD): treating the high-pressure bladder is usually enough to achieve continence.

- **Bladder treatments:** intravesical botulinum toxin, detrusor myectomy (auto-augmentation), bladder augmentation (ileocystoplasty). All will usually require ISC for bladder emptying.
- Long-term SPC.
- Sacral deafferentation + ISC or Brindley implant (SARS).

Low-pressure sphincter. Treat the bladder first. If bladder treatment alone fails, consider a urethral bulking agent, a transvaginal tape (TVT) or bladder neck closure in women, or an artificial urinary sphincter in either sex (Fig. 14.5).

Detrusor areflexia + low-pressure sphincter

- Urethral bulking agents.
- TVT.
- Bladder neck closure in women.
- Artificial urinary sphincter.

The artificial urinary sphincter (AUS)

The AUS essentially consists of two balloons connected by tubing to a control pump. One of the balloons is configured as a cuff around the bulbar urethra or bladder neck. The other balloon (placed deep to the rectus muscle) applies a constant pressure (usually 61–70cmH_2O pressure) to the cuff via a control pump located in the scrotum or labia (Fig. 14.5; The AMS (American Medical Systems) 800 AUS). Pressure in the cuff is maintained until the control pump is squeezed by the patient. This forces fluid from the cuff (so it temporarily no longer occludes the urethra) into the balloon. Pressure from the balloon then refills the cuff via delay resistors in the control pump over a minute or so.

Indications

Incontinence

- Following prostatectomy (post-TURP or radical prostatectomy).
- In the neuropathic patients (SCI, spina bifida) due to intrinsic sphincter deficiency.
- Following trauma to the pelvis or perineum.

Relative contraindications

- Poor bladder compliance (risk of dangerous and silent elevation of bladder pressure, with the development of hydronephrosis).
- Untreated involuntary bladder contractions (persistent incontinence common).
- Urethral stricture. Incision can expose the underlying cuff, leading to AUS infection.
- Poor cognitive function such that the patient is unable to appreciate the need to deflate the cuff several times a day.

Preparation prior to insertion

- Videourodynamics (to assess bladder pressure and confirm the presence of sphincter weakness incontinence). Usually not necessary in 'simple' post-radical prostatectomy patients (cause of incontinence usually obvious).
- Flexible cystoscopy to exclude urethral stricture.
- Urine culture. Treat infection with an appropriate antibiotic for a week or so before insertion.

Bulbar cuff placement: for post-radical prostatectomy incontinence, previous surgery or trauma (pelvic fracture) in the region of bladder neck (increased risk of rectal perforation).

Bladder neck cuff placement: women (obviously), children (bulbar urethra too small for the available cuff sizes), men who wish to maintain fertility by preserving antegrade ejaculation, neuropathic patients where ISC is or may be required.

A deactivation button prevents return of fluid from the balloon to the cuff so allowing catheterization or instrumentation.

Outcomes

Improved continence in 60–90%. Complications in 5–30%—infection, urethral erosion, urethral loosening under the cuff (atrophy), device ('mechanical') failure.[1]

Alternatives

- Injectable urethral bulking agents.
- **Male urethral sling:** three types—bulbourethral (suprapubic to suburethral); bone anchored perineal (InVance™); transobturator (AdVance™). Said to improve continence by bulbar urethral repositioning (rather than compression). Good (short-term) outcomes for less severe incontinence—five or fewer pads per day; poor outcome if six or more pads per day.[2] Long-term outcomes and those for transobturator slings remain undetermined.
- **Extraurethral retropubic adjustable compression devices:** under local or regional anaesthesia, two small silicone balloons are introduced percutaneously via a perineal approach and positioned on each side of the urethra close to the bladder neck. Subcutaneous ports allow volume adjustment post-operatively to increase (for persistent leakage) or decrease urethral resistance (for voiding difficulty). Questions remain over its safety (e.g. 10% urethral or bladder perforation, balloon migration, fluid leakage) and continence outcomes.

1 Hussain M, Greenwell TJ, Venn SN, Mundy AR (2005) The current role of the artificial urinary sphincter for the treatment of urinary incontinence. *J Urol* **174:**418–24.

2 Castle EP, Andrews PE, Itano N (2005) The male sling for post-prostatectomy incontinence: mean follow-up of 18 months. *J Urol* **173:**1657.

Table 14.1 Summary of treatment for incontinence

	High bladder pressure	**Low bladder pressure**
High sphincter pressure	Lower bladder pressure by ISC + anticholinergics *or* botulinum toxin type A *or* augmentation	ISC*
Low sphincter pressure	Lower bladder pressure by (ISC + anticholinergics *or* botox or augmentation) + urethral bulking agent TVT *or* bladder neck closure *or* artificial urinary sphincter	Urethral bulking agent, TVT, bladder neck closure, artificial urinary sphincter

* High sphincter pressure is usually enough to keep patient dry.

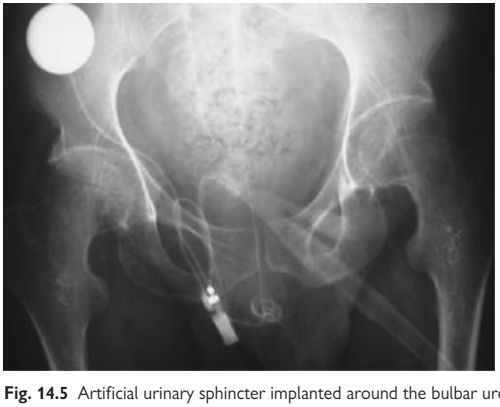

Fig. 14.5 Artificial urinary sphincter implanted around the bulbar urethra.

Management of recurrent urinary tract infections (UTIs) in the neuropathic patient

Causes of recurrent UTIs

- Incomplete bladder emptying.
- Kidney stones.
- Bladder stones.
- Presence of an indwelling catheter (urethral or suprapubic).

History

What the patient interprets as a UTI may be different from your definition of UTI. The neuropathic bladder is frequently colonized with bacteria and often contains pus cells (pyuria). From time to time, it becomes cloudy due to the precipitation of calcium, magnesium, and phosphate salts in the absence of active infection. The presence of bacteria, pus cells, or cloudy urine in the presence of non-specific symptoms (abdominal pain, tiredness, headaches, feeling 'under the weather') is frequently interpreted as a UTI.

Indications for treatment of UTI in the neuropathic patient

It is impossible to eradicate bacteria or pus cells from the urine in the presence of a foreign body (e.g. a catheter). In the absence of fever and cloudy smelly urine, we do not prescribe antibiotics, the indiscriminate use of which encourages growth of antibiotic-resistant organisms. We prescribe antibiotics to the chronically catheterized patient where there is a combination of fever, cloudy, smelly urine and where the patient feels unwell. Culture urine and immediately start empirical antibiotic therapy with nitrofurantoin, ciprofoxacin, or trimethoprim (the antibiotics sensitivities of our local 'bacterial flora'), changing to a more specific antibiotic if the organism is resistant to the prescribed one.

Investigations

For recurrent UTIs (= frequent episodes of fever, cloudy, smelly urine and feeling unwell), organize the following:

- KUB X-ray—looking for kidney and bladder stones.
- Renal and bladder USS to determine the presence/absence of hydronephrosis and to measure pre-void bladder volume and post-void residual urine volume.

Treatment

In the presence of fever and cloudy, smelly urine, culture the urine and start antibiotics empirically (e.g. trimethoprim, nitrofurantoin, amoxicillin, ciprofloxacin), changing the antibiotic if the culture result suggests resistance to your empirical choice. 'Response' to treatment is suggested by the patient feeling better and their urine clearing and becoming non-offensive to smell. Persistent fever with constitutional symptoms (malaise, rigors)

despite treatment with a specific oral antibiotic in an adequate dose is an indication for admission for treatment with intravenous antibiotics.

Management of recurrent UTIs (Table 14.2)

If there is residual urine present, optimize bladder emptying by IC (males, females) or external sphincterotomy for DSD (males). IC can be done by the patient (ISC) if hand function is good (paraplegic) or by a carer if tetraplegic. An indwelling catheter is an option, but the presence of a foreign body in the bladder may itself cause recurrent UTIs (though in some, it seems to reduce UTI frequency).

Table 14.2 Summary of treatment for recurrent UTIs

Low bladder pressure	High bladder pressure + DSD*
ISC	ISC
IDC	IDC
	External sphincterotomy—surgical, botox, stent
	Deafferentation/SARS

Remove stones, if present—cystolitholapxy for bladder stones, PCNL for staghorn stones.

* A new potential option for DSD is augmentation of external sphincter nitric oxide (NO), a neuro-transmitter which relaxes the external sphincter, thereby encouraging antegrade flow of urine and potentially, therefore, lowering residual urine volume. NO donors such as nifedipine or GTN can be used. There is theoretical and some experimental evidence to support this.[1,2]

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Management of hydronephrosis in the neuropathic patient

An overactive bladder (detrusor hyperreflexia) or poorly compliant bladder is frequently combined with a high-pressure sphincter (DSD). Bladder pressures during both filling and voiding are high. At times, the bladder pressure may overcome the sphincter pressure and the patient leaks small quantities of urine. For much of the time, however, the sphincter pressures are higher than the bladder pressures and the kidneys are chronically exposed to these high pressures. They are hydronephrotic on USS and renal function slowly, but inexorably, deteriorate.

Treatment options for hydronephrosis

Bypass the external sphincter

- IDC (indwelling catheter).
- ISC + anticholinergics.

Treat the external sphincter

- Sphincterotomy: surgical incision via a cystoscope inserted down the urethra (electrically heated knife or laser), botulinum toxin type A injections into sphincter, urethral stent.
- Deafferentation* + ISC or SARS.

Treat the bladder

- Intravesical botulinum toxin type A + ISC.
- Augmentation + ISC.
- Deafferentation[1] + ISC or SARS.

* Deafferentation converts the high-pressure sphincter into a low-pressure sphincter and the high-pressure bladder into low-pressure bladder.

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Bladder dysfunction in multiple sclerosis, Parkinson's disease, spina bifida, after stroke, and in other neurological disease

Multiple sclerosis (MS)

Seventy-five percent of patients with MS have spinal cord involvement and in these patients, bladder dysfunction is common. The most common symptoms in patients with MS are urgency, frequency, nocturia, and urge incontinence (due to DH) occurring in 32–97% of individuals, depending on the duration and severity of their MS.[1] Bladder pressures are rarely high enough to cause upper tract problems (hydronephrosis). The mainstays of treatment are anticholinergics, ISC, and bladder botox injections.

Parkinson's disease (PD)

PD is a cause of parkinsonism (tremor, rigidity, bradykinesis—slow movements) and is due to the degeneration of dopaminergic neurons in the substantia nigra in the basal ganglia. The principal urological manifestation of PD is the development of LUTS, affecting 30–40% of patients with PD.[2] In the 30–40% of patients with PD and LUTS, nocturia is reported by 90%, urinary frequency and urgency by 70%, and urge incontinence by >40% (the symptoms that classically respond least well to TURP).

The most common urodynamic abnormality is DH (the basal ganglia may have an inhibitory effect on the micturition reflex). L-dopa seems to have a variable effect on these symptoms and DH, improving symptoms in some and making them worse in others. Impaired detrusor contractility can also occur, albeit uncommonly. Sphincter function during spontaneous (desired) voiding is synergic, i.e. there is no sphincter dyssynergia. Thus, the patient with PD has unobstructed voiding, unless they have coexistent benign prostatic obstruction. Poor striated sphincter function can also occur. Both DH and poor striated sphincter function can predispose to post-TURP incontinence.[3]

Urological lore is that patients with PD have had a poor outcome after TURP[3] (*de novo* urinary incontinence rate of 20%). However, this is probably because of inclusion of patients with multisystem atrophy in previous studies,[3] which is associated with a particularly poor outcome after TURP.[4] If a patient with PD has urodynamically proven BOO, symptomatic outcomes after TURP can be good[4], at least in patients with mild PD of less than 5y duration.

Multiple system atrophy (MSA; formerly Shy–Drager syndrome)

A cause of parkinsonism characterized clinically by postural hypotension and detrusor areflexia. Loss of cells in the pons leads to DH (symptoms of bladder overactivity), loss of parasympathetic neurons due to cell loss in the intermediolateral cell column of the sacral cord causes poor bladder emptying, and loss of neurons in Onuf's nucleus in the sacral anterior

horns leads to denervation of the striated sphincter causing incontinence. The presentation is usually with DH (i.e. symptoms of bladder overactivity), followed over the course of several years by worsening bladder emptying.

Spina bifida

The term 'spina bifida' (more correctly, spinal dysraphism) describes the clinical manifestations arising from the failure of fusion of the neural and bony elements of the spine. The entity of spina bifida includes spina bifida cystica (myelomeningocele and meningocele) and spina bifida occulta (lipomeningocele, intradural lipoma, and tethered cord).

Urinary incontinence, recurrent UTI, bladder and renal stone formation, and reflux nephropathy are common problems.

McGuire introduced the concept of detrusor leak point pressure as an indicator of risk of upper tract deterioration in spina bifida patients.[5] In 42 patients with myelodysplasia followed over 15y, urethral urine leakage occurred in 20 patients at intravesical pressures <40cmH_2O (the detrusor leak point pressure) and in 22 at pressures >40cmH_2O. While no patient with a leak point pressure <40cmH_2O had VUR and only two had ureteral dilatation on intravenous urography, in contrast, VUR was present in 15 patients (68%) and ureteral dilatation in 18 (81%) in those patients with a leak point pressure >40cmH_2O. As a result of this study (later supported by others), an end fill pressure <40cmH_2O is taken as an indication that upper tract deterioration will not occur and an end fill pressure >40cmH_2O is taken as an indication of the potential for upper tract deterioration.

The hallmark urodynamic finding in spina bifida is loss of bladder compliance combined with increased outlet resistance secondary to abnormal bladder neck function or DSD[6] (62% of patients; 38% had what was described as detrusor areflexia which, in reality, described a group of 34 patients, 30 of who had poor bladder compliance with high end fill pressures). Most patients have a fixed (static) external sphincter and 10–15% of patients have DESD.

The mainstay of management is directed towards maintaining a low-pressure, continent bladder with anticholinergics combined with ISC.[7] In those with increased detrusor leak point pressures, this decreases the probability of upper tract deterioration.[8] Where anticholinergics fail to achieve continence or fail to eliminate hydronephrosis, the next step is to try bladder botox injections combined with ISC, though the poorly compliant bladder that is so characteristic of spina bifida seems to be more resistant to botox than the purely hyperreflexic bladder.

If anticholinergics or botox combined with ISC are not be able to achieve safe storage pressures in the small capacity, poorly compliant bladder augmentation cystoplasty with or without a Mitrofanoff stoma to make ISC easier (especially in the wheelchair-bound patient) may be required to achieve safe lowering of bladder pressure. Where continence cannot be achieved by reducing bladder pressure alone, bladder neck closure, urethral support (e.g. a TVT in women), or an artificial sphincter may be required. Leak point pressure can predict (with reasonable accuracy) those patients who have adequate bladder outlet resistance (those with a

leak point pressure >40cmH_2O generally) to obviate the need for bladder outlet surgery.

Those patients with spina bifida and impaired cognitive ability (who represent a significant proportion of the spina bifida population) may not be able to cope with the requirement for regular and frequent bladder emptying with ISC or with the use of the AUS. For such patients, an SPC may be a safer method of achieving continence and protecting renal function. Furthermore, while it is possible to improve continence with LUT reconstructive surgery, there is evidence that this may not be paralleled with substantial improvements in overall quality of life.[9] Quality of life scores seem to be no different between patients with spina bifida who undergo successful surgery for incontinence and matched controls who do not (it is difficult to improve quality of life by correcting just one system in a complex, multisystem disability such as spina bifida).

Cerebrovascular accidents

DH occurs in 70%, DSD in 15%. Detrusor areflexia can occur.[10] Frequency, nocturia, urgency, and urge incontinence are common. Retention occurs in 5% in the acute phase. Incontinence within the first 7 days after a CVA predicts poor survival.[11]

Other neurological disease

Frontal lobe lesions (e.g. tumours, arteriovenous malformations (AVMs))
May cause severe frequency and urgency (frontal lobe has inhibitory input to the pons).

Brainstem lesions (e.g. posterior fossa tumours)
Can cause urinary retention or bladder overactivity.

Transverse myelitis
Severe tetraparesis and bladder dysfunction which often recovers to a substantial degree.

Peripheral neuropathies
The autonomic innervation of the bladder makes it 'vulnerable' to the effects of peripheral neuropathies such as those occurring in diabetes mellitus and amyloidosis. The picture is usually one of reduced bladder contractility (poor bladder emptying, i.e. chronic low-pressure retention).

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Neuromodulation in neuropathic and non-neuropathic lower urinary tract dysfunction

This is the electrical activation of *afferent* nerve fibres to modulate their function.

Electrical stimulation applied anywhere in the body preferentially depolarizes nerves (higher current amplitudes are required to directly depolarize muscle). In patients with LUT dysfunction, the relevant spinal segments are S2–4. *Indications:* urgency, frequency, urge incontinence, chronic urinary retention where behavioural and drug therapy has failed.

Several sites of stimulation are available, the electrical stimulus being applied directly to nerves or as close as possible:

- SNS.
- Pudendal nerve: direct pelvic floor electrical stimulation (of bladder, vagina, anus, pelvic floor muscles) or via stimulation of dorsal penile or clitoral nerve (DPN, DCN).
- Posterior tibial nerve stimulation (PTNS).[1]

PTNS

PTN (L4,5; S1–3) shares common nerve roots with those innervating the bladder. PTNS can be applied transcutaneously (stick-on surface electrodes) or percutaneously (needle electrodes). Percutaneous needle systems include the SANS (Stoller) and the UrgentPC system. Stimulation is applied via an acupuncture needle inserted just above the medial malleolus with a reference (or returns) electrode—30min of stimulation per week, over 12 weeks. Thereafter, 30min of treatment every 2–3 weeks can be used to maintain the treatment effect in those who respond. PTNS has not been compared with placebo ('sham' stimulation) and, therefore, reported efficacy may represent a placebo response. In a single-blinded, placebo-controlled study (gastrocnemius muscle stimulation without PTNS), 71% of patients receiving PTNS (12 treatments; 3 per week over 4 weeks) reported >50% reduction in urge incontinence episodes.[2]

SNS (sacral nerve modulation—SNM)

A sacral nerve stimulator (Medtronic Interstim) delivers continuous electrical pulses to S3 via an electrode inserted through the sacral foramina and connected to an electrical pulse generator which is implanted subcutaneously. Supported by NICE[3] for patients with urge incontinence who have failed lifestyle modification and behaviour and drug therapy.

A test stimulation (the peripheral nerve evaluation, PNE) is performed, under local anaesthetic, by a percutaneous test electrode placed in S3 foramina to confirm an appropriate clinical response (a reduction in urgency, frequency, or incontinence episodes). A permanent implant is offered if there is a 50% reduction in frequency and urgency. This is placed in a subcutaneous pocket and is connected to the sacral electrode. It can be switched on and off and the amplitude varied within set limits. About 50–60% of patients have a successful PNE. A multicentre study, randomizing non-neuropathic patients with a successful PNE test

to immediate vs delayed (for 6 months) implantation (the control group), showed significantly better symptomatic outcomes in the implant group, 50–70% reporting resolution of their urge incontinence and 80% reporting >50% reduction in incontinence episodes, persisting for at least 3–5y.[4] Longer term follow-up studies report a durable response.[5,6] Numbers of neuropathic patients treated with SNS are too small to draw meaningful conclusions.[5]

For non-obstructive urinary retention of those responding to PNE (68 of 177, 38%) and who were subsequently implanted, 58% no longer required ISC at 18 months of follow-up,[7] results mirrored by others (50–55% stopping ISC) at a mean of 41–43 months (70% with Fowler's syndrome stopped ISC).[8,9]

The exact mechanism of action of SNM in patients with bladder dysfunction is not known.

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Chapter 15

Urological problems in pregnancy

Physiological and anatomical changes in the urinary tract

Upper urinary tract

- **Renal size enlarges**: by 1cm, secondary to increased interstitial volume and distended renal vasculature, with renal volume increasing up to 30%.
- **Dilatation of the collecting systems**: producing physiological hydronephrosis and hydroureters (right > left side), which starts in the second month of pregnancy and is maximal by the middle of the second trimester. It is caused by mechanical obstruction by the growing uterus and ovarian venous plexus and smooth muscle relaxation due to progesterone.
- **Renal plasma flow (RPF) rate**: goes up early in the first trimester, reaching an increase of ~75% by 16 weeks' gestation. This is maintained until 34 weeks' gestation, followed by a decline of ~25% towards term.
- **GFR**: increases by 50% by the end of the first trimester, which is maintained until term. GFR has returned to normal levels by 3 months after delivery.
- **Renal function and biochemical parameters**: are affected by changes in RPF and GFR. Creatinine clearance increases and serum levels of creatinine, urea, and urate fall in normal pregnancy due to glomerular hyperfiltration (Table 15.1). Raised GFR causes an increased glucose load at the renal tubules and results in glucose excretion (physiological glycosuria of pregnancy which tends to be intermittent). Of note, patients with persistent glycosuria should be screened for diabetes mellitus. Proteinuria is only increased in women with pre-existing proteinuria before pregnancy. Urine output is increased.
- **Salt and water handling**: a reduction in serum sodium causes reduced plasma osmolality. The kidney compensates by increasing renal tubular reabsorption of sodium. Plasma renin activity is increased 10-fold and levels of angiotensinogen and angiotensin are increased 5-fold. Osmotic thresholds for ADH and thirst decrease.
- **Acid–base metabolism**: serum bicarbonate is reduced. Increased progesterone stimulates the respiratory centre, resulting in reduced PCO_2.

Lower urinary tract

- **Bladder**: displacement occurs (superiorly and anteriorly) due to the enlarging uterus. The bladder becomes hyperaemic and raised oestrogen levels cause hyperplasia of muscle and connective tissues. Bladder pressures can increase over pregnancy (from 9 to 20cmH_2O), with associated rises in absolute and functional urethral length and pressures.
- **Haematuria**: there is an increased risk of non-visible haematuria due to elevation of the trigone and increased bladder vascularity. Persistent non-visible haematuria, patients with associated risk factors (i.e. smoking), or visible haematuria will need further investigation

similar to non-gravid patients. Placenta precreta (placenta invades the bladder) can cause haematuria and should be excluded as a cause.

- **LUTS**: urinary frequency (>7 voids during the day) and nocturia (≥1 void at night) increase over the duration of gestation (incidence of 80–90% in third trimester). Urgency is reported in up to 60% and urge incontinence may develop in 10–20%, predominantly in the third trimester. These effects are contributed to by pressure on the bladder from the enlarging uterus, causing reduced functional capacity. Nocturia is also exacerbated due to the increased excretion of water (whilst lying down) that tends to be retained during the day. Normal bladder function returns in the majority soon after delivery.
- **Acute urinary retention**: is uncommon during pregnancy, but may occur at 12–14 weeks' gestation in association with a retroverted uterus, which resolves by 16 weeks. Fibroids and other uterine anomalies may predispose to retention. Post-partum urinary retention occurs in up to 18%, associated with epidural use, assisted or first delivery, and long duration of labour.
- **Stress urinary incontinence**: occurs in around 22% and increases with parity. It is partly caused by the placental production of peptide hormones (relaxin), which induces collagen remodelling and consequent softening of tissues of the birth canal. Infant weight, duration of first and second stages of labour (vaginal delivery), and instrumental delivery (ventouse extraction or forceps delivery) increase risks of post-partum stress incontinence.

Table 15.1 Biochemistry reference intervals

Substance	Non-pregnant	Pregnant
Sodium (mmol/L)	135–145	132–141
Urea (mmol/L)	2.5–6.7	2–4.2
Urate (μmol/L)	150–390	100–270
Creatinine (μmol/L)	70–150	24–68
Creatinine clearance (mL/min)	90–110	150–200
Bicarbonate (mmol/L)	24–30	20–25

Parity = pregnancies that resulted in delivery beyond 28 weeks' gestation; post-partum = after delivery of the baby; gravid = pregnant.

Urinary tract infection (UTI)

Pregnancy does not alter the incidence of lower UTI. However, physiological and anatomical changes associated with pregnancy can alter the course of infection, causing an increased risk of recurrent UTI and progression to acute pyelonephritis.

Asymptomatic bacteriuria

An asymptomatic lower UTI which affects 5–10% of pregnant women, with a 20–40% risk of developing pyelonephritis during pregnancy. This risk is reduced if the bacteriuria is treated and, therefore, urine screening in pregnancy is advocated.

Symptomatic UTI

- **Cystitis**: affects 1–3% and presents with urinary frequency, urgency, suprapubic pain, and dysuria.
- **Acute pyelonephritis**: is more frequently seen than in non-pregnant women, affecting around 1–2%. It is most common in the third trimester and is most likely to affect the right side. Most are due to undiagnosed or inadequately treated lower UTI. It presents with fever, flank pain, nausea, and vomiting, often with an elevated WCC.

Risk factors for UTI

Previous history of recurrent UTIs, pre-existing anatomical or functional urinary tract abnormality (i.e. VUR), diabetes. Physiological changes in pregnancy include hydronephrosis with decreased ureteric peristalsis, causing urinary stasis. Up to 75% of pyelonephritis occurs in the third trimester when these changes are most prominent.

Pathogenesis

The most common causative organism is *E. coli*. An increased risk of gestational pyelonephritis is associated with *E. coli* containing the virulence factor 'Dr adhesin'. Other common organisms include *Klebsiella* and *Proteus*.

Complications

UTI generally increases the risk of preterm delivery, low fetal birth weight, intrauterine growth retardation, and maternal anaemia. Acute pyelonephritis can be complicated by progression to septic shock, signs of preterm labour, and adult respiratory distress syndrome.

Screening tests

MSU: should be obtained at the first antenatal visit (week 10) and sent for urinalysis and culture to look for bacteria, protein, and blood. Repeated MSU investigation (urine dipstick ± culture) is recommended at later antenatal visits to examine for signs of bacteriuria (usually leukocyte esterase and nitrite-positive), protein, and glucose, particularly in high-risk patients with a history of urinary tract anomalies or recurrent UTI. (see 📖 p. 177; Table 6.2 for the recommended criteria for diagnosing UTI.)

Treatment

All proven episodes of UTI should be treated (asymptomatic or symptomatic), guided by urine culture sensitivities for 3–7 days, with follow-up cultures 1 week later and at one other point before delivery. Antibiotics that are safe to use during pregnancy include ***penicillins*** (i.e. ampicillin, amoxicillin, penicillin V) and ***cephalosporins*** (i.e. cefaclor, cefalexin, cefotaxime, ceftriaxone, cefuroxime) (Table 15.2). Moderate to severe pyelonephritis or women with pyelonephritis who develop signs of preterm labour require hospital admission for IV antibiotics (cephalosporin or aminopenicillin) until apyrexial. This is followed by oral antibiotics to complete a total of 10–14 days of therapy and repeated cultures for the duration of pregnancy.

Table 15.2 Antibiotics to avoid in pregnancy*

Trimester	Antibiotic	Potential risk to the fetus
1,2,3	Tetracyclines	Effects on skeletal development and dental discol-oration (maternal hepatotoxicity)
1,2,3	Quinolones	Arthropathy
1,2,3	Chloramphenicol	Neonatal 'grey' syndrome in third trimester
1	Trimethoprim	Teratogenic risk (folate antagonist)
2,3	Aminoglycosides	Auditory or vestibular nerve damage
3	Sulphonamides	Neonatal haemolysis; methaemoglobinaemia
Avoid at term	Nitrofurantoin	Neonatal haemolysis

* See BNF for full details.

Of note, antibiotics which undergo excretion by glomerular filtration may need dose adjustment in pregnancy due to increased renal clearance of these drugs.

Hydronephrosis of pregnancy

Hydronephrosis is dilatation of the renal collecting system (pelvis and calyces). It can be associated with hydroureters (dilatation of the ureters) and represents a normal physiological event in pregnancy which is usually asymptomatic. Hydronephrosis develops from 6–10 weeks' gestation. By 28 weeks' gestation, 90% of pregnant women have hydronephrosis. The incidence appears to be higher in first pregnancies. It usually resolves within 2 months of delivery.

Anatomical causes

As the uterus enlarges, it rises out of the pelvis and rests upon the ureters, compressing them at the level of the pelvic brim. In addition, the ureters become elongation and mildly tortuous, with lateral displacement due to the gravid uterus. The right ureter is generally more dilated than the left due to extrinsic compression from the overlying congested right uterine vein and dextrorotation of the gravid uterus. The left ureter tends to be cushioned from compression by the colon. Ureteric dilatation tends to be from above the pelvic brim.

Physiological causes

Early onset of upper urinary tract dilatation is attributed to increased levels of progesterone, which causes smooth muscle relaxation. This mechanism, coupled with mechanical obstruction, contributes to the reduced peristalsis observed in the collecting system during pregnancy.

Diagnostic dilemmas

The hydronephrosis of pregnancy poses diagnostic difficulties in women presenting with flank pain thought to be due to a renal or ureteric calculi (see 📖 p. 488). To avoid using ionizing radiation in pregnant women, renal USS is often used as the initial imaging technique in those presenting with flank pain. In the non-pregnant patient, the presence of hydronephrosis is taken as surrogate evidence of ureteric obstruction. Because hydronephrosis is a normal finding in the majority of pregnancies, its presence ***cannot*** be taken as a sign of a possible ureteric stone. USS is an unreliable way of diagnosing the presence of stones in pregnant (and in non-pregnant) women. In a series of pregnant women, USS had a sensitivity of 34% (i.e. it 'misses' 66% of stones) and a specificity of 86% for detecting an abnormality in the presence of a stone (i.e. false positive rate of 14%).[1] Measurement of resistive index (RI)* (derived from measuring the velocity of intrarenal blood flow using Doppler) improves the sensitivity and specificity of the diagnosis of ureteric obstruction, along with attempts to visualize ureteric jets. Pregnant women with obstruction secondary to stones have a higher difference in RI between affected and unaffected kidneys than women with non-obstructive hydronephrosis. Colour Doppler and transvaginal USS enhance the diagnostic accuracy further. MRU is a second-line investigation for evaluating painful hydronephrosis in the second and third trimesters.

* Resistive index (RI) = peak systolic velocity (PSV) minus end-diastolic velocity (EDV) divided by peak systolic velocity (PSV) or RI = (PSV – EDV)/PSV.

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Chapter 16

Paediatric urology

Embryology: urinary tract

Following fertilization, a blastocyte (sphere of cells) is created, which implants into the uterine endometrium on day 6. The early embryonic disc of tissue develops a yolk sac and amniotic cavity, from which are derived the ectoderm, endoderm, and mesoderm. Organ formation occurs between 3 and 10 weeks' gestation. Most of the genitourinary tract is derived from the mesoderm.

Upper urinary tract

The ***pronephros*** (precursor of the kidney; *pro* = (Gk) before) is derived from an intermediate plate of mesoderm, which functions between weeks 1–4. It then regresses. The ***mesonephros*** (*meso* = (Gk) middle) functions from weeks 4–8 and is also associated with two duct systems—the mesonephric duct and adjacent to this, the paramesonephric duct (*para* = (Gk) beside) (Fig. 16.1a). The ***mesonephric (Wolffian) ducts*** develop laterally and advance downwards to fuse with the cloaca (Latin = sewer), a part of the primitive hindgut. By week 5, ureteric buds grow from the distal part of the mesonephric ducts and by a process of reciprocal induction, they stimulate the formation of the *metanephros* (permanent kidney; *meta* = (Gk) after) when they reach the renal tissue. Branching of the ureteric bud forms the ureter, renal pelvis, calyces, and collecting ducts. Glomeruli and nephrons (distal convoluted tubules, proximal convoluted tubules, and loop of Henle) are derived from metanephric mesenchyme (metanephros). During weeks 6–10, the caudal end of the fetus grows rapidly and the fetal kidney effectively moves up the posterior abdominal wall to the lumbar region. Urine production starts at week 10.

Thus, in both males and females, the mesonephric duct forms the ureters and renal collecting system. The paramesonephric duct essentially forms the female genital system (Fallopian tubes, uterus, upper vagina); in males, it regresses. The mesonephric ducts also form the male genital duct system (epididymis, vas deferens, seminal vesicles) and central zone of the prostate; in females, it regresses (see 📖 p. 648).

Lower urinary tract

Bladder

The mesonephric ducts and ureters drain into the cloaca. During weeks 4–6, the cloaca is subdivided into the *urogenital canal or sinus* (anteriorly) and the *anorectal canal* (posteriorly) by a process of growth, differentiation, and remodelling (Fig. 16.1b).[1] The bladder is formed by the upper part of the urogenital canal. Bladder smooth muscle (detrusor) is developed from adjacent pelvic mesenchyme. The trigone develops separately, arising from a segment of the mesonephric duct. The bladder dome is initially connected to the allantois, but this connection later regresses to become a fibrous cord (urachus).

Urethra

The inferior portion of the urogenital canal forms the entire urethra in females and the posterior urethra in males. Closure of the urogenital groove creates the male anterior urethra. The mesonephric ducts separate from the ureters (Fig. 16.1c) and travel caudally to join the posterior urethra in males (where they differentiate into the male genital duct system at 8–12 weeks).

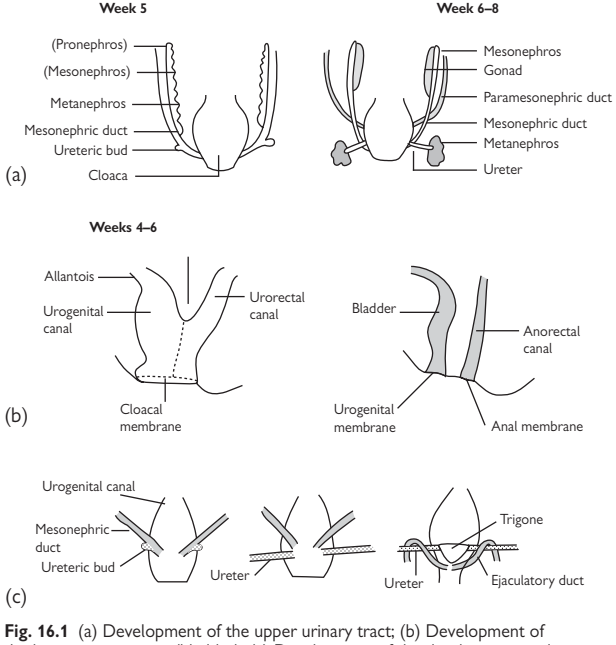

Fig. 16.1 (a) Development of the upper urinary tract; (b) Development of the lower urinary tract (bladder); (c) Development of the distal ureters and mesonephric ducts.

1 Penington EC, Hutson JM (2003) The absence of lateral fusion in cloacal partition. *J Paediatr Surg* **38**:1287–95.

Embryology: genital tract

Sexual differentiation and gonadal development is determined by the sex chromosomes (XY, male; XX, female). The gonads produce hormones which influence the subsequent differentiation of internal and external genitalia.

Both sexes

Gonads develop from the ***genital ridges*** (formed by cells of the mesonephros and coelomic epithelium). At 5–6 weeks, primordial germ cells migrate from the yolk sac to populate the genital ridges. Primitive sex cords are formed, which support germ cell (sperm and ova) development.

From 4 weeks, the ***mesonephric (Wolffian)*** *ducts* are incorporated into the genital system when renal function is taken over by the definitive kidney. At 6 weeks, coelomic epithelium creates the ***paramesonephric (Müllerian) ducts*** which develop laterally and are fused to the urogenital sinus at their bases.

Males

Embryos are genetically programmed to be female unless the ***testis-determining gene (SRY) is present, in which case the embryo will differentiate into a male. The SRY gene*** is located on the Y chromosome. It stimulates medullary sex cords in the primitive testis to differentiate into Sertoli cells which produce ***Müllerian inhibiting substance (MIS)*** at 7–8 weeks. The sex cords differentiate into seminiferous cords, which later form the seminiferous tubules of the testis within which the primordial germ cells differentiate into spermatogonia. MIS triggers regression of the paramesonephric ducts, testosterone secretion from Leydig cells of the testis, and the initial phase of testicular (abdominal) descent. The androgens testosterone and dihydrotestosterone (DHT) are responsible for masculinization of the fetus.

During weeks 8–12, the mesonephric ducts differentiate into the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts. Under the influence of DHT, proliferation and budding of the urethral endoderm gives rise to prostatic acini and glands and by a process of reciprocal induction, forms the prostatic capsule and smooth muscle from the surrounding mesenchyme (completed by week 15).

After week 23, the second androgen-dependent phase of testicular descent occurs. The testes rapidly descend from the abdomen (via the inguinal canal during weeks 24–28) and into the scrotal sac, aided by calcitonin gene-related polypeptide acting on the gubernaculum. The testis is enclosed in a diverticulum of peritoneum called the processus vaginalis. The distal part persists as the tunica vaginalis around the testis, the remainder usually regresses.

External genitalia develop from week 7. Urogenital folds form around the opening of the urogenital sinus and labioscrotal swellings develop on either side. The penile shaft and glans are formed by elongation of the genital tubercle and fusion of urogenital folds. The scrotum is created by fusion of labioscrotal folds.

Females (Figs. 16.2 and 16.3)

The genital ridge forms secondary sex cords (primitive sex cords degenerate) which surround the germ cells to create ovarian follicles (week 15). These undergo meiotic division to become primary oocytes which are later activated to complete gametogenesis at puberty. Oestrogen is produced from week 8 under the influence of the aromatase enzyme. In the absence of MIS, the mesonephric ducts regress and the paramesonephric ducts become the Fallopian tubes, uterus, and upper two-thirds of the vagina. The sinovaginal sinus is developed at the junction of the paramesonephric ducts and the urogenital sinus. This forms the lower third of the vagina.

The genital tubercle forms the clitoris; the urogenital folds become the labia minora and the labioscrotal swellings form the labia majora.

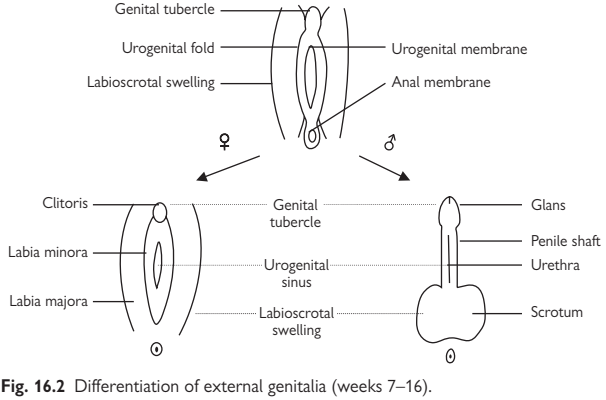

Fig. 16.2 Differentiation of external genitalia (weeks 7–16).

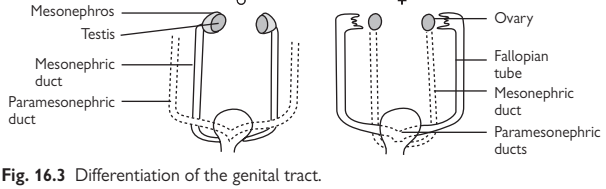

Fig. 16.3 Differentiation of the genital tract.

Undescended testes (UDT)

The first phase of testicular descent from the genital ridge to internal inguinal ring occurs under the influence of MIS acting on the gubernaculum (around 7–8 weeks' gestation). The second phase of testicular descent through the inguinal canal into the scrotum occurs at 24–28 weeks' gestation under the influence of testosterone. Failure of descent results in cryptorchidism or congenital UDT.

Incidence

Four percent at birth for a full-term neonate, however, many will spontaneously descend after birth and the incidence at 1y is 1.3–1.8%. The incidence of unilateral UDT is greater than bilateral UDT.

Classification

- **Retractile**: an intermittent active cremasteric reflex causes the testis to retract up and out of the scrotum.
- **Ectopic (<5%)**: abnormal testis migration below the external ring of the inguinal canal (to perineum, base of penis, or femoral areas) (Fig. 16.4).
- **Incomplete descent (~95%)**: testis may be intra-abdominal, intra-inguinal, or pre-scrotal (Fig. 16.4).
- **Atrophic/absent**.
- **Acquired UDT (or testicular ascent)**: testes that were down in the scrotum have ascended. Risk higher with retractile testes and a patent processus vaginalis. It occurs around 7–9y old and the incidence is 1–2%.[1] Approximately 20% will fail to return to the scrotum by puberty. Orchidopexy is recommended as the 'ascended' testis is at the same risk of degenerative changes as congenital UDT.

Risk factors

- Preterm infants (incidence at <30 weeks' gestation is 40%).
- Low birthweight or small for gestational age.
- Twins.
- Family history of UDT.

Aetiology

- Abnormal testis or gubernaculum (tissue that guides the testis into the scrotum during development).
- Endocrine abnormalities: low level of androgens, HCG, LH, calcitonin gene-related peptide, or MIS.
- Decreased intra-abdominal pressure (prune belly syndrome, gastroschisis).

Pathology

UDT demonstrate the degeneration of Sertoli cells, loss of Leydig cells, atrophy, and abnormal spermatogenesis. Male fertility depends on the transformation of gonocytes to dark adult spermatocytes within the first 3 months of post-natal life. This appears to be defective in UDT.

Long-term complications

- Relative risk of cancer is 8-fold higher in UDT. There is a 4% lifelong risk of cancer with an intra-abdominal testis. Majority are seminomas. There is a slightly increased risk of cancer in the contralateral, normally descended testis.
- Reduced fertility (paternity rate in unilateral UDT is 80–90% and in bilateral UDT is 45–65%). Paternity rates improve if orchidopexy is performed before 2y of age.
- Increased risk of testicular torsion or trauma.
- Increased risk of indirect inguinal hernias (due to a patent processus vaginalis).

Evaluation

Examine the scrotum and inguinal region to elucidate if a testis is palpable and to identify its location. Retractile testes may be brought back down into the bottom of the scrotum without tension. Assess for associated congenital defects. If neither testis is palpable, consider chromosome analysis (to exclude an androgenized female) and endocrine analysis (high LH and FSH with a low testosterone indicates anorchia, confirmed with serum inhibin B). For the impalpable testis, USS is of limited use. Most proceed directly to examination under anaesthetic ± diagnostic laparoscopy and treatment.

Treatment

- **Inguinal UDT**: is treated with orchidopexy between 6–18 months old. Surgery consists of inguinal exploration, mobilization of spermatic cord, ligation of processus vaginalis, and securing the testis into a dartos pouch in the scrotal wall. Risks include testicular atrophy (5%), damage to vas (1–2%), and re-ascent of the testis.
- **Intra-abdominal testes**: require a laparoscopic approach to mobilize the testis for orchidopexy as a single or 2-stage (Fowler–Stephens) procedure. The Fowler–Stephens approach involves initial clipping or division of spermatic vessels to provide extra length (the testis then relies on collateral blood flow from the vas). Six months later, the testis is then mobilized on its vas with its new collateral vessels and brought down into the scrotum. Success rates are ~85%. Intra-abdominal testes with a short vas may need microvascular autotransplantation. This involves high intra-abdominal ligation of the spermatic vessels, the testis is brought down into the scrotum, and the vessels are re-anastomosed to the inferior epigastric vessels. Small, atrophic intra-abdominal testes (nubbin) require orchidectomy ± orchidopexy of the contralateral normally descended testis.

Overall success rates of orchidopexy vary according to position of the UDT: 92% for inguinal testes, 87% for canalicular testes, and 74% for abdominal testes.[3]

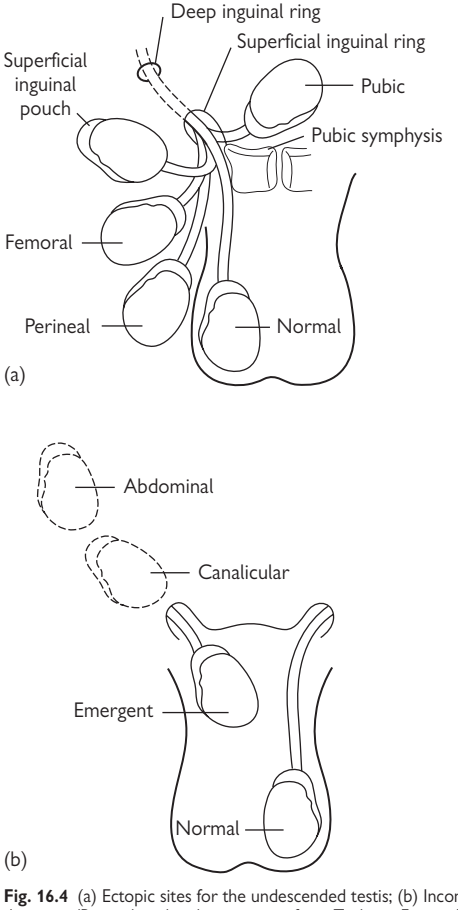

Fig. 16.4 (a) Ectopic sites for the undescended testis; (b) Incomplete descent of the testis (Reproduced with permission from Taylor & Francis Books, UK).

1 Hack WW, Sijstermans K, van Dijk J, *et al.* (2007) Prevalence of acquired undescended testis in 6-year, 9-year and 13-year-old Dutch schoolboys. *Arch Dis Child*;**92**:17–20.

2 Brewster S, Cranston D, Noble J, Reynard J (2001) *Urology a Handbook for Students*. BIOS Scientific Publishers Limited.

3 Docimo SG (1995) The results of surgery for cryptorchidism: a literature review and analysis. *J Urol* **154**:1148–52.

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Urinary tract infection (UTI)

Definitions: UTI is a bacterial infection of the urine, which may involve the lower urinary tract/bladder (cystitis) or upper urinary tract/kidney (pyelonephritis) (see 📖 p. 176).

Classification: children may be asymptomatic or symptomatic.

Simple UTI: presents with mild dehydration and pyrexia.

Severe UTI: presents as fever ≥38°C, unwell, vomiting, with moderate to severe dehydration.

Atypical UTI: includes features of serious illness/septicaemia, poor urinary flow, abnormal renal function, failure to respond to treatment in <48h, and non-*E. coli* infection.

Recurrent UTI: in children, describes either one episode of cystitis with one episode of pyelonephritis, ≥2 episodes of pyelonephritis, or ≥3 episodes of cystitis. It may be due to bacterial persistence, unresolved infection, or re-infection.

Incidence: up to age 1, the incidence in boys is higher than girls (male: female ratio is 3:1), but thereafter, the incidence in girls becomes greater (school age males 1%; females 3%).

Pathology: common bacterial pathogens are *E. coli*, Enterococcus, *Pseudomonas*, *Klebsiella*, *Proteus*, and *S. epidermidis*. Bacteria enter via the urethra to cause cystitis and ascending infection causes pyelonephritis. Alternatively, there can be haematogenous spread from other systemic infections.

Risk factors

- **Age**: neonates and infants have increased bacterial colonization of the periurethral area and an immature immune system.
- **VUR** (see 📖 p. 662).
- **Previous UTI**.
- **Genitourinary abnormalities**: pelvi- or vesicoureteric obstruction, ureterocele, posterior urethral valves, labial adhesions.
- **Voiding dysfunction**: abnormal bladder activity, compliance or emptying.
- **Gender**: female > male after 1y old.
- **Foreskin**: uncircumcised boys have a 10-fold higher risk of UTI in the first year due to bacterial colonization of the glans and foreskin.
- **Faecal colonization**: contributes to perineal bacterial colonization.
- **Chronic constipation**.

Presentation

- **Neonates and infants:** fever, irritability, vomiting, lethargy, diarrhoea, poor feeding, failure to thrive, abdominal pain, offensive urine, haematuria.
- **Children:** fever, nausea, suprapubic pain, dysuria, frequency, voiding difficulties, changes to continence, abdominal or flank pain, haematuria.

Investigation

Urine analysis and culture: advised with unexplained fever ≥38°C or if symptomatic of UTI. Clean catch specimen where possible. In toilet-trained children, an MSU specimen is considered diagnostic with $\geq 10^5$ colony-forming units (CFU)/mL in asymptomatic children and $\geq 10^4$CFU/mL if symptomatic. In young children, a catheterized urine specimen with ≥10CFU/mL) of one pathogen or a suprapubic aspirate with $\geq 10^2$CFU/mL are diagnostic of UTI. Collection bag specimens are less reliable due to skin flora contamination.

Imaging: refer to NICE recommendations (Tables 16.1–16.3).[1]

- USS is the first-line investigation. It identifies bladder and kidney abnormalities (hydronephrosis, stones).
- DMSA renogram can demonstrate and monitor renal scarring.
- MCUG detects urethral and bladder anomalies (anatomical and functional), VUR, and ureteroceles.

Management

Infants <3 months (and children at risk of serious illness): are managed according to the 'feverish illness in children' guidelines.[2] For children aged 3 months to 3y, antibiotics are recommended (before urine culture results are available) for specific symptoms of UTI and for non-specific symptoms where the risk of intermediate to serious infection is high (i.e. associated anatomical or functional abnormality).[2] In children older than 3y, antibiotics are indicated if urine dipstick analysis is positive for nitrites ± leukocyte esterase or if there is good clinical evidence of UTI.

Infants <3 months: paediatric referral and treat with IV antibiotic such as third-generation cephalosporin (cefotaxime or ceftriaxone).[2]

Infants and children >3 months with pyelonephritis: paediatric referral; 7–10 days of oral cephalosporin or co-amoxiclav or IV cefotaxime or cefriaxone for 2–4 days followed by oral antibiotics for a total of 10 days.

Infants and children >3 months with cystitis: oral antibiotics for 3 days (trimethoprim, nitrofurantoin, cephalosporin, or amoxicillin), and reassess. ***The choice of antibiotics should be directed by local hospital guidelines.***

Asymptomatic bacteriuria does not require antibiotics or routine follow-up. Antibiotic prophylaxis is not recommended following a first-time simple UTI, but can be considered after recurrent symptomatic UTI.[3] Advice on preventing UTI should be given, including good intake of fluids, regular voiding, and treatment of constipation.

Follow-up: recurrent UTI or abnormal imaging requires paediatric assessment. Long-term follow-up is needed for bilateral renal anomalies, impaired renal function, hypertension, and/or proteinuria. Follow-up should include recordings of growth (height, weight), BP, and urine dipstick testing.

Table 16.1 Recommended imaging regimen for infants <6 months[1]

Imaging	Responds well to treatment <48h	Atypical UTI	Recurrent UTI
USS during UTI	No	Yes	Yes
USS within 6 weeks	Yes	No	No
DMSA 4–6 months following UTI	No	Yes	Yes
MCUG	No	Yes	Yes

Table 16.2 Recommended imaging regimen for infants/children 6 months to 3y[1]

Imaging	Responds well to treatment <48h	Atypical UTI	Recurrent UTI
USS during UTI	No	Yes	No
USS within 6 weeks	No	No	Yes
DMSA 4–6 months following UTI	No	Yes	Yes
MCUG	No	No	No*

* MCUG may be considered for hydronephrosis, poor urinary flow, family history of VUR, or non-*E. coli* UTI.

Table 16.3 Recommended imaging regimen for children >3y[1]

Imaging	Responds well to treatment <48h	Atypical UTI	Recurrent UTI
USS during UTI	No	Yes	No
USS within 6 weeks	No	No	Yes
DMSA 4–6 months following UTI	No	No	Yes
MCUG	No	No	No

1 National Institute for Health and Excellence (2007) Urinary tract infection: diagnosis, treatment and long-term management of urinary tract infection in children [online]. Available from: http://www.nice.org.uk/CG54.

2 National Institute for Health and Excellence (2007) Feverish illness in children—assessment and initial management in children younger than 5 years [online]. Available from: http://www.nice.org.uk/CG047.

3 Williams G, Craig JC (2011) Long-term antibiotics for preventing recurrent urinary tract infection in children. *Cochrane Database Syst Rev* **3**:CD001534.

Antenatal hydronephrosis

Definition

Generally defined as a maximal anteroposterior renal pelvis diameter (RPD) of ≥5mm on antenatal USS.

Incidence

The incidence of antenatal hydronephrosis (RPD ≥5mm) is approximately 0.6% on second trimester (20 weeks' gestation) USS. The incidence of antenatal USS-detected congenital anomalies of the urinary tract is 0.1–4%. An increasing degree of hydronephrosis is related to increased risk of urinary tract pathology and requirement for surgery.[1,2] However, in around 65%, antenatal hydronephrosis will resolve and overall, <5% will require nephrological or surgical intervention.[3]

Aetiology

Causes include transient hydronephrosis (48%), physiological hydronephrosis (15%), PUJO, VUR, megaureter, multicystic dysplastic kidney (MCDK), renal cysts, posterior urethral valves (PUV), ectopic ureter, and ureterocele (also see Table 16.4).[3]

Table 16.4 Clinically significant causes of antenatal hydronephrosis[3]

Cause	Incidence (%)	USS features
PUJO (see 📖 p. 672)	11	Most have RPD >15mm with no ureteric dilatation. Bilateral in 10–40%
VUR (see 📖 p. 662)	9	Ureter dilated to bladder ± dilatation of pelvicalyceal system
Mega ureter (see 📖 p. 666)	4	Dilated ureter >7mm; left side affected more commonly than right side
MCDK (see 📖 p. 676)	2	Kidney is replaced by cysts of varying size; 30% risk of abnormality in the contralateral kidney, i.e. PUJO, VUR
Ureterocele (see 📖 p. 670)	2	Cystic area in the bladder, usually associated with a duplex kidney and hydronephrosis due to obstruction or reflux
PUV (see 📖 p. 674)	1	Bilateral hydroureteronephrosis and distended, thick-walled bladder, dilated posterior urethra, oligohydramnios, and pulmonary hypoplasia

Antenatal management

- 20 weeks' gestation USS. If necessary, repeat the scan to observe for changes when the bladder empties. Note the gender of fetus.
- Repeat USS later in pregnancy if hydronephrosis to assess for persisting or increasing renal dilatation.
- Antenatal counselling to discuss differential diagnosis, prognosis, and investigations required post-natally. Particularly important for BOO (i.e. PUV), unilateral RPD >30mm, bilateral RPD >15mm, MCKD, and ureterocele.
- Arrange delivery at an appropriate centre for cases requiring specialist intervention (i.e. with paediatric urology, nephrology, and neonatal ITU on site).

General principles of post-natal management

Specific post-natal investigation and management will depend on the underlying diagnosis and severity of hydronephrosis and are described individually later in this chapter. The important principles of post-natal management include:

- Clinical assessment, including BP reading. Examine for a palpable bladder (PUV), abdominal mass (PUJO, MCKD).
- Start prophylactic antibiotics immediately (trimethoprim 2mg/kg daily) until the diagnosis is established. Exceptions to this include: RPD <10mm and normal calyces (give UTI advice); MCDK with normal contralateral kidney and ectopic kidney with no dilatation.
- Renal function blood tests (particularly if distended bladder, ureterocele, bilateral hydronephrosis, and unilateral hydronephrosis in a solitary kidney).

Imaging

- **Post-natal USS**: generally recommended at 1 and 6 weeks' post-natal,[3] although it can be delayed longer for lower risk anomalies. If possible, avoid USS in the first 48h post-delivery as normal urine output is only established after this time. Exceptions that require immediate USS are conditions with obstruction needing urgent surgery—PUV and ureterocele.
- **MCUG**: is deferred until the child is older (~3-6 months) unless there is an urgent clinical indication (BOO/PUV) where it is performed as soon as possible after birth. Other indications for MCUG include duplex kidney, ureterocele, and renal scarring,[4] where it is used to detect associated VUR.
- **DMSA**: is a static scan which provides an accurate measurement of renal split function. It is used to confirm non-function of multicystic kidney, differential function of upper and lower moieties of a duplex kidney, and renal damage associated with VUR and UTI (renal cortical scarring). It is performed at 6–12 weeks old.
- **MAG3**: is a dynamic scan used to identify obstruction where there is no demonstrable reflux and significant hydronephrosis persists (RPD >10mm). Usually deferred until the infant is 6–12 weeks old. It also provides an approximation of renal split function and is particularly useful for the diagnosis of PUJO.

Consider urgent referral to paediatric urology for:
- BOO (PUV).
- Ureterocele associated with obstruction or infection.

Consider referral to paediatric nephrology or urology for:
- Bilateral RPD >15mm with no reflux.
- Non-refluxing megaureters.
- Dilatation of a solitary kidney.
- Dilatation of any moiety of a duplex kidney.
- Unilateral RPD >30mm.
- Progressive increase in dilatation or cortical thinning.
- Differential function <40%.
- Development of symptoms such as pain/UTI.

(Please refer to local hospital guidelines as these will differ between different hospitals and tertiary centres.)

1 Passerotti CC, Kalsih LA, Chow J, *et al.* (2011) The predictive value of the first postnatal ultrasound in children with antenatal hydronephrosis. *J Pediatr Urol* **7**:128–36.

2 Grignon A, Filiom R, Filiatrault D, *et al.* (1986) Urinary tract dilatation *in utero*. Classification and clinical application. *Radiology* **160**:645–7.

3 Woodward M, Frank D (2002) Postnatal management of antenatal hydronephrosis. *BJU Int* **89**:149–56.

4 Mears AL, Raza SA, Sinha AK, Misra D (2007) Micturating cystourethrograms are not necessary for all cases of antenatally diagnosed hydronephrosis. *J Pediatr Urol* **3**:264–7.

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Vesicoureteric reflux (VUR)

Definition: VUR results from abnormal retrograde flow of urine from the bladder into the upper urinary tract.

Epidemiology: overall incidence in children is 1–2%; younger > older; girls > boys (female : male ratio = 5:1); Caucasian > Afro-Caribbean. The offspring of an affected parent has up to 70% incidence of VUR; siblings of an affected child have 30% risk of reflux. Screening of offsprings and siblings is controversial and many would only recommend it if there is significant renal scarring in the index case.

Pathogenesis: the ureter passes obliquely through the bladder wall (1–2cm) where it is supported by muscular attachments which prevent urine reflux during bladder filling and voiding. The normal ratio of intramural ureteric length to ureteric diameter is 5:1. Reflux occurs when the intramural length of ureter is too short (ratio <5:1) (Paquin's law). The degree of reflux is graded I–V (see 📖 p. 408; Fig. 8.3). The appearance of the ureteric orifice changes with increasing severity of reflux, classically described as stadium, horseshoe, golf hole, or patulous.

Classification

- **Primary reflux**: results from a congenital abnormality of the VUJ. An anatomical cause is seen with duplex kidneys (and ureters). The Weigert–Meyer rule states the lower moieity ureter enters the bladder proximally and laterally, resulting in a shorter intramural tunnel which predisposes to reflux (see 📖 p. 423; Fig. 8.10). A genetic cause is also recognized.
- **Secondary reflux**: results from urinary tract dysfunction associated with elevated intravesical pressures, creating damage to the VUJ. Causes include: PUV (reflux seen in 50%), urethral stenosis, neuropathic bladder, DSD. Inflammation associated with infection (acute cystitis) can also distort the VUJ, causing reflux. Treatment is of the underlying condition.

Complications

VUR (associated with UTI) can result in reflux nephropathy and renal scarring, causing hypertension (10–20%) and rarely, progressive renal failure.

Presentation

Symptoms of UTI (fever, dysuria, suprapubic and abdominal pain), failure to thrive, vomiting, diarrhoea. It is important to elicit associated symptoms and signs of bladder and/or bowel dysfunction: urinary frequency, urgency, prolonged voiding intervals, daytime wetting, holding manoeuvres to prevent wetting, and constipation.

Investigation

- Baseline measurements: height, weight, BP as well as serum creatinine if there are bilateral renal cortical abnormalities.
- Urine analysis to assess for bacteriuria and proteinuria.
- Urine culture if evidence of UTI.
- Renal tract USS initially and then annually, as indicated.

- DMSA renogram to detect and monitor associated renal cortical scarring (most likely in grades III–V reflux, younger children, recurrent febrile UTI, and underlying renal tract abnormality on USS).
- MCUG to diagnose and grade reflux, establish reversible causes, and follow-up after 12–24 months to assess for resolution of higher grade VUR treated conservatively and after endoscopic treatment (Fig. 16.5).
- (Video)urodynamics if suspicious of voiding dysfunction.

Management

The majority of primary VUR grades I–II will resolve spontaneously (80%),[1] with overall 50% resolution in grades III–V.[2] Reflux tends to improve with age as the length of the intramural ureter increases with growth (Table 16.5). General advice includes good fluid intake, regular voiding, perineal hygiene, treatment of constipation, and use of probiotics. Provide parents with UTI advice and emphasize the need to seek medical attention early if the child has an unexplained febrile illness or suspected UTI. It is important to treat any coexisting bladder or bowel dysfunction.

Medical treatment

The need for antibiotic prophylaxis in VUR remains controversial. A NIH randomized placebo-controlled study of children with VUR (RIVUR Study) aims to further investigate this. The Swedish reflux trial in children has reported that prophylactic antibiotics and endoscopic surgery decreases (febrile) infection rates in girls, but not in boys, as compared to surveillance alone.[3]

Currently, low-dose antibiotic prophylaxis is given to keep the urine sterile and lower the risk of renal damage in young children (≤1y old) with a history of febrile UTI[4] and until reflux resolves in higher grades of VUR (III–V). Whilst on treatment, growth, BP, and urine should be monitored (for proteinuria and bacteriuria), with an annual renal tract USS. If the child remains well, antibiotics may be discontinued when they are toilet-trained (dry day and night). If febrile UTI recurs after conservative or surgical resolution of VUR, reinvestigate for bladder dysfunction and recurrence of VUR.[4] Longer term follow-up into adolescence is recommended if there is any renal abnormality on USS or DMSA, even if VUR has resolved.[4]

Surgery

Indications for surgery include: high-grade VUR (girls benefit more than boys), breakthrough febrile UTI despite antibiotic prophylaxis, and non-compliance with medical therapy. Circumcision reduces the risk of UTI in boys with VUR[5] and is used for those with anatomical anomalies and recurrent or breakthrough UTI.

Surgical techniques include endoscopic injection, ***ureteric re-implantation performed by open surgery*** (98% success) or ***laparoscopically***. Endoscopic injection of Deflux® is the first-line surgical treatment. Indications for ureteric re-implantation include failure of Deflux®, duplex renal system, and renal ectopia.

Endoscopic injection

Deflux® is a hyaluronic acid/dextranomer bulking agent which is injected intramurally within the distal ureter and also at the ureteric orifice ('HIT'

technique) with 80–90% success rates, although recent studies have suggested that repeat treatments may be required.[6] Deflux® is most effective for VUR grades I–III. It has replaced the traditional subtrigonal injection ('STING') of bulking agent (collagen) into the ureteric orifice.

Open surgery

- **Intravesical methods**: involve opening the bladder, mobilizing the ureter and advancing it across the trigone (Cohen repair), or reinsertion into a higher, medial position in the bladder (Leadbetter–Politano repair). The aim is to place the mobilized ureter into a submucosal tunnel whose total length is five times the diameter of the ureter in order to prevent further reflux. Success rates with open surgery are around 98%.
- **Extravesical techniques**: involve suturing the distal ureteric end directly onto the bladder and constructing a tunnel of detrusor muscle around it (Lich–Gregoir procedure).

Table 16.5 Example of the percentage incidence and spontaneous resolution of VUR according to grade[7]

Grade of VUR	Incidence (%)	Spontaneous resolution (%)
I	7	83
II	54	60
III	31	46
IV	6	9
V	2	0

1 Arant BS Jr (1992) Medical management of mild and moderate vesicoureteric reflux: follow-up studies of infants and young children. A preliminary report of the Southwest Pediatric Nephrology Study Group. *J Urol* **148**:1683–7.

2 Smellie JM, Jodal U, Lax H, *et al.* (2001) Outcome at 10 years of severe vesicoureteric reflux managed medically: report of the International Reflux Study in Children. *J Pediatr* **139**:656–63.

3 Brandström P, Esbjömer E, Herthelius M, *et al.* (2010) The Swedish reflux trial in children: III. Urinary tract infection pattern. *J Urol* **184:**286–91.

4 Peters CA, Skoog SJ, Arant BS, *et al.* (2010) Summary of the AUA Guideline on management of primary vesicoureteric reflux in children. *J Urol* **184**:1134–44.

5 Singh-Grewal D, Macdessi J, Craig J (2005) Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. *Arch Dis Child* **90**:853–8.

6 Holmdahl G, Brandström P, Läckgren G, *et al.* (2010) The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. *J Urol* **184:**280–5.

7 Skoog SJ, Belman AB, Majd M (1987) A nonsurgical approach to the management of primary vesicoureteric reflux. *J Urol* **138**:941–6.

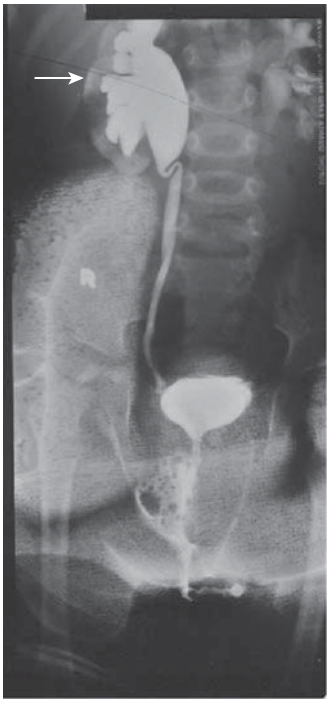

Fig. 16.5 MCUG demonstrating grade III VUR and intrarenal reflux (shown by arrow) in a child. Image kindly provided with permission from Professor S. Reif.

Megaureter

Classification

Megaureter is the term for a dilated ureter, usually larger than 7mm in diameter, which may be a primary condition or secondary to another underlying problem. It can be classified into four different groups:

- Obstructed.
- Refluxing.
- Non-refluxing, non-obstructed.
- Refluxing and obstructed.

Primary megaureter can be refluxing or obstructed and is associated with either a simplex renal system or a duplex. Obstruction is due to either a stenotic or aperistaltic distal ureter, which results in a dilated and tortuous ureter proximally.

Secondary megaureter may be:

- Unilateral—secondary to obstruction or scarring from stones and tumour or following ureteric surgery (i.e. subtrigonal injection of bulking agent around the ureteric orifice, 'STING').
- Bilateral cases are due to BOO (i.e. PUV), prune belly syndrome, and neuropathic bladder dysfunction.

Incidence

Megaureter affects approximately 1 in 2000 children. Males are more commonly affected than females; the left ureter is more commonly affected than the right side.

Presentation

Megaureter is the underlying cause for prenatal ultrasound-detected fetal hydronephrosis in around 4% of cases,[1] associated with a dilated ureter (>7mm) (see 📖 p. 658). After birth, UTI is the most common presentation. When associated with an undetected obstructed megaureter, this may present as urosepsis with an infected, obstructed system, which is a urological emergency and requires urgent decompression and antibiotics.

Investigation

- **Renal tract USS**: should be performed within the first post-natal week to assess for the persistence of ureteric dilatation. Repeat USS checks will then be guided by the underlying diagnosis, i.e. if there is no renal compromise or obstruction, at 6 weeks, and again at 1y.
- **MCUG**: is performed early if there is concern of obstruction (i.e. BOO), otherwise deferred until the infant is 3–6 months old. It can help to distinguish between obstruction and reflux and may also identify the cause of obstruction.
- **MAG3 renogram**: provides a measurement of split renal function and helps to differentiate between obstructed and non-obstructed megaureter. An ipsilateral PUJ obstruction may be identified in 13%. It is usually performed 6–12 weeks after delivery.

Conservative management

Empirical treatment is to start antibiotic prophylaxis at birth whilst the diagnosis is being established (trimethoprim 2mg/kg daily). If the differential renal function is >40%, patients can be managed with expectant or conservative treatment and follow-up renal tract USS. If the ureteric dilatation resolves or improves and the child remains well, they may be discharged at the age of 5 with UTI advice. Prophylactic antibiotics can be continued if infection is a feature, however, recurrent, breakthrough, or severe UTI would be an indication for surgical intervention.

Surgical treatment

Up to 12 months old

Endoscopic or open cystotomy and insertion of a ureteric stent is the procedure of choice in this young age group. Definitive surgical correction with ureteric re-implantation is deferred until after 6 to 12 months old if possible as this is associated with less morbidity and better outcomes.

After 12 months old

The aims of surgery are to excise the stenotic or aperistaltic distal ureteric segment and perform an intravesical ureteric re-implantation with a Cohen repair, bringing the ureter across the trigone in a submucosal tunnel.

For more severely dilated and capacious ureters, it is often necessary to taper the ureter before re-implantation. This can be achieved by placation of the ureter (Starr technique), folding of the ureter (Kalicinski technique), or by ureteric excision. The choice of re-implantation surgery is then a Leadbitter–Politano repair which has the advantage of creating a longer anti-refluxing submucosal tunnel. This is often coupled with a psoas hitch to help prevent kinking and further obstruction of the ureter. For bilateral cases of megaureter, a transureteroureterostomy can be performed. Here, one ureter is excised distally and attached to drain into the contralateral ureter so only one ureter drains urine from both kidneys into the bladder. This ureter can then be plicated and re-implanted as before. Nephroureterectomy is indicated if the megaureter is associated with a non-functioning or poorly functioning kidney.

Follow-up after surgery

Renal tract USS and MAG3 renogram should be performed after 1y to reassess the degree of ureteric dilatation and for pelvicalyceal dilatation. Prophylactic antibiotics may be continued in children with persistent reflux, but can be stopped once the child is fully toilet-trained if they remain well.

1 Woodward M, Frank D (2002) Postnatal management of antenatal hydronephrosis. *BJU Int* **89**:149–56.

Ectopic ureter

An ectopic ureter is caused by the ureteric bud which arises from an abnormal (high or low) position on the mesonephric duct during embryological development. There is a direct correlation between the location of the ectopic ureter and the degree of ipsilateral renal hypoplasia or dysplasia.[1] Eighty percent is associated with a duplicated collecting system. A duplex kidney has an upper and a lower moiety, each with its own renal pelvis and ureter. The two ureters may join to form a single ureter or they may pass down individually to the bladder (complete duplication). In this case, the upper renal moiety ureter always opens onto the bladder below and medial to the lower moiety ureter (***Weigert–Meyer rule***), predisposing to ectopic placement of the ureters and ureteric orifices (see 📖 p. 423; Fig. 8.10).

Incidence: about 1 in 2000. Female to male ratio is ≥3:1. Most ectopic ureters in females are associated with a duplex kidney whereas most ectopic ureters in males are associated with a single renal system.

Other drainage sites of ectopic ureters

- **Females:** bladder neck, urethra, vagina, vaginal vestibule, uterus.
- **Males:** posterior urethra, seminal vesicles, ejaculatory duct, vas deferens, epididymis, bladder neck.

Presentation

May present with an antenatal diagnosis of hydronephrosis and dilated ureter to the bladder. Later presentations include acute or recurrent UTI. Obstruction of the ectopic ureter can lead to hydroureteronephrosis which may present post-natally as an abdominal mass or pain.

- **Females:** when the ureteric opening is below the urethral sphincter, girls present with persistent vaginal discharge or incontinence despite successful toilet training.
- **Males:** the ureter is always sited above the external urethral sphincter so boys do not develop incontinence. UTIs may trigger epididymitis (usually recurrent).

Investigation

- **Post-natal USS**: may demonstrate ureteric dilatation and hydronephrosis. USS is performed immediately if obstruction is suspected (i.e. ectopic ureter associated with ureterocele), otherwise it is performed at week 1 and 6 post-natally.
- **MCUG**: is used to assess whether there is reflux into the ectopic ureter (or lower renal moiety).
- **MAG3 renogram**: is used when MCUG has excluded reflux and is used to investigate for obstruction and estimate split renal function.
- **DMSA renogram**: is used to assess split renal function and differential function between upper and lower pole moieties of a duplex kidney to help plan surgery. Assesses for renal cortical scars when reflux is present.
- **Cystourethroscopy**: may identify the ectopic ureteric orifice.
- **MRU**: identifies duplex systems and gives information on upper and lower renal moieties.

Treatment

Commence prophylactic trimethoprim (2mg/kg daily) whilst conducting post-natal investigation. An ectopic ureter without an ureterocele, but associated with upper renal moiety dilatation, requires urgent treatment to decompress the system and avoid the, complication of an infected, obstructed system (pyoureteronephrosis).

Management is mainly expectant if there are no symptoms and no evidence of acute obstruction or dilatation. Where an ectopic ureter is associated with a poorly functioning renal upper pole moiety or single-system kidney, surgery is an option. This includes open or laparoscopic upper moiety heminephrectomy or total nephrectomy with excision of the associated ureter. Ureteropyelostomy and uretero-ureterostomy can be considered in duplex systems where the upper renal pole has reasonable function. Where some useful function is retained in a single-system kidney, the distal ureter can be resected and re-implanted into the bladder.

1 Mackie GG, Stephens FD (1975) Duplex kidneys: a correlation of renal dysplasia with position of the ureteric orifice. *J Urol* **114**:274–80.

Ureterocele

Definition: an ureterocele is a cystic dilatation of the distal ureter as it drains into the bladder.

Incidence: 1 in 5000–12,000 clinical paediatric admissions[1] (although 1 in 500 are found at autopsy).[2] Female to male ratio is 4:1, predominantly affecting Caucasians. Ten percent of ureteroceles are bilateral.

Classification

Ureteroceles may be associated with a single or duplex renal system. Eighty percent are associated with the upper moiety of a duplex kidney.

They are further classified into intravesical or extravesical ureteroceles.

Intravesical (20%): the ureterocele is completely confined within the bladder. These tend to be associated with single systems and are more common in males. Subtypes include:

- **Stenotic**: small, stenotic ureteric orifice associated with obstruction.
- **Non-obstructed**: large ureteric orifice that tends to balloon open when filled by peristalsis of urine.

Extravesical (or ectopic) (80%): when the ureterocele extends to the bladder neck or urethra and tend to occur with duplex systems; most commonly in females. Subtypes include:

- **Sphincteric**: ureterocele extends into bladder neck and urethra. The orifice is wide and usually opens proximal to the external sphincter.
- **Sphincterostenotic**: similar to sphincteric ureterocele, but the ureteric orifice is stenosed.
- **Cecoureterocele**: ureterocele prolapses posterior to the urethra and anterior to the vagina, but the orifice is within the bladder (affects girls only). Can cause urethral obstruction.
- **Blind ectopic**: similar to sphincteric, but no ureteric orifice.

Presentation: most present with antenatal hydronephrosis. Later presentation in infants may be with symptoms of UTI, an abdominal mass, or pain. Association with ureteric duplication increases the risk of reflux and reflux nephropathy. Extravesical ureteroceles can also cause BOO and bilateral hydroureteronephrosis (urological emergency) or ureteric obstruction and unilateral hydroureteronephrosis, which require urgent assessment and intervention. A prolapsing ureterocele can present as a vaginal mass in girls.

Investigation

- **USS renal tract:** shows a thin-walled cyst in the bladder often associated with a duplex system and ectopic (dilated) ureter. If there are concerns about obstruction, USS should be performed immediately after birth with a view to urgent surgical treatment.
- **MCUG**: can identify ureterocele location, size, and associated VUR (reflux into the lower moiety of an associated duplex kidney is seen in 50%). This should be performed early in the post-natal period if there is evidence of BOO, otherwise defer 3–6 months.

- **MAG3 renogram**: is used to exclude obstruction.
- **DMSA renogram**: is used to assess renal moiety function and demonstrate renal cortical abnormalities in the presence of reflux.
- **Cystoscopy**: can be used for diagnosis and endoscopic treatment.

Treatment

Commence prophylactic antibiotics at birth (trimethoprim 2mg/kg daily). Urgent surgical intervention is required for obstruction.

- **Endoscopic incision/puncture**: emergency treatment for infected or obstructed ureteroceles. Puncture is also indicated for elective management of intravesical ureteroceles with normal renal function. Rarely, these may require further surgery, including ureterocele excision and ureteric re-implantation to preserve renal function and prevent reflux.
- **Uretero-ureterostomy or uretero-pyelostomy (from upper to lower pole moiety)**: option for ectopic ureteroceles associated with a duplex system, with good function in the upper moiety and no reflux in the lower moiety.
- **Upper pole heminephrectomy**: option for ectopic ureterocele associated with a duplex system with poor function in the upper moiety and no reflux in the lower moiety.
- **Upper pole heminephrectomy, ureterocele excision, and ureteric re-implantation**: option for ectopic ureterocele associated with a duplex system with poor function in the upper moiety and reflux in the lower moiety.
- **Nephroureterectomy**: indicated for significant lower moiety reflux with poor function in both renal moieties or for poor renal function in single system.

1 Malek RS, Kelalis PP, Burke EC, *et al.* (1972) Simple and ectopic ureterocele in infants and childhood. *Surg Gynaecol Obst* **134**:611–6.

2 Uson AC, Lattimer JK, Melicow MM (1961) Ureteroceles in infants and children: a report based on 44 cases. *Pediatrics* **27**:971–7.

Pelviureteric junction (PUJ) obstruction

Definition: a blockage of the ureter at the junction with the renal pelvis, resulting in a restriction of urine flow.*

Epidemiology: childhood incidence is estimated at 1 in 1000. Boys are affected more than girls (ratio 2:1 in newborns). The left side is more often affected than the right side (ratio 2:1). They are bilateral in 10–40%.

Aetiology

In children, most PUJ obstruction is congenital. ***Intrinsic*** obstruction may be due to aberrant development of ureteric/renal pelvis muscle, aberrant insertion of the ureter into the renal pelvis, abnormal collagen, or ureteric folds or polyps. ***Extrinsic*** causes include compression of the PUJ by aberrant crossing vessels. Coexisting VUR is found in up to 25%.

Presentation

PUJ obstruction is the most common cause of hydronephrosis (without ureteric dilatation) found on antenatal USS. Infants may also present with an abdominal mass, UTI, and haematuria. Older children present with flank or abdominal pain (exacerbated by diuresis), UTI, nausea and vomiting, and haematuria following minor trauma.

Investigation

If prenatal USS has shown a large or bilateral hydronephrosis, a follow-up renal tract USS should be performed soon after birth. If there is a prenatal unilateral hydronephrosis (and the bladder is normal), the scan is deferred until day 3–7 (to allow normal physiological diuresis to occur, which may spontaneously improve or resolve the hydronephrosis). MAG3 renogram is performed at 6–12 weeks for diagnosis and to assess split renal function. Significant obstruction is unlikely if the anteroposterior renal pelvis diameter is <15mm.

Treatment

Conservative: infants are placed on prophylactic trimethoprim (2mg/kg daily) until the diagnosis is established. Children may be observed with USS and MAG3 renogram if they remain stable, with good renal function and no other complications (such as infection or stones).

Surgery: pyeloplasty is indicated if children are symptomatic, have a significant hydronephrosis (>30mm AP renal pelvis diameter) or impaired split renal function (<40%). Techniques include open or laparoscopic Anderson–Hynes dismembered pyeloplasty. Success rates are around 90–95%. Postoperative follow-up is with USS (± MAG3 renogram). Where renal function is poor (<10–15%) on the side of the PUJ obstruction, options include temporary percutaneous drainage or ureteric stent to assess the potential for recovery (i.e. suggesting a pyeloplasty could improve function) or nephrectomy where the impairment is severe or irreversible.

* Of note, pelviureteric junction (PUJ) is also referred to as ureteropelvic junction (UPJ).

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Posterior urethral valves (PUV)

PUV are derived from an abnormal congenital membrane arising from the verumontanum and attaching obliquely to the anterior urethra (beyond the external urethral sphincter), resulting in lower urinary tract obstruction. An alternative term is COPUM or congenital obstructive posterior urethral membrane. Urethral instrumentation or spontaneous partial rupture of the membrane is thought to cause the classical appearance of two valve-like folds in the prostatic urethra.

Incidence: 1 in >5000 males.

Pathology: PUV may arise through an abnormal insertion of the Wolffian ducts into the urogenital sinus during fetal development.

Presentation

Prenatal USS: the majority are diagnosed prenatally, with 60% identified on USS at 20 weeks. They account for 1% of cases of antenatal hydronephrosis. Features include: bilateral hydroureteronephrosis, dilated and thick-walled bladder, dilated posterior urethra (keyhole sign), thick-walled bladder, oligohydramnios (reduced amniotic fluid), and renal dysplasia. Early diagnosis is associated with poor prognosis.

Newborn and infants: respiratory distress secondary to pulmonary hypoplasia, palpable abdominal mass (hydronephrotic kidneys or distended bladder), ascites, UTI sepsis, electrolyte abnormalities (renal impairment), failure to thrive.

Older children: milder cases may present later with recurrent UTI, poor urinary stream, incomplete bladder emptying, poor growth and incontinence. There is a risk of renal failure, VUR, and voiding dysfunction (over- or underactive bladder), also described as 'valve bladder syndrome'.

Associated features: 'pop-off valve syndrome' is seen in 20%. It describes mechanisms by which high urinary tract pressure is dissipated to allow normal renal development. It includes leaking of urine from a small bladder or renal pelvis rupture (urinary ascites), unilateral reflux into a non-functioning kidney (VUR with renal dysplasia or VURD), and formation of bladder diverticuli.

Management

Commence prophylactic antibiotics immediately (trimethoprim 2mg/kg daily) and drain the bladder with a paediatric feeding tube or suprapubic catheter if this proves difficult. Check serum electrolyes and arrange for urgent post-natal renal tract USS and MCUG.

Definitive treatment is with cystoscopy and transurethral ablation of the valve. The most important incision is made at the 12 o'clock position with either cold knife or electrocautery. Complications of surgery include urethral strictures. A temporary cutaneous vesicostomy is indicated (communicating stoma between the bladder dome and suprapubic abdominal wall, allowing free drainage of urine) when the urethra is too small for the resectoscope. Alternatives are ureterostomy drainage with valve ablation performed at a later stage. Any underlying bladder dysfunction should be diagnosed and treated.

Long-term monitoring

Monitor children for linear growth (height, weight, and head circumference), renal function, BP, urine analysis (for proteinuria, osmolality), USS, and formal GFR with chromium EDTA. Renography (MAG3 and DMSA) are also performed to assess split renal function and look for evidence of obstruction or reflux. Videourodynamic studies are used to assess and aid in the management of any associated voiding dysfunction.

Prognosis

Thirty-five percent have long-term poor renal function; 20% develop end-stage renal failure. Bladder dysfunction is common despite treatment of outflow obstruction. This includes bladder overactivity, incontinence, and bladder underactivity associated with chronic urinary residuals and poor concentration of urine (with polyuria). From age 16y, care should be transferred to an adult urologist or nephrologist. Problems may arise with retrograde ejaculation, impotence and reduced libido (related to renal impairment), and abnormal prostatic or seminal vesicle secretions, contributing to reduced fertility.

Cystic kidney disease

Congenital cystic kidney disease can be is classified into non-genetic and genetic types.

Non-genetic

Multicystic dysplastic kidney (MCDK)

The cysts of a 'multicystic' kidney are not due to dilatation of renal collecting ducts (as in polycystic disease), but instead, the entire kidney is dysplastic and non-functioning, with immature dysplastic stroma and non-communicating cysts of various sizes. The proximal ureter is atretic in about 66%.

Incidence

The incidence of unilateral MCKD is 1 in 4000, with a male to female ratio of 2:1. Bilateral disease occurs in 10% of cases and is incompatible with life.

Presentation

MCDK is detected on antenatal USS (20 weeks' gestation). A 34-week antenatal USS is performed to assess for contralateral anomalies.

Clinical types and associated disorders

MCKD may be simple (contralateral kidney is normal on USS) or complicated (contralateral side is abnormal). Unilateral disease is associated with VUR or PUJ obstruction in the contralateral kidney in ~30%. An ureterocele will be associated with MCKD in 10% of cases.

Management

Post-natal renal tract USS is performed at 1 week after birth.

Simple MCDK

This does not require prophylactic antibiotics. Repeat USS and DMSA renogram are performed at 6 weeks to confirm there is no renal function in the MCDK. Affected kidneys (especially those <6cm) tend to involute. Most can be treated conservatively with surveillance of growth, BP, urine analysis, and USS follow-up. Consider surgical removal for MCDK >6cm (which tend to grow), any solid component, hypertension, symptoms, or parental preference

Complicated MCDK

Prophylactic antibiotics are started at birth. Post-natal USS and MAG3 renogram are performed to investigate obstruction (i.e. contralateral PUJ obstruction). MCUG and DMSA renogram are performed to exclude reflux.

Risks

The risk of developing hypertension or Wilms' tumour (see 📖 p. 238) with MCDK is rare and routine nephrectomy to prevent the development of these conditions is no longer recommended. Follow-up of BP, growth, proteinuria, and renal tract USS is recommended.

Multilocular cystic nephroma

Presents in young children with a flank mass, loin pain, or haematuria. Diagnosis is on USS or CT, demonstrating multilocular cysts in the renal parenchyma, which may extend into the collecting system. It is included in a spectrum of disease that is closely associated with Wilms' tumour and so the recommended treatment used to be partial or full nephrectomy, but many specialists will monitor these now rather than proceed directly to surgery.

Genetic

Autosomal recessive polycystic kidney disease (ARPKD)

A disease of infancy and childhood where renal collecting tubules and ducts become cystically dilated and numerous small cysts form in the renal cortex and medulla bilaterally. Incidence of 1 in 10 000–40 000. Severe forms present early and have a poor prognosis. Prenatal USS demonstrates oligohydramnios (amniotic fluid <200mL) and large, 'bright' homogeneously hyperechogenic kidneys which can cause obstructed labour and respiratory problems (secondary to pulmonary hypoplasia). Neonates have large flank masses, limb and facial anomalies. All cases are associated with congenital hepatic fibrosis. Infants may develop fatal uraemia and respiratory failure; older children present with renal failure, hypertension, and portal hypertension. Most develop end-stage renal failure by adulthood, requiring haemodialysis, nephrectomy (to control hypertension), and subsequent renal transplantation.

Autosomal dominant polycystic kidney disease (ADPKD) (see 🕮 p. 404)

Typically presents in adulthood, although older children can present with complications of haematuria, flank pain, flank mass, UTI, proteinuria, hypertension, and intracerebral bleeds (secondary to berry aneurysm rupture). ADPKD is the most commonly inherited renal disease with an incidence of ~1 in 1000. It is characterized by multiple expanding cysts of both kidneys that ultimately destroys the intervening parenchyma and accounts for 10% of all chronic renal failure. Ninety percent of cases are due to a defective PKD1 gene located on chromosome 16; the remainder is due to a defective PKD2 gene on chromosome.[4]

Familial juvenile nephronophthisis

An autosomal recessive disorder which develops in early childhood and accounts for up to 20% of paediatric renal failure. ***Medullary cystic disease*** is a similar (autosomal dominant) condition which develops in later childhood. Histology in both conditions shows interstitial nephritis associated with corticomedullary cysts. Disease progression causes a reduction in kidney size. Features include polyuria and polydipsia (due to a salt-losing nephropathy), anaemia, growth retardation, hypertension, and chronic renal failure. Initial treatment includes salt replacement. Dialysis and renal transplantation are later options.

Others

Renal cysts are also a feature of autosomal dominant conditions, including ***von Hippel–Lindau syndrome*** (cerebellar and retinal haemangioblastomas, phaeochromocytoma, pancreatic cysts, renal cell carcinoma (RCC)) and ***tuberous sclerosis*** (adenoma sebaceum, epilepsy, learning difficulties associated with renal angiomyolipoma, and RCC).

Hypospadias

Hypospadias is a congenital deformity where the opening of the urethra (the meatus) is sited on the underside (ventral) part of the penis, anywhere from the glans to the perineum. It is often associated with a 'hooded' foreskin (prepuce) and chordee (ventral curvature of the penile shaft). It occurs in 1 in 250 live male births. There is an 8% incidence in offsprings of an affected male and a 14% risk in male siblings.

Classification

Hypospadias can be classified according to the anatomical location of the urethral meatus (Fig. 16.6). Most common are anterior hypospadias accounting for 50–80% of cases.

- **Anterior** (or distal): glandular, coronal, and subcoronal.
- **Middle**: distal penile, midshaft, and proximal penile.
- **Posterior** (or proximal): penoscrotal, scrotal, and perineal.

Aetiology

Hypospadias results from incomplete closure of urethral folds on the undersurface of the penis during embryological development. This is related to a defect in the production or metabolism of fetal androgens or the number and sensitivity of androgen receptors in the tissues. Chordee is caused by abnormal urethral plate development or an intrinsic abnormality of the corpora cavernosa and the 'hooded' foreskin is due to failed fusion of the preputial folds (resulting in a lack of ventral foreskin).

Associated anomalies

- Undescended testes.
- Inguinal hernia ± hydrocele.
- Disorders of sexual development (i.e. mixed gonadal dysgenesis).
- Persistence of Müllerian structures (i.e. dilated utricle).

Diagnosis

A full clinical examination to establish the diagnosis, assess the penis and urethral plate, and detect associated abnormalities needing treatment. Patients with unilateral or bilateral absent or impalpable testes and hypospadias should undergo chromosomal and endocrine investigation to exclude disorders of sex development. Posterior hypospadias can be associated with other urinary tract malformations and requires USS investigation.

Treatment

Surgery is indicated where deformity is severe, interferes with voiding, or is predicted to interfere with sexual function. Repair is performed between 6–18 months of age. Androgens have been used preoperatively to help increase tissue size. Surgery aims to correct penile curvature (orthoplasty), reconstruct a new urethra, and bring the new meatus to the tip of the glans using urethroplasty, glansplasty, and meatoplasty techniques.

Single-stage repair

Distal (and selected cases of middle and proximal hypospadias) can be treated by a Snodgrass procedure (tubularized incised plate (TIP) urethroplasty). The penis is degloved and an artificial erection created to assess for chordee which may be corrected with dorsal plication. The glans wings are incised to separate them from the urethral plate which is incised in the midline to widen it and allow tubularization and a layered suture closure over a catheter. A dartos pedicle is used to cover the repair. Reconstruction of the glans is with layered suture repair (glansplasty).The catheter is removed 7 days later.

Two-stage repair (free graft repair)

Many proximal and some middle hypospadias may require a two-stage procedure which consists of initial preparation of the urethral plate and insertion of a free graft (prepuce or buccal mucosa). A fine catheter is placed into the bladder and an occlusive dressing applied. The dressing is removed under general anaesthesia around 7 days later, the graft examined for viability, and the catheter removed. The second stage of tubularization of the neo-urethra and closure is performed around 6 months later.

Other repairs described for hypospadias

Distal hypospadias repairs

- TIP urethroplasty.
- Tubularization (Thiersch Duplay). Operation of choice if wide urethral plate and deep glans groove available for reconstruction.
- Meatal advancement and glanuloplasty (MAGPI).
- Meatal-based flaps (Mathieu procedure).

Middle hypospadias repairs

- TIP urethroplasty.
- Tubularization (Thiersch Duplay).
- Onlay island flap (OIF) using a preputial graft.
- Meatal-based flaps.

Proximal hypospadias repairs

- Free graft (two-stage repair).
- Transverse preputial island flap (TPIF).
- OIF repair.
- TIP urethroplasty.

Complications

Overall complication rate of 4–7% in the short to medium term. Complications increase with time and severity of hypospadias. They include urethrocutaneous fistula, urethral stricture, meatal stenosis, spraying of urine, voiding dysfunction, urethral diverticulum, recurrent chordee, sexual dysfunction, poor cosmesis, and failure of repair or graft requiring re-operation.

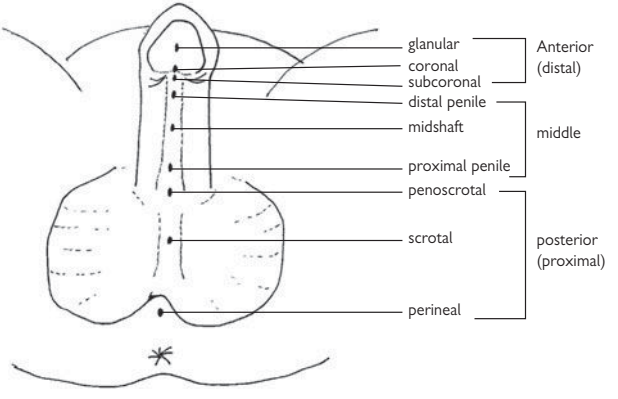

Fig. 16.6 The anatomical classification of hypospadias according to the location of the urethral meatus.

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Disorders of sex development

See Tables 16.6 and 16.7.

Disorders of sex development (DSD) are defined as congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical. They are estimated to affect 1 in 4500 births. DSD is divided into:

- **Sex chromosome DSD** (disorders of gonadal differentiation): these include conditions with seminiferous tubule dysgenesis (Klinefelter's syndrome 47XXY and 46XX testicular DSD), Turner's syndrome (45XO), ovotesticular DSD (46XX/46XY, 46XX, or 46XY with both ovarian and testicular tissue and ambiguous genitalia), mixed gonadal dysgenesis 45XO/46XY mosaicism (streak gonads and a spectrum of ambiguous genitalia), and 46XX (pure) gonadal dysgenesis (females with streak gonads). Refer to summary (Table 16.6).
- **46XY DSD** (previously male pseudohermaphroditism): 46XY karyotype with *defects of testosterone production* (3β-hydroxysteroid dehydrogenase or 17α-hydroxylase enzyme deficiencies; testicular dysgenesis; Leydig cell aplasia) or *defects of testosterone metabolism* (5α-reductase deficiency), resulting in varying degrees of feminization. Also included are *disorders of MIS* or MIS receptor defects, resulting in persistent Müllerian duct syndrome (male phenotype with uterus, Fallopian tubes, and upper vagina).

Complete androgen insensitivity syndrome (CAIS), caused by ***androgen resistance***, is the most common cause of 46XY DSD. Where the family history is positive, karyotyping can be performed at birth. Sporadic cases are difficult to detect. In CAIS, the phenotype and external genitalia are female, however, internal genitals are usually absent (or rudimentary). At puberty, there is breast development, scanty pubic and axillary hair, a short blind-ending vagina, and patients are often tall. They may present at this time for investigation of primary amenorrhoea, with raised LH and testosterone. Undescended testes may be palpable in the inguinal canal and will require removal after puberty due to malignancy risk. Oestrogen replacement is then given.

In comparison, incomplete or partial androgen insensitivity syndrome (PAIS) presents with a wide spectrum of phenotypes, most commonly with a degree of ambiguous genitalia.

- **46XX DSD** (previously female pseudohermaphroditism): 46XX karyotype with ovaries and internal genitalia, but a partially masculinized phenotype and ambiguous external genitalia due to intrauterine exposure to androgens.

The most common type is ***congenital adrenal hyperplasia (CAH)*** due to 21-hydroxylase deficiency (in 95%), an autosomal recessive disorder. CAH accounts for around 85% of all infants with ambiguous genitalia. Formation of hydrocortisone is impaired, resulting in a compensatory increase in adrenocorticotrophin hormone (ACTH) and testosterone production. Some forms have a 'salt-wasting' aldosterone deficiency which can present in the first few weeks of life with adrenal crisis (severe vomiting and dehydration), requiring rehydration and steroid replacement

therapy with mineralocorticoids and glucocorticoids. Rarer causes of CAH are 11β-hydroxylase deficiency and 3β-hydroxysteroid dehydrogenase deficiency (see Fig. 16.7).

Disorders of ovarian development (i.e. 46XX gonadal dysgenesis, 46XX testicular DSD) can also be included in this category.

Evaluation

- A detailed **history** may uncover a positive family history of DSD. Maternal ingestion of drugs such as steroids or contraceptives during pregnancy should be ascertained.
- General **examination** may show associated syndrome anomalies (Klinefelter's and Turner's syndromes) or failure to thrive and dehydration (salt-wasting CAH). Assess external genitalia for phallus size and location of urethral meatus. Careful palpation may confirm the presence of testes which excludes a diagnosis of 46XX DSD. Patients with bilateral undescended testes or unilateral undescended testis with hypospadias should be also suspected of having a DSD.
- **Abdominal/pelvic USS** can help locate the gonads.
- **Diagnostics laparoscopy or laparotomy** with gonadal biopsy may be required to clarify diagnosis.
- **Chromosomal analysis** confirms karyotype.
- **Serum tests**: serum electrolytes, testosterone, and DHT analysis test for salt-wasting CAH. A raised serum 17-hydroxyprogesterone is seen in 21-hydroxylase deficiency. HCG stimulation test can diagnose androgen resistance and 5α-reductase deficiency.

Management

A multidisciplinary approach is required with full parental input. In cases of ambiguous genitalia, advise parents to delay registering the birth until a diagnosis is established and gender has been assigned. The Registry Office has special provision for this situation. Gender assignment of ambiguous genitalia is guided by the functional potential of gonadal tissue, reproductive tracts, and genitalia, with the aim of optimizing psychosocial well-being and producing a stable gender identity. This is ultimately decided by a full multidisciplinary team (paediatric urologists, endocrinologist, geneticists, and psychologists) in tertiary specialist centres. Patients have a higher risk of gonadal malignancy, which requires surveillance and/or removal of gonadal tissues and hormone replacement. Patients with hypogonadism will require hormone replacement and artificial induction of puberty.

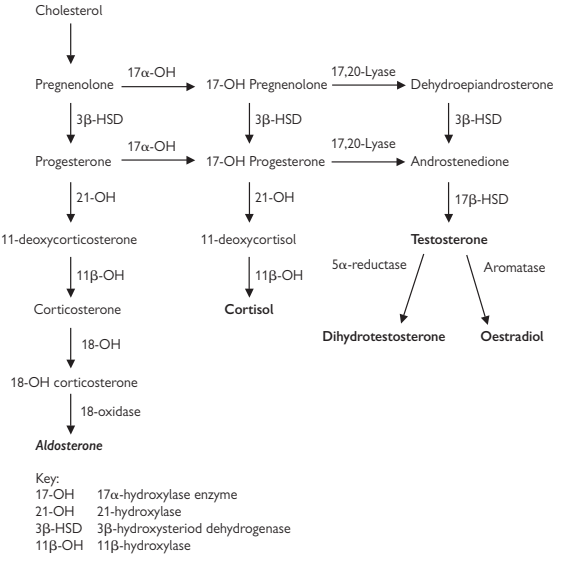

Fig. 16.7 Metabolic pathways for adrenal steroid synthesis.

Table 16.6 Proposed revised nomenclature[1]

Old terminology	Proposed new terminology
Intersex	Disorders of sex development (DSD)
Male pseudohermaphrodite	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
True hermaphrodite	Ovotesticular DSD
Testicular feminization	Androgen insensitivity syndrome, complete (CAIS)
46XX male	46XX testicular DSD

1 Hughes IA, Houk C, Ahmed SF, *et al.* (2006) Consensus statement on management of intersex disorders. *Arch Dis Child* 91(7):554–63.

Table 16.7 Disorders of sex development

Disorder	Karyotype	Gonad	Genitalia	Other features	Treatment
Disorder of gonadal differentiation					
Klinefelter's syndrome	47XXY	Seminiferous tubule dysgenesis, small testes	Male	Tall, gynaecomastia, azoospermia, mild mental retardation, ↑ FSH/LH, ↓ testosterone	Androgen replacement
46XX testicular DSD	46XX (SRY +ve)	Seminiferous tubule dysgenesis	Male	Shorter stature, gynaecomastia, infertile, hypospadias, ↑ FSH/LH, ↓ testosterone	Androgen replacement
Turner's syndrome	46XO	Streak ovaries	Female	Short stature, sexual infantilism, web neck, widespread nipples, wide carrying angle, coarctation, renal anomalies	Growth hormone, oestrogen replacement therapy
Ovotesticular DSD	46XX, XY, 46XX/46XY	Ovary and testis	Ambiguous or male	Hypospadias (80%) in 'males'; cliteromegaly in 'females'	Gender assignment surgery
Mixed gonadal dysgenesis	46XO/46XY	Unilateral undescended testis and streak gonad	Ambiguous	Wide phenotypic spectrum from Turner's syndrome-like female to male. Includes hypospadias	Gender assignment, gonadectomy (as ↑ cancer risk), screen for Wilms' tumour
46XX 'pure' gonadal dysgenesis	46XX	Streak ovaries	Female	Normal stature, sexual infantilism, primary amenorrhoea	Cyclic hormone replacement

(*Continued*)

Table 16.7 (*Continued*)

Disorder	Karyotype	Gonad	Genitalia	Other features	Treatment
46XY DSD					
3β-dydroxysteroid dehydrogenase	46XY	Testes	Ambiguous	Salt-wasting, ↓ cortisol, ↓ aldosterone	Glucocorticoid and mineralocorticoid replacement
17α-hydroxylase deficiency	46XY	Testes	Ambiguous	↓ Cortisol (causing ↑ ACTH), resulting in ↓ steroids, hypokalaemia, hypertension	Glucocorticoid replacement
Complete androgen insensitivity syndrome	46XY	Testes	Female	Androgen resistance, female phenotype, short blind-ending vagina, breasts at puberty	Gonadectomy after puberty, oestrogen replacement therapy
Incomplete androgen insensitivity syndrome	46XY	Testes	Ambiguous	Wide spectrum, including hypospadias, infertility, gynaecomastia, pseudovagina	Gender assignment surgery ± gonadectomy and hormone
5α-reductase deficiency	46XY	Testes	Ambiguous	Failure to convert testosterone to DHT in androgen-sensitive cells, hypospadias, small phallus, short vagina, virilization at puberty	Reconstructive surgery ± hormonal support

46XX DSD					
Congenital adrenal hyperplasia	46XX	Ovaries	Ambiguous	Simple virilization or salt-wasting aldosterone deficiency	Glucocorticoid, mineralocorticoid replacement and surgery
Transplacental androgens	46XX	Ovaries	Ambiguous	Virilization by maternal drug use in pregnancy or maternal adrenal tumours	External genitalia reconstruction as required

Exstrophy–epispadias complex

Exstrophy–epispadias complex describes a spectrum of congenital malformations affecting the abdominal wall, pelvis, genitourinary tract, and sometimes also the spine and anus. It includes bladder exstrophy, epispadias, and cloacal exstrophy.

Classic bladder exstrophy

This is the most common manifestation and results from defective development of the anterior bladder and lower abdominal walls, resulting in the posterior bladder wall lying exposed on the abdomen. Virtually all cases are associated with epispadias (see 📖 p. 690).

Epidemiology: incidence is 71 in 30 000 live births. Male to female ratio is 5:1. Increased risk in offspring of affected patients and with younger maternal age and increased parity.

Embryology: classically described as an embryological malformation causing abnormal overdevelopment of the cloacal membrane, which prevents in-growth of lower abdominal (mesenchymal) tissues. The cloacal membrane normally perforates to form the urogenital and anal openings, but in exstrophy, premature rupture results in a triangular defect below the umbilicus. The timing of rupture determines the type of resulting defect (bladder exstrophy, cloacal exstrophy, or epispadias). Other theories challenge this and suggest abnormal development of the bony pelvis or maldevelopment of the genital hillocks below their normal position, with midline fusion below rather than above the cloacal membrane (resulting in premature cloacal rupture prior to mesenchymal in-growth).

Associated anomalies

- **Bone defects**: diastasis (widening) of the symphysis pubis due to outward rotation of the pelvic bones along the sacroiliac joints.
- **Musculofascial defects**: umbilical hernias, inguinal hernias, divarication of rectus abdominis, abnormal pelvic floor, low lying umbilicus.
- **Genital defects**: *Males*—short, broad penis with lateral splaying of the corporal cavernosa, short urethral plate, epispadias, deficiency of dorsal foreskin. *Females*—bifid clitoris, stenotic vaginal orifice, short anteriorly placed vaginal canal, uterine prolapse in adult life.
- **Urinary tract defects**: exposed bladder plate; majority suffer VUR due to lateral displacement of the ureteric orifices.
- **GI tract defects**: anteriorly displaced anus, rectal prolapse, abnormal anal sphincter contributes to faecal incontinence.

Investigation

Typical features seen on prenatal USS include a lower abdominal wall mass, absent bladder filling, low-set umbilicus, small genitalia, abnormal iliac crest widening. Diagnosis can help planning of delivery in a centre with facilities to perform early surgical correction.

Management

At birth, cover the bladder with plastic film and irrigate regularly with sterile saline. Trauma to the bladder mucosa can result in squamous metaplasia, cystitis cystica or adenocarcinoma, and squamous cell carcinoma after chronic exposure.

Surgery: aims to provide a continent reservoir for urine storage, preserve renal function, and create functional and cosmetically acceptable external genitalia. Selected cases are suitable for a one-stage complete primary repair of bladder exstrophy (CPRE), involving closure of the bladder plate and epispadias repair. However, many require staged procedures.

- **Newborn**: pelvic osteotomy (cutting bone to correct deformity) with external fixation and closure of bladder, abdominal wall, and posterior urethra.
- **6–18 months**: epispadias repair (see 🕮 p. 689).
- **4–5y**: bladder neck reconstruction (Young–Dees–Leadbetter procedure) and anti-reflux surgery (ureteric re-implantation) is performed when there is adequate bladder capacity and children can participate in voiding protocols. Where bladder capacity is too small, bladder augmentation and/or urinary diversion is required.

Surgical complications: increased risk of malignancy in urinary or orthotopic bladder, fistula, hypospadias, bladder stones, infection (UTI, epididymitis), incontinence.

Cloacal exstrophy

This is the most severe form of exstrophy–epispadias complex. Characterized by an exomphalos (midline abdominal defect with bowel covered in a thin sac of amnion and peritoneum), below which are two halves of an exstrophied bladder separated by an exstrophied bowel segment. It is associated with a bifid or micro-penis and the absence of one or both testes. The incidence is between 1 in 200 000 and 1 in 400 000; male to female ratio is 6:1. There is a high risk of associated congenital anomalies. Surgical reconstruction may require terminal colostomy, pelvic osteotomy, anterior bladder reconstruction ± augmentation cystoplasty. Gender assignment may need to be considered in males.

Primary epispadias

In epispadias, the urethra opens onto the dorsal surface of the penis, anywhere from the glans, penile shaft, or most commonly, the penopubic region. An incomplete urethral sphincter mechanism (seen with posterior urethral epispadias) results in a high risk of incontinence. Epispadias is also associated with dorsal chordee (causing an upward curvature of the penis) and with incomplete foreskin dorsally. Epispadias is part of the exstrophy–epispadias complex (see 📖 p. 688). Primary epispadias (without exstrophy) is rare.

Associated anomalies

Diastasis of the symphysis pubis results in splaying and rotation of the corpora cavernosa, laterally placed neurovascular bundles, and shortening of the penile shaft. There is reduced male fertility, with paternity rates of ~36%. Females have a bifid clitoris, poorly developed labia, and demonstrate a spectrum of urethral deformities, ranging from a patulous urethral orifice to a urethral cleft affecting the entire length of the urethra and sphincter. There is >40% risk of VUR which commonly requires ureteric re-implantation.

Incidence: affects 1 in 117 000 males; rarely seen in females (1 in 400 000).

Management

Males: urethroplasty with functional and cosmetic reconstruction of the external genitalia (penile lengthening and correction of chordee) at 6–18 months. The modified Cantwell–Ransley technique is commonly used in males. It describes mobilizing the urethra to the ventral aspect of the penis, with advancement of the urethral meatus onto the glans with a reverse meatal advancement glanuloplasty. The corporal bodies are separated and rotated medially above the urethra and re-approximated. From age 4–5y, when children can be toilet-trained, bladder neck reconstruction can be performed (Youngs–Dees–Leadbetter procedure). This achieves continence and any bladder residuals may then be emptied by urethral catheterization. If this surgery fails, insertion of artificial urinary sphincters may be tried. Some patients may require bladder augmentation and Mitrofanoff reconstruction to achieve continence.

Females: surgery involves urethral repair reinforced with pubic fat, along with clitoral reconstruction ± bladder neck repair.

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Urinary incontinence in children

Normal bladder control

- **Neonates**: sacral spinal cord reflex triggers voiding when the bladder is full.
- **Infants**: primitive reflexes are suppressed, bladder capacity increases, and voiding frequency is reduced.
- **2–4y**: development of conscious bladder sensation and voluntary control.

Lower urinary tract symptoms and types of incontinence[1]

Urinary incontinence can be divided into primary types (never been dry) or secondary (re-emergence of incontinence after being dry for 6 months).

- **Overactive bladder syndrome**: like adults, this is manifest as urgency ± urge incontinence, usually with frequency and nocturia. The symptoms are usually caused by detrusor overactivity, but can be due to other forms of voiding dysfunction.
- **Extraordinary daytime urinary frequency**: small volume, frequent voiding during the daytime (after bladder control is achieved). It is usually self-limiting.
- **Stress urinary incontinence**: leak of urine with exertion. It is seen in patients with cystic fibrosis, but otherwise is rare in non-neuropaths.
- **Giggle incontinence**: a rare condition mainly affecting girls, with urinary incontinence triggered by laughing. Bladder function is normal between episodes.
- **Vaginal reflux**: urine refluxes into the vagina, then dribbles into the underwear on standing. Improved by correcting toilet posture. Occasionally, it may be caused by labial adhesions which can be treated with topical oestrogen cream or divided, if necessary.
- **Voiding postponement**: children with incontinence may demonstrate holding manoeuvres (leg crossing, squatting, Vincent's curtsey) to defer micturition and increase voiding intervals. It may be associated with behavioural and psychological disturbances.
- **Underactive bladder**: large capacity bladder, poor contractility, infrequent voids, and may need to strain to empty the bladder.
- **Nocturnal enuresis** (see 📖 p. 694).
- **Dysfunctional voiding** (previously called Hinman's syndrome or non-neurogenic neurogenic bladder): it results from external urethral sphincter contraction during voiding, leading to a staccato flow pattern on uroflowmetry. It has a multifactorial aetiology which includes abnormal learned voiding patterns. It can result in incomplete bladder emptying, UTI, urge incontinence, and is associated with bowel dysfunction (constipation). Severe cases may results in a small, trabeculated bladder, VUR, hydronephrosis, and renal damage.

Evaluation

- **History**: enquire about UTIs; voiding habits (frequency, urgency, primary or secondary incontinence, daytime and/or night-time symptoms), family history, bowel problems, social history, behavioural and psychosocial problems.
- **Examination**: palpate the abdomen for distended bladder or enlarged kidneys. Inspect external genitalia for congenital anomalies (i.e. epispadias). Exclude any neurological causes (hairy patch, lipoma, dimple on lower back may indicate lumbosacral spine abnormalities; examine lower limb reflexes).
- **Investigations**: urinalysis (infection, protein, glucose), voiding diary, flow rate, PVR. In selected cases—USS renal tract (to assess for hydronephrosis, bladder size), MCUG (to assess for VUR, PVR), videourodynamics (if suspicion of neuropathic bladder or sphincter dysfunction, or difficulty in clinical diagnosis), MRI spine (if clinical suspicion of neurological cause).

Management

Conservative

Education of the family and child are essential. Children may need bladder retraining, timed voiding, change of voiding posture, and avoidance of bladder irritants. Diet should be modified to avoid constipation, and use laxatives if it does occur. Psychological counseling and support should be available. Many conditions respond and improve with these measures alone.

Specific management

- **Overactive bladder syndrome**: where conservative methods have failed, anticholinergic medication (i.e. oxybutynin) is indicated. Some patients also respond well to neuromodulation of the bladder with transcutaneous electrical nerve stimulation (TENS). More invasive methods usually reserved for neuropathic patients include botulinum toxin A injection into the bladder and ileocystoplasty.
- **Giggle incontinence**: treatment options include anticholinergic medications, imipramine and Ritalin (methyphedinate).
- **Underactive bladder**: symptomatic children may need antibiotics for UTI and ISC, if tolerated. It can be self-limiting and resolve.
- **Nocturnal enuresis** (see 🕮 p. 694): first-line active treatments are enuresis alarms and desmopressin.
- **Dysfunctional voiding:** in addition to conservative techniques, anticholinergic medication may be useful and TENS can be used to neuromodulate the overactive bladder. ISC ± α-blockers may be needed for patients with underactive bladder and incomplete emptying. Antibiotics prophylaxis may be required for recurrent UTI. The condition tends to resolve spontaneously.

1 Hoebeke P, Bower W, Combs A. *et al.* (2010) Diagnostic evaluation of children with daytime incontinence. *J Urol* **183**:699–703.

Nocturnal enuresis

Nocturnal enuresis (NE) is defined as intermittent incontinence whilst sleeping.[1] **Monosymptomatic nocturnal enuresis (MNE)** is defined as (nocturnal) enuresis in children without any other LUTS and without a history of bladder dysfunction.[1] MNE accounts for <50% of children with bedwetting. **Non-monosymptomatic nocturnal enuresis (NMNE)** includes children with associated voiding dysfunction. **Primary NE** refers to children that have never been dry for more than a 6-month period; **Secondary NE** refers to the re-emergence of bedwetting after a period of being dry for at least 6 months.

Prevalence

Nocturnal enuresis is estimated to affect up to 15% of 5y olds[2] and 10% of 7y old children (Table 16.8).[3] There is 15% spontaneous resolution of symptoms per year.[1] The prevalence in adults is ~0.5%.

Table 16.8 Prevalence of nocturnal enuresis

Age (y)	Females (%)	Males (%)
5	10–15	15–20
7	7–15	15–20
9	5–10	10–15
16	1–2	1–2

Pathophysiology

Three main factors that interact to produce nocturnal enuresis are:

- **Altered ADH secretion**: an abnormal decrease in ADH levels at night causes increased urine production (nocturnal polyuria).
- **Altered sleep/arousal mechanism**: impaired 'arousal from sleep' response to a full bladder.
- **Reduced nocturnal functional bladder capacity*** (± nocturnal detrusor overactivity).

Familial predisposition, psychological factors, UTI, and constipation are also considered to contribute to nocturnal enuresis.

History

The aim is to establish the underlying pathophysiological factors to guide treatment. Enquire about the frequency of episodes and whether it is a new or recurrent problem. Specifically ask about daytime urinary symptoms, urgency, holding manoeuvres, symptoms of UTI, and daytime incontinence. Enquire about bowel habit (constipation, incontinence). Establish any underlying contributory medical conditions, a family history, and psychosocial history.

Examination

Physical examination in a child with MNE is usually normal. Examination of the abdomen and genitals, neurological exam, lower limb sensation, and examination of the spine in children with associated voiding dysfunction (NMNE) is recommended.

Investigations

- **Voiding diary**: to assess for nocturnal polyuria and functional bladder capacity.
- **Urinalysis**: to assess for infection, the presence of glucose (diabetes) or protein (UTI, renal disease).

Management

General advice should be given to children and their parents. Active treatment is usually deferred until age 6y. First-line treatments are enuresis alarm and desmopressin.[4,5]

Behavioural

- **Reassurance and counselling**: including motivational techniques and reward systems to improve the child's self-esteem.
- **Bladder training**: regular daytime toileting, emptying the bladder before bed, avoiding bladder stimulants (i.e. blackcurrant drinks, caffeine), reduced fluid intake in the hours before sleep. Adjust diet to avoid constipation and treat it with laxatives if it occurs.
- **Conditioning therapy**: an enuretic alarm is connected to the child's underwear, which is triggered with the first few drops of urine, waking the child from sleep (60–70% successful response).

Pharmacological

- Desmopressin (synthetic analogue of ADH) given orally (tablet or buccal melt) just before bedtime with no further drinks. It produces an antidiuretic response. Overall ~30% achieve a full response to desmopressin and a further 40% have a partial response.
- Anticholinergics can be used to suppress detrusor overactivity when conservative methods have failed.
- Imipramine, a tricyclic antidepressant with anticholinergic and antispasmodic properties (used only selectively in children).

A full response to treatment is 14 consecutive dry nights or an 90% improvement in the number of wet pads.[4] Patients with nocturnal polyuria (and normal bladder function) tend to have a good response to desmopressin. Patients with functionally reduced bladder capacity (which may be associated with occult bladder dysfunction) benefit most from a combination of enuresis alarm, bladder training, and anticholinergic drugs (i.e. oxybutynin) ± desmopressin.

* Aged-based 'normal' bladder capacity in children is calculated as: child <2y: bladder capacity (mL) is estimated as 7.5mL/kg; child >2y: bladder capacity in mL = 30 (age + 2).

1 Neveus T, van Gontard A, Hoebeke P, *et al.* (2006) The standardization of terminology of lower urinary tract function in children and adolescents: report from the standardization committee of the International Children's Continence Society. *J Urol* **176**:314–24.

2 Forsythe WI, Redmond A (1974) Enuresis and spontaneous cure rate: study of 1129 patients. *Arch Dis Child* **49**:259–63.

3 Hellstrom AL, Hansson E, Hansson S, *et al.* (1990) Micturition habits and incontinence in 7-year-old Swedish school entrants. *Eur J Paediatr* **149**:434–7.

4 National Institute for Health and Clinical Excellence (2010) Nocturnal enuresis—the management of bedwetting in children and young people [online]. Available from: http://www.nice.org.uk/cg111.

5 Neveus T, Eggert P, Evans J, *et al.* (2010) Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. *J Urol* **183**:441–7.

Chapter 17

Urological surgery and equipment

Preparation of the patient for urological surgery

The degree of preparation is related to the complexity of the procedure. Certain aspects of examination (pulse rate, BP) and certain tests (haemoglobin, electrolytes, creatinine) are important, not only to assess fitness for surgery, but also as a baseline against which changes in the post-operative period may be measured.

- Assess cardiac status (angina, arrhythmias, previous MI, BP, ECG, CXR). We assess respiratory function by pulmonary function tests (FVC, FEV_1) for all major surgery and any surgery where the patient has symptoms of respiratory problems or a history of chronic airways disease (e.g. asthma).
- Arrange an anaesthetic review where there is, for example, cardiac or respiratory comorbidity.
- Culture urine, treat active (symptomatic) infection with an appropriate antibiotic, starting a week before surgery, and give prophylactic antibiotics at the induction of anaesthesia.
- Consider stopping aspirin and NSAIDs 10 days prior to surgery.
- Obtain consent.
- Measure haemoglobin and serum creatinine and investigate and correct anaemia, electrolyte disturbance, and abnormal renal function. If blood loss is anticipated, group and save a sample of serum or cross-match several units of blood, the precise number depending on the speed with which your blood bank can deliver blood, if needed. In our own unit, our policy is (other units may have a different policy) (Box 17.1):
  - The patient may choose to store their own blood prior to the procedure.

Box 17.1 The Group and Save and Cross Match policy in Oxford (consult your local hospital policy)

TURBT	Group and save
TURP	Group and save
Open prostatectomy	Cross-match 2 units
Simple nephrectomy	Cross-match 2 units
Radical nephrectomy	Cross-match 4 units
(renal vein or IVC extension)	Cross match 6 units
Cystectomy	Cross-match 4 units
Radical prostatectomy	Cross-match 2 units
PCNL	Group and save

Should aspirin and other antiplatelet drugs be stopped prior to minor urological procedures and urological surgery?

Aspirin and TRUS biopsy

In the UK, 65% of urologists routinely stop aspirin prior to TRUS biopsy; 35% do not.[1] Four of 297 urologists (1.3%) reported cerebrovascular side effects from stopping aspirin. There remains no consensus guidance on whether to stop or continue aspirin.

Aspirin and TURP

There is wide variation in the management of aspirin in men undergoing TURP. In a recent audit of UK urologists, 38% said they did not stop aspirin prior to TURP, but of those that said they did stop it, a substantial number still proceeded with TURP if the aspirin had inadvertently not been stopped.[2] Overall, 75% either did not bother stopping aspirin or proceeded with TURP if patients were inadvertently still taking it, presumably because of a perceived increased risk of serious cardiovascular events. Some studies suggest an increased risk of bleeding and the need for blood transfusion in those on aspirin while others report no increased risk. There is only one RCT and this showed that aspirin did increase blood loss after TURP, but not enough to increase the requirement for blood transfusion.[3] The risks of short-term withdrawal of aspirin prior to TURP have not been established, although there are anecdotal reports of serious adverse cardiovascular events. So should aspirin be stopped or continued prior to TURP? The short answer is that there is no substantial body of evidence to support stopping it or continuing it and as the majority continue to do TURP with patients on aspirin, but a substantial minority stop it, either behaviour is reasonable. Since bleeding times return to normal within 48h of stopping aspirin (the time taken for new platelets to reach sufficient numbers to compensate for impaired function of circulating platelets), it seems reasonable to stop it 2 days before surgery and to restart it within a few days of surgery when it is obvious that post-operative bleeding has stopped (usually when it is deemed safe to remove the catheter).

Drug-eluting cardiac stents and antiplatelet agents

Be careful in patients receiving the newer antiplatelet drugs such as clopidogrel or ticlopidine (with or without aspirin) since bleeding times can increase 3-fold.[4] Severe intractable bleeding can occur following 'minor' procedures such as prostate biopsy or bladder biopsy. Patients with coronary artery stents are treated with dual anticoagulation with aspirin and clopidogrel for several months after stent insertion to reduce the risk of stent thrombosis. The precise duration of antiplatelet therapy has not been established, but 9–12 months is currently recommended by the American Heart Association. Seek advice from a cardiologist about the safety of stopping these drugs. Consider delaying invasive procedures (e.g. prostate or bladder biopsy) if the risk of bleeding is deemed to be unacceptable in the presence of the continued need for anticoagulation.

Bowel preparation

Indicated if large bowel is to be used (bowel prep is not required if small bowel alone is to be used, e.g. ileal conduit, ileal neo-bladder reconstruction). Use a simple mechanical prep (Citramag® or Picolax®—magnesium salts), two doses starting the morning before surgery with clear fluid-only diet.

1 Masood J, Hafeez, Calleary J, Barua JM (2007) Aspirin use and transrectal ultrasonography-guided prostate biopsy: a national survey. *Br J Urol Int* **99:**965–6.

2 Enver MK, Hoh I, Chinegwundoh FI (2006) The management of aspirin in transurethral prostatectomy: current practice in the UK. *Ann R Coll Surg Engl* **88**:280–3.

3 Nielsen JD, Holm-Nielsen A, Jespersen J, *et al.* (2000) The effect of low-dose acetylsalicylic acid on bleeding after transurethral prostatectomy—a prospective, randomized, double-blind, placebo-controlled study. *Scan J Urol Nephrol* **34**:194–8.

4 Stephen Jones J (2007) Urologists: be aware of significant risks of stopping anticoagulants in patients with drug eluting coronary stents. *BJU Int* **99:**1330–1.

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Antibiotic prophylaxis in urological surgery

The precise antibiotic prophylaxis policy that you use will depend on your local microbiological flora. Your local microbiology department will provide regular advice and updates on which antibiotics should be used, both for prophylaxis and treatment. The policy shown here and in Table 17.1 is our own local policy.

Since the last edition of this book, there has been a move away from cefuroxime in an attempt to reduce the risk of antibiotic-induced *C. difficile* colitis. There has also been a similar move away from the use of fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin) because they are a risk factor for the development of *C. difficile*-associated diarrhoea and pseudomembranous colitis (and also for MRSA since they are secreted onto the skin and many staphylococci are resistant to them).* Trimethoprim, gentamicin, penicillin, and co-amoxiclav are less likely to cause *C. difficile*-associated disease.

Culture urine before any procedure and use specific prophylaxis (based on sensitivities) if culture positive.

We avoid ciprofloxacin in inpatients because it is secreted onto the skin and causes MRSA colonization. For most purposes, nitrofurantoin provides equivalent cover without being secreted onto the skin. We do use ciprofloxacin if there is known *Proteus* infection (all *Proteus* species are resistant to nitrofurantoin).

Patients with artificial heart valves

Patients with heart murmurs and those with prosthetic heart valves: 1g of IV amoxicillin with 120mg of gentamicin should be given at induction of anaesthesia, with an additional dose of oral amoxicillin, 500mg 6h later (substituting vancomycin 1g for those who are penicillin-allergic).

Patients with joint replacements

The advice is conflicting.

* *C. difficile* is a Gram-positive, anaerobic, spore-forming bacillus. Most common cause of nosocomial diarrhoea and antibiotic-associated colitis. Disease arises as a consequence of faeco-oral transmission of *C. difficile* spores (Ribotype 027 seems to be particularly pathogenic). Once colonization has occurred, progression to diarrhoea or colitis depends on coexisting conditions and host immune response. *C. difficile* toxins A and B are responsible for pathogenicity. They bind to intestinal epithelial receptors. Inflammatory cytokines cause fluid secretion, mucosal destruction, and tissue necrosis. Other risk factors for *C. difficile*-associated disease: age >65y. Use of proton pump inhibitors, laxatives, nasogastric tubes, prolonged hospital stay. Treatment for diarrhoea and colitis: stop causative antibiotics, isolate and barrier nurse (wash hands with soap and water as alcohol hand rubs are ineffective against spores), oral metronidazole (oral vancomycin reserved for serious or recurrent infection).

AAOS/AUA advice

Joint advice of the American Academy of Orthopaedic Surgeons (AAOS) and the American Urological Association (AUA)—antibiotic prophylaxis is not indicated for urological patients with pins, plates, or screws or for most patients with total joint replacements. It is recommended for all patients undergoing urological procedures, including TURP *within 2 years of a prosthetic joint replacement*, for those who are immunocompromised (e.g. rheumatoid patients, those with SLE, drug-induced immunosuppression, including steroids), and for those with a history of previous joint infection, haemophilia, HIV infection, diabetes, and malignancy.

Antibiotic regime: single dose of a quinolone, such as 500mg of ciprofloxacin, 1–2h preoperatively + ampicillin 2g IV + gentamicin 1.5mg/kg 30–60min preoperatively (substituting vancomycin 1g IV for penicillin-allergic patients).

UK advice

In the UK, a Working Party of the British Society for Antimicrobial Chemotherapy has stated that patients with prosthetic joint implants (including total hip replacements) do not require antibiotic prophylaxis and consider that it is unacceptable to expose patients to the adverse effects of antibiotics when there is no evidence that such prophylaxis is of any benefit. This advice is based on the rationale that joint infections are caused by skin organisms that get onto the prosthesis at the time of the operation and that the role of bacteraemia as a cause of seeding outside the immediate post-operative period has never been established.

We use the same antibiotic prophylaxis as for patients without joint prostheses.

Table 17.1 Oxford Urology procedure: specific antibiotic prophylaxis protocol for urological surgery

Procedure	Antibiotic prophylaxis
Catheter removal	Nitrofurantoin 100mg PO 30min before catheter removal
Change of male long-term catheter	Gentamicin 1.5mg/kg IM or IV 20min before*
Flexible cystoscopy or GA cystoscopy	Nitrofurantoin 100mg PO 30–60min before procedure
Transrectal prostatic biopsy	Ciprofloxacin 500mg PO and metronidazole 400mg 20min prebiopsy and for 48h post-biopsy (ciprofloxacin 500mg bd, metronidazole 400mg tds)
ESWL	500mg PO ciprofloxacin 30min before treatment (nitrofurantoin does not cover Proteus, a common 'stone' bacterium)
PCNL	Co-amoxiclav 1.2g IV tds starting the day before, hours before operation, and 3 doses post-operatively; gentamicin (3–5mg/kg) commencing the day prior to surgery, with a further dose 24 hours later
Ureteroscopy	Gentamicin 1.5mg/kg IV at induction
Urogynaecological procedures (e.g. colposuspension)	Co-amoxiclav 1.2g IV and metronidazole 500mg IV at induction of anaesthesia
TURPs and TURBTs — both for non-catheterized patients (i.e. elective TURP for LUTS) and patients with catheters (undergoing TURP for retention)	Nitrofurantoin 100mg + IV gentamicin at induction (1.5mg/kg); nitrofurantoin 100mg PO 30min before catheter removal
Radical prostatectomy	Co-amoxiclav 1.2g IV + 240mg IV gentamicin + 500mg IV metronidazole at induction
	240mg of gentamicin
	24h post-op; 48h IV co-amoxiclav 1.2g tds; ciprofloxacin PO 5 days

Table 17.1 (*Continued*)

Procedure	Antibiotic prophylaxis
Cystectomy or other procedures involving the use of bowel (e.g. augmentation cystoplasty)	Co-amoxiclav 1.2g IV + 500mg IV metronidazole at induction; further 2 doses of co-amoxiclav 1.2g and metronidazole 500mg post-operatively
Artificial urinary sphincter insertion	Vancomycin 1g 1.5h before leaving the ward (infuse over 100min)** + co-amoxiclav 1.2g IV + 3mg/kg IV gentamicin at induction; continue IV cefuroxime, gentamicin, and vancomycin (1g bd) for 48h

* Sepsis rate (necessitating admission to hospital) may be as high as 1% without antibiotic cover.

** OR teicoplanin if vancomycin allergic—400mg at induction and bd thereafter for a total of 48h; meropenem may be substituted for vancomycin in 'vancomycin-free' hospitals. About 9% of patients undergoing flexible cystoscopy develop bacteruria (>105 CFU/mL of urine). A randomized, placebo controlled trial of ciprofloxacin 500mg or trimethoprim 200mg in 2083 patients undergoing flexible cystoscopy showed a significant reduction of bacteriuria to 3 and 5%, respectively. While both antibiotics reduce the risk of bacteriuria, ciprofloxacin is more effective—after adjustment for baseline bacteriuria (~74% had bacteriuria before cystoscopy), the odds of bacteriuria for those taking trimethoprim were 4 times greater than those on ciprofloxacin (Johnson MI, Merrilees D, Robson WA *et al.* (2007) Oral ciprofloxacin or trimethoprim reduces bacteriuria after flexible cystoscopy. *Br J Urol Int* **100**:826–9).

Complications of surgery in general: DVT and PE

Venous thromboembolism (VTE) is uncommon after urological surgery, but it is considered the most important non-surgical complication of major urological procedures. Following TURP, 0.1–0.2% of patients experience a pulmonary embolus (PE)[1] and 1–5% of patients undergoing major urological surgery experience symptomatic VTE.[2] The mortality of PE is in the order of 1%.[3]

Risk factors for DVT and PE

Increased risk: open (vs endoscopic) procedures, malignancy, increasing age, duration of procedure.

Categorization of VTE risk

American College of Chest Physicians (ACCP) Guidelines on the prevention of VTE[2] and British Thromboembolic Risk Factors (THRIFT) Consensus Group[4] categorize the risk of VTE:

- Low-risk patients: those <40 undergoing minor surgery (surgery lasting <30min) and no additional risk factors. No specific measures to prevent DVT are required in such patients other than early mobilization. Increasing age and duration of surgery increases the risk of VTE.
- High-risk patients: include those undergoing non-major surgery (surgery lasting >30min) who are aged >60.

Additional risk factors (that indicate the requirement for additional prophylactic measures, e.g. the addition of SC heparin and/or intermittent pneumatic calf compression (IPC)

- Active heart or respiratory failure.
- Active cancer or cancer treatment.
- Acute medical illness.
- Age >40y.
- Antiphospholipid syndrome.
- Behcet's disease.
- Central venous catheter in situ.
- Continuous travel >3h up to 4 weeks before surgery.
- Immobility (paralysis or limb in plaster).
- Inflammatory bowel disease (Crohn's disease/ulcerative colitis).
- Myeloproliferative diseases.
- Nephrotic syndrome.
- Obesity (BMI >30kg/m^2).
- Paraproteinaemia.
- Paroxysmal nocturnal haemoglobinuria.
- Personal or family history of VTE.
- Recent myocardial infarction or stroke.
- Severe infection.
- Use of oral contraceptive or hormone replacement therapy.
- Varicose veins with associated phlebitis.

- Inherited thrombophilia.
- Factor V Leiden.
  - Prothrombin 2021A gene mutation.
  - Antithrombin deficiency.
  - Protein C or S deficiency.
  - Hyperhomocysteinaemia.
  - Elevated coagulation factors (e.g. Factor VIII).

Prevention of DVT and PE

See Table 17.2.

Diagnosis of DVT

Signs of DVT are non-specific (i.e. cellulitis and DVT share common signs—low-grade fever, calf swelling, and tenderness). If you suspect a DVT, arrange a Doppler USS. If the ultrasound probe can compress the popliteal and femoral veins, there is no DVT; if it cannot, there is a DVT.

Diagnosis of PE

Small PEs may be asymptomatic. ***Symptoms***: include breathlessness, pleuritic chest pain, haemoptysis. ***Signs***: tachycardia, tachypnoea, raised JVP, hypotension, pleural rub, pleural effusion.

Tests

- **CXR:** may be normal or show linear atelectasis, dilated pulmonary artery, oligaemia of affected segment, small pleural effusion.
- **ECG:** may be normal or show tachycardia, right bundle branch block, inverted T waves in V1–V4 (evidence of right ventricular strain). The 'classic' SI, QIII, TIII pattern is rare.
- **Arterial blood gases:** low PO2 and low PCO2.
- **Imaging:** CT pulmonary angiogram (CTPA)—superior specificity and sensitivity when compared with ventilation perfusion (VQ) radioisotope scan.
- **Spiral CT:** a negative CTPA rules out a PE with similar accuracy to a normal isotope lung scan or a negative pulmonary angiogram.

Treatment of established DVT

- **Below-knee DVT:** above-knee thromboembolic stockings (AK-TEDs), if no peripheral arterial disease (enquire for claudication and check pulses) + unfractionated heparin 5000U SC 12-hourly.
- **Above-knee DVT:** start a low molecular weight heparin (LMWH) and warfarin and stop heparin when INR is between 2 and 3. Continue treatment for 6 weeks for post-surgical patient; lifelong if underlying cause (e.g. malignancy).
- LMWH.

Treatment of established PE

Fixed dose of SC LMWH seems to be as effective as adjusted dose IV unfractionated heparin for the treatment of PE found in conjunction with a symptomatic DVT.[3] Rates of haemorrhage are similar with both forms of heparin treatment. Start warfarin at the same time and stop heparin when INR is 2–3. Continue warfarin for 3 months.

Options for prevention of VTE

- Early mobilization.
- AK-TEDs—provide graduated, static compression of the calves, thereby reducing venous stasis. More effective than below-knee TEDS for DVT prevention.[5]
- SC heparin (low-dose unfractionated heparin (LDUH) or LMWH). In unfractionated preparations, heparin molecules are polymerized—molecular weights from 5000–30 000Da. LMWH is depolymerized—molecular weight 4000–5000Da.
- IPC boots, which are placed around the calves, are intermittently inflated and deflated, thereby increasing the flow of blood in calf veins.[6]
- For patients undergoing major urological surgery (radical prostatectomy, cystectomy, nephrectomy), AK-TEDS with IPC intra-operatively, followed by SC heparin (LDUH or LMWH) should be used. For TURP, many urologists use a combination of AK-TEDS and IPCs; relatively few use SC heparin.[7]

Contraindications to AK-TEDS

- Any local leg conditions with which stockings would interfere, such as dermatitis, vein ligation, gangrene, recent skin grafts.
- Peripheral artery occlusive disease (PAOD).
- Massive oedema of legs or pulmonary oedema from congestive cardiac failure.
- Extreme deformity of the legs.

Contraindications to heparin

- Allergy to heparin.
- History of haemorrhagic stroke.
- Active bleeding.
- Significant liver impairment—check clotting first.
- Thrombocytopenia (platelet count $<100 \times 10^9$/L).

Management of anticoagulation in the perioperative period

Liaise with whoever is responsible for the patient's anticoagulation (e.g. anticoagulant clinic). Warfarin should be stopped either 4 days (if the target INR is 2.5) or 5 days (if the target INR is higher) before surgery. Determine the INR the day before surgery to reduce the risk of cancellation. Administer oral vitamin K (2.5mg) if the INR is ≥2.0. Check the INR on the day of surgery.

The main decision is whether to give bridging therapy with treatment dose heparin (unfractionated heparin or LMWH) and if not, whether preoperative prophylactic LMWH is advised when the INR is <2.0. For pragmatic purposes, to save monitoring the INR as an outpatient, this could be instituted 2–3 days after warfarin is stopped, i.e. on the morning after two doses have been omitted.

A controversial group of patients are those with a prosthetic (non-caged) aortic valve and no other risk factor. It is acceptable not to use bridging therapy with treatment dose heparin in these patients particularly if the bleeding risk is high.[8,9]

Table 17.2 Pre- and post-operative risks

	Pre-operative	Post-operative*
High risk, e.g. VTE within 1 month. Prosthetic mitral valve, AF, and history of stroke	Treatment dose heparin (either IV UFH or SC LMWH)**	Treatment dose heparin (either IV UFH or SC LMWH)
Non-high Risk, e.g. AF without previous stroke	Nil/prophylactic LMWH***	Prophylactic LMWH

* Continue until INR >2.0 for two consecutive days.

** Stop full dose IV UFH 6h preoperatively and check APTT, omit full dose SC LMWH on day of surgery.

*** For patients with VTE within 1–3 months or cancer, we would suggest prophylactic LMWH preoperatively.

1 Donat R, Mancey–Jones B (2002) Incidence of thromboembolism after transurethral resection of the prostate (TURP). *Scan J Urol Nephrol* **36**:119–23.

2 Geerts WH, Heit JA, Clagett PG, *et al.* (2001) Prevention of venous thromboembolism. (American College of Chest Physicians (ACCP) Guidelines on prevention of venous thromboembolism) *Chest* **119**:132S–175S.

3 Quinlan DJ, McQuillan A, Eikelboom JW (2004) Low molecular weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism. *Ann Intern Med* **140**:175–83.

4 Lowe GDO, Greer IA, Cooke TG, *et al.* (1992) Risk of and prophylaxis for venous thromboembolism in hospital patients. Thromboembolic Risk Factors (THRIFT) Consensus Group. *BMJ* **305**:567–74.

5 Howard A, Zaccagnini D, Ellis M, Williams A, Davies AH, Greenhalgh RM (2004) Randomized clinical trial of low molecular weight heparin with thigh-length or knee-length antiembolism stockings for patients undergoing surgery. *Br J Surg* **91**:842–7.

6 Soderdahl DW, Henderson SR, Hansberry KL (1997) A comparison of intermittent pneumatic compression of the calf and whole leg in preventing deep venous thrombosis in urological surgery. *J Urol* **157**:1774–6.

7 Golash A, Collins PW, Kynaston HG, Jenkins BJ (2002) Venous thromboembolic prophylaxis for transurethral prostatectomy: practice among British urologists. *J R Soc Med* **95**:130–1.

8 Dunn AS, Turpie AG (2003) Perioperative management of patients receiving oral anticoagulants: a systematic review. *Arch Intern Med* **163:**901–8.

9 Kearon C (2003) Managment of anticoagulation before and after elective surgery. *Am Soc Hematol Educat Program Book*, pp. 528–34.

Fluid balance and the management of shock in the surgical patient

Daily fluid requirement

Can be calculated according to patient's weight:

- For the first 10kg: 100mL/kg per 24h (= 1000mL).
- For the next 10kg (i.e. from 10–20kg): 50mL/kg per 24h (= 500mL).
- For every kg above 20kg: 20mL/kg per 24h (= 1000mL for a patient weighing 70kg).

Thus, for every 24h, a 70kg adult will require 1000mL for their first 10kg of weight, plus 500mL for their next 10kg of weight, and 1000mL for their last 50kg of weight = total 24h fluid requirement, 2500mL.

Daily sodium requirement is 100mmol and for potassium, 70mmol. Thus, a standard 24h fluid regimen is 2L of 5% dextrose + 1L of normal saline (equivalent to about 150mmol Na^+), with 20mmol K^+ for every litre of infused fluid.

Fluid losses from drains or nasogastric aspirate are similar in composition to plasma and should be replaced principally with normal saline.

Shock due to blood loss

Inadequate organ perfusion and tissue oxygenation. The causes are hypovolaemia, cardiogenic, septic, anaphylactic, and neurogenic. The most common cause in the surgical patient is hypovolaemia due to blood and other fluid loss. Haemorrhage is an acute loss of circulating blood volume.

Haemorrhagic shock may be classified as:

- **Class I:** up to 750mL of blood loss (15% of blood volume); normal pulse rate (PR), respiratory rate (RR), BP, urine output, and mental status.
- **Class II:** 750–1500mL (15–30% of blood volume); PR >100; decreased pulse pressure due to increased diastolic pressure; RR 20–30; urinary output 20–30mL/h.
- **Class III:** 1500–2000mL (30–40% of blood volume); PR >120; decreased BP and pulse pressure due to decreased systolic pressure; RR 30–40; urine output 5–15mL/h; confusion.
- **Class IV:** >2000mL (>40% of blood volume); PR >140; decreased pulse pressure and BP; RR >35; urine output <5mL/h; cold, clammy skin.

Management

- Remember 'ABC': 100% oxygen to improve tissue oxygenation.
- ECG, cardiac monitor, pulse oximetry.
- Insert two short and wide IV cannulae in the antecubital fossa (e.g. 16 G). A central venous line may be required.
- Infuse 1L of warm Hartmann's solution or if severe haemorrhage, then start a colloid instead (e.g. Gelofusin®). Aim for a urinary output of 0.5mL/kg/h and maintenance of BP.
- Check FBC, coagulation screen, U & E, and cardiac enzymes.
- Cross-match 6U of blood.
- Arterial blood gases to assess oxygenation and pH.
- Obvious and excessive blood loss may be seen from drains, but drains can block so assume there is covert bleeding if there is a tachycardia (and low BP). If this regimen fails to stabilize pulse and BP, return the patient to the operating room for exploratory surgery.

Patient safety in the urology theatre

It is a fundamental part of safe surgical practice to cross-check that the following have been done prior to starting an operation or procedure. The process of cross-checking should be done with another member of staff, using several sources of information (e.g. the notes, consent form, X-ray images) to confirm the following.

- **Patient identification:** confirm you are operating on the right patient by a process of 'active' identification (i.e. ask the patient their name, date of birth, and their address to confirm that you are talking to the correct patient).
- **Ensure you are doing the correct procedure and on the correct side by cross-checking with the notes and X-rays:** for lateralized procedures (e.g. nephrectomy, PCNL), the correct side of the operation should be confirmed by cross-checking with the X-rays and with the X-ray report as well as referring to the notes. Where it is possible for the sides of an IVU to be incorrectly labelled, this cannot happen with a CT scan where the location of the liver (right side) and the spleen (left side) provides confirmation of what side is what.
- **Appropriate antibiotic prophylaxis has been given.**
- **DVT prophylaxis has been administered** (e.g. heparin, AK-TEDS, IPC boots).
- **Blood is available, if appropriate.**
- **The patient is safely and securely positioned on the operating table:** pressure points padded, not touching metal (to avoid diathermy burns), body straps securely in place.

Develop an approach to operating that involves members of your team. Listen to the opinions of staff who are junior to you. They may sometimes be able to identify errors that are not obvious to you. Cultivate the respect of the recovery room staff. They may express concern about a patient under their care—listen to their concerns, take them seriously, and if all is well, reassure them. It does no harm for your patients or for your reputation to develop the habit of visiting every patient in the recovery room to check that all is well. You may be able to identify a problem before it has developed into a crisis and at the very least, you will gain a reputation for being a caring surgeon.

Transurethral resection (TUR) syndrome

Arises from the infusion of a large volume of hypotonic irrigating solution into the circulation during endoscopic procedures (e.g. TURP, TURBT, PCNL). Occurs in 0.5% of TURPs.

Pathophysiology

Biochemical, haemodynamic, and neurological disturbances occur.

- Dilutional hyponatraemia is the most important—and serious—factor leading to the symptoms and signs. The serum sodium usually has to fall to <125mmol/L before the patient becomes unwell.
- Hypertension—due to fluid overload.
- Visual disturbances may be due to the fact that glycine is a neurotransmitter in the retina.

Diagnosis: symptoms, signs, and tests

Confusion, nausea, vomiting, hypertension, bradycardia, visual disturbances, seizures. If the patient is awake (spinal anaesthesia), they may report visual disturbances (e.g. flashing lights).

Preventing development of TUR syndrome and definitive treatment

Use a continuous irrigating cystoscope (provides low-pressure irrigation), limit resection time, avoid aggressive resection near the capsule, and reduce the height of the irrigant solution.[1]

For prolonged procedures, where a greater degree of fluid absorption may occur, measure serum Na and give 20–40mg of IV furosemide to start offloading the excess fluid that has been absorbed. If the serum sodium comes back as being normal, you will have done little harm by giving the furosemide, but if it comes back at <125mmol/L, you will have started treatment already and thereby may have prevented the development of severe TUR syndrome.

Techniques for measuring fluid overload

- Weighing machines can be added to the ordinary operating table.[2]
- Adding a little alcohol to the irrigating fluid and constantly monitoring the expired air with a breathalyser[3] allows an estimation of the volume of excess fluid which has been absorbed.

1 Madsen PO, Naber KG (1973) The importance of the pressure in the prostatic fossa and absorption of irrigating fluid during transurethral resection of the prostate. *J Urol* **109**:446–52.

2 Coppinger SW, Lewis CA, Milroy EJG (1995) A method of measuring fluid balance during transurethral resection of the prostate. *Br J Urol* **76**:66–72.

3 Hahn RG (1993) Ethanol monitoring of extravascular absorption of irrigating fluid. *Br J Urol* **72**:766–9.

Catheters and drains in urological surgery

Catheters

Made from latex or silastic (for patients with latex allergy or for long-term use—better tolerated by the urethral mucosa).

Types

- Self-retaining (also known as a Foley, balloon, or 2-way catheter) (Fig. 17.1). An inflation channel can be used to inflate and deflate a balloon at the end of the catheter, which prevents the catheter from falling out.
- A 3-way catheter (also known as an irrigating catheter). Has a third channel (in addition to the balloon inflation and drainage channels) which allows fluid to be run into the bladder at the same time as it is drained from the bladder (Fig. 17.2).

Size

The size of a catheter is denoted by its circumference in mm. This is known as the 'French' or 'Charriere' (hence Ch) gauge. Thus a 12 Ch catheter has a circumference of 12mm.

Uses

- Relief of obstruction (e.g. BOO due to BPE causing urinary retention—use the smallest catheter that you can pass; usually a 12 Ch or 14 Ch is sufficient in an adult).
- Irrigation of the bladder for clot retention (use a 20 Ch or 22 Ch 3-way catheter).
- Drainage of urine to allow the bladder to heal if it has been opened (trauma or deliberately, as part of a surgical operation).
- Prevention of ureteric reflux, maintenance of a low bladder pressure, where the ureter has been stented (post-pyeloplasty for PUJO).
- To empty the bladder before an operation on the abdomen or pelvis (deflating the bladder gets it out of harm's way).
- Monitoring of urine output post-operatively or in the unwell patient.
- For delivery of bladder instillations (e.g. intravesical chemotherapy or immunotherapy).
- To allow identification of the bladder neck during surgery (e.g. radical prostatectomy, operations on or around the bladder neck).

Drains

Principally indicated for the prevention of accumulation of urine, blood, lymph, or other fluids. Particularly used after the urinary tract has been opened and closed by suture repair. A suture line takes some days to become completely watertight and during this time, urine leaks from the closure site. A drain prevents accumulation of urine (a urinoma), the very presence of which can cause an ileus and if it becomes infected, an abscess can develop.

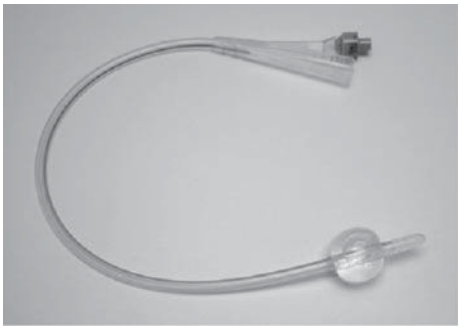

Fig. 17.1 A Foley catheter with the balloon inflated.

Fig. 17.2 2- and 3-way catheters.

- **Tube drains** (e.g. a Robinson's drain; Figs. 17.3 and 17.4): provide passive drainage (i.e. no applied pressure). Used to drain suture lines at a site of repair or anastomosis of the urinary tract. Avoid placing the drain tip on the suture line as this may prevent healing of the repair. Suture it to adjacent tissues to prevent it from being dislodged.
- **Suction drains** (e.g. Hemovac®; Figs. 17.5 and 17.6): provide active drainage (i.e. air in the drainage bottle is evacuated, producing a negative pressure when connected to the drain tube to encourage evacuation of fluid). Used for the prevention of accumulation of blood (a haematoma) in superficial wounds. Avoid in proximity to a suture line in the urinary tract—the suctioning effect may encourage continued flow of urine out of the hole, discouraging healing.

As a general principle, drains should be brought out through a separate stab wound, rather than through the main wound, since the latter may result in bacterial contamination of the main wound with subsequent risk of infection. Secure the drain with a thick suture to prevent it from inadvertently 'falling out'.

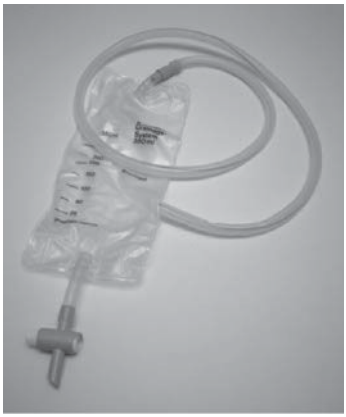

Fig. 17.3 A Robinson's (passive) drainage system.

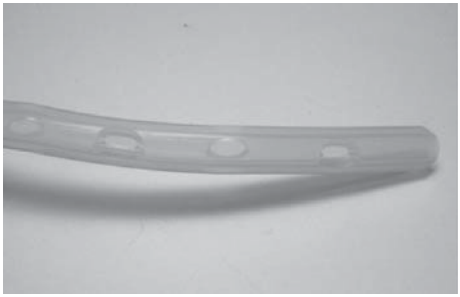

Fig. 17.4 Note the eyeholes of the Robinson's catheter.

Failure to deflate catheter balloon for removal of a urethral catheter

From time to time, an inflated catheter balloon will not deflate when the time comes for removal of the catheter.

- Try inflating the balloon with air or water—this can dislodge an obstruction.
- Leave a 10mL syringe firmly inserted in the balloon channel and come back an hour or so later.
- Try bursting the balloon by overinflation.
- Cut the end of the catheter off, proximal to the inflation valve—the valve may be 'stuck' and the water may drain out of the balloon.
- In the female patient, introduce a needle alongside your finger into the vagina and burst the balloon by advancing the needle through the anterior vaginal and bladder wall.
- In male patients, balloon deflation with a needle can also be done under USS guidance. Fill the bladder with saline using a bladder syringe so that the needle can be introduced percutaneously and directed towards the balloon of the catheter under USS control.
- Pass a ureteroscope alongside the catheter and deflate the balloon with the rigid end of a guidewire or with a laser fibre (the end of which is sharp).

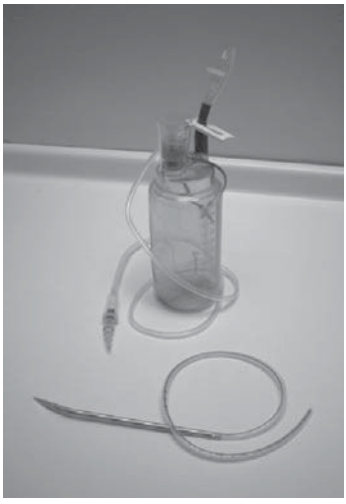

Fig. 17.5 A Redivac suction drain showing the drain tubing attached to the needle used for insertion and the suction bottle.

Fig. 17.6 The eyeholes at the tip of the suction drain.

Guidewires

An essential tool for endourological procedures.

Uses

As a track over which catheters or instruments can be passed into the ureter, collecting system of the kidney (retrograde or antegrade), or the bladder.

Types

Many different types of guidewire are available. They are classified according to their size, tip design, rigidity, and surface coating. These specific properties determine their use. All are radio-opaque so X-ray screening can be used to determine their position. They come prepackaged in a coiled sheath to allow ease of handling and storage (Fig. 17.7).

Size

'Size' refers to diameter measured in inches (length is usually around 150cm). Most common size are 0.035 inches (2.7 Ch) and 0.038 inches (2.9 Ch). Also available as 0.032 inches (2.5 Ch).

Tip design

Shape of tip—straight or angle (Fig. 17.8); a straight tip is usually adequate for most uses. Occasionally, an angled tip is useful for negotiating an impacted stone or for placing the guidewire in a specific position. Similarly, a J-shaped tip can negotiate an impacted stone—the curved leading edge of this guidewire type can sometimes suddenly flick past the stone (in this situation, a straight guidewire can inadvertently perforate the ureter, thereby creating a false passage).

Surface coating

Most standard guidewires are coated with polytetrafluoroethylene (PTFE) which has a low coefficient of friction, thus allowing easy passage of the guidewire through the ureter and of instruments over them. Some guidewires are coated with a polymer which, when wet, is very slippery (hydrophilic coating). In some cases, the entire length of the guidewire is so coated (e.g. Terumo Glidewire) and in others, just the tip (e.g. Sensor guidewire). The virtually friction-free surface of Glidewires makes them liable to slip out of the ureter and they, therefore, make unreliable safety wires (they can be exchanged for a wire with greater friction via a ureteric catheter). If allowed to become dry, these wires have a high coefficient of friction, which makes them difficult to manipulate.

Tip rigidity

The tip of all guidewires, over at least 3cm, is soft and, therefore, flexible. This reduces—although does not completely remove—the risk of ureteric perforation.

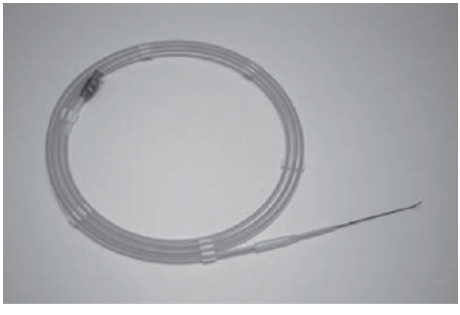

Fig. 17.7 Guidewires come prepackaged in a sheath for ease of handling.

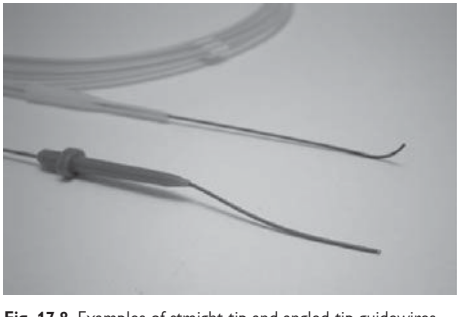

Fig. 17.8 Examples of straight-tip and angled-tip guidewires.

Shaft rigidity

Stiff guidewires are easier to manipulate than floppy ones and help to straighten a tortuous ureter (e.g. Amplatz Ultrastiff is particularly useful for this). Very malleable wires such as the Terumo Glidewire can be very useful for passing an impacted stone (for the same reason as J tip wires).

Some guidewires provide a combination of properties—a soft, floppy, hydrophilic-coated tip, with the remainder of the guidewire being stiff (e.g. Sensor guidewire).

Irrigating fluids and techniques of bladder washout

Glycine is used for endoscopic surgery requiring application of diathermy

Normal saline is used for:

- Irrigation of bladder following TURP, TURBT.
- Irrigation during ureteroscopy, PCNL.

Blocked catheter post-TURP and clot retention

Avoiding catheter blockage following TURP—keep the catheter bag empty; ensure a sufficient supply of irrigant solution.

The bladder will be painfully distended. Irrigant flow will have stopped.A small clot may have blocked the catheter or a chip of prostate may have stuck in the eye of the catheter. Attach a bladder syringe to the end of the catheter and pull back (Fig. 17.9). This may suck out the clot or chip of prostate and flow may restart. If it does not, draw some irrigant up into the syringe until it is about half full and forcefully inject this fluid into the bladder. This may dislodge (and fragment) a clot that has stuck to the eye of the catheter. If the problem persists, change the catheter. You may see the obstructing chip of prostate on the end of the catheter as it is withdrawn.

Blocked catheter post-TURBT

Use the same technique as for post-TURP catheter blockage, but avoid vigorous pressure on the syringe—the wall of the bladder will have been weakened at the site of tumour resection and it is possible to perforate the bladder, particularly in elderly women who have thin bladder walls.

Blocked catheters following bladder augmentation or neo-bladder

The suture line of the augmented bladder is weak and overvigorous bladder washouts can rupture the bladder.

Fig. 17.9 A bladder syringe—the tip is designed to fit onto a catheter.

JJ stents

These are hollow tubes with a coil at each end, which are inserted through the bladder (usually) into the ureter and thence into the renal pelvis. They are designed to bypass a ureteric obstruction (e.g. due to a stone) or drain the kidney (e.g. post-renal surgery). They have a coil at each end (hence, the alternative name of 'double pigtail' stent—the coils have the configuration of a pig's tail—or the less accurate name of J stent).

These prevent migration downwards (out of the ureter) or upwards (into the ureter). They are, therefore, 'self-retaining'. Made of polymers of variable strength and biodurability. Some stents have a hydrophilic coating which absorbs water and thereby, makes them more slippery and easier to insert. Stents are impregnated with barium- or bismuth-containing metallic salts to make them radio-opaque so that they can be visualized radiographically to ensure correct positioning.

Types

Classified by size and length. Common sizes are 6 or 7 Ch (Fig. 17.10). Common lengths for adults are 22–28cm. Multilength stents are of variable length, allowing them to accommodate to ureters of different length. A new stent design, the Polaris™ loop (Boston Scientific), is said to reduce bladder irritation and to make removal easier.

Stent materials

Polyurethane; silicone; C-flex; Silitek; Percuflex; biodegradable (experimental—obviates the need for stent removal and eliminates the possibility of the 'forgotten stent'). Some are coated (by chemical bonding) with a hydrogel (e.g. HydroPlus™) which provides a low friction surface so making insertion easier, encrustation less likely, and in theory, makes the stent more comfortable (whether this is the case in practice has not been established).

Indications and uses

- Relief of obstruction: from ureteric stones; benign (i.e. ischaemic) ureteric strictures; malignant ureteric strictures. The stent will relieve the pain caused by obstruction and reverse renal impairment if present.
- Prevention of obstruction: post-ureteroscopy (routine stenting after 'uncomplicated'* ureteroscopy is not necessary).
- Indications for J stenting post-ureteroscopy:
  - Ureteric injury.
  - Solitary kidney.
  - Large residual stone burden.
  - Raised creatinine (implying overall impaired renal function).
  - Ureteric stricture.
- Prevention of obstruction post-ESWL.
- Indications for J stenting post-ESWL:1
  - Stents reduce the incidence of steinstrasse with large renal calculi (1.5–3.5cm, 6% with a stent, and 13% without develop a steinstrasse post-ESWL).
  - Solitary kidney.

Fig. 17.10 A JJ stent.

  - Raised creatinine (implying overall impaired renal function).
  - (The analysis by the Joint AUA/EAU Nephrolithiasis Guideline Panel 2007[2] found no improvement in stone fragmentation with stenting, i.e. stents do not enhance ESWL efficacy.)
- 'Passive' dilatation of ureter prior to ureteroscopy.
- To ensure antegrade flow of urine following surgery (e.g. pyeloplasty) or injury to ureter.
- Following endopyelotomy (endopyelotomy stents have a tapered end, from 14 to 7 Ch, to keep the incised ureter 'open').
- Post-renal transplantation (stenting of re-implanted ureter).

An alternative to the J stent

A short-term 4 or 6 Ch ureteric catheter, attached to a 12 Ch urethral catheter (to stop the ureteric catheter from falling out), is an alternative form of post-ureteroscopy drainage.

In an RCT of 24h of ureteric catheter drainage post-ureteroscopy compared with no drainage, the non-catheterized group were more likely to report renal colic (45% vs 2%) and to have loin pain (76% vs 20%) than the ureteric catheterized group.[3] Analgesic use was greater in the non-catheterized group (67% vs 20%). Twenty percent of non-catheterized patients and 5% of catheterized returned to hospital for analgesia (but no patient required readmission). The only disadvantage of this technique was a higher reported rate of urethral irritation (37% vs 4%) in the catheterized patients. It has the obvious advantage of ease of removal of the catheter

* The definition of 'uncomplicated' ureteroscopy is not precise. 'Complicated' ureteroscopy has been variously defined as (a) ureteral perforation (i.e. mucosal injury); (b) severe ureteric oedema at the site of the stone; (c) impaction (which means difficulty getting a guidewire past the stone ('cork in a bottle' stone); (d) prolonged operation (no precise definition of what 'long' is); (e) one where ureteral dilatation was carried (to define such ureteroscopies as 'complicated' is contentious because some urologists routinely 'dilate' with a dual lumen catheter to allow double guidewire placement. Does this automatically make all their ureteroscopies 'complicated'?).

without the need for a second procedure and avoids the potential risk of the forgotten stent.

Symptoms and complications of stents

- **Stent symptoms:** common (78%)—suprapubic pain, LUTS (frequency, urgency—stent irritates trigone), haematuria, inability to work.4 More than 80% of patients have stent-related pain that affects daily activities, 32% report sexual dysfunction, and 58% report reduced work capacity and loss of income. A-blockers may help reduce pain with voiding and overall analgesic use.
- **UTI:** development of bacteriuria after stenting is common. In a small proportion, sepsis can develop. In such cases, consider placement of a urethral catheter to lower the pressure in the collecting system and prevent reflux of infected urine. Stents coated with the antibacterial triclosan are no better than non-coated stents in preventing stent-associated UTI.
- **Incorrect placement:** too high (distal end of stent in ureter; subsequent stent removal requires ureteroscopy; can be technically difficult; percutaneous removal may be required). Too low (proximal end not in renal pelvis; stent may not, therefore, relieve obstruction).
- **Stent migration** (up the ureter or down the ureter and into bladder).
- **Stent blockage:** catheters and stents become coated with a biofilm when in contact with urine (a protein matrix secreted by bacteria-colonizing stent). Calcium, magnesium, and phosphate salts become deposited. Biofilm build-up can lead to stent blockage or stone formation on the stent (Fig. 17.11). Stents coated with heparin are no better than non-coated stents in preventing stent biofilm formation or encrustation.
- **The 'forgotten stent':** rare, but potentially very serious as the biofilm may become encrusted with stone, making removal technically very difficult. If the proximal end only is encrusted, PCNL may be required to remove the stone and then the stent. If the entire stent is encrusted, open removal via several incisions in the ureter may be necessary.

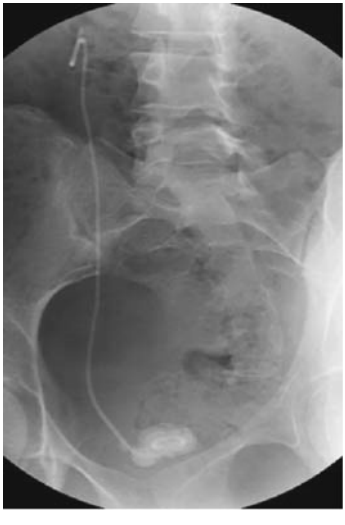

Fig. 17.11 An encrusted stent.

Commonly asked questions about stents

Does urine pass though the centre of the stent?

No, it passes around the outside of the stent. Reflux of urine occurs through the centre.

Should I place a JJ stent after ureteroscopy? (see Indications and uses)

A stent should be placed if:

- There has been ureteric injury (e.g. perforation—indicated by extravasation of contrast).
- There are residual stones that might obstruct the ureter.
- The patient has had a ureteric stricture that required dilatation.
- Solitary kidney.
- Raised creatinine (implying overall impaired renal function).

Routine stenting after ureteroscopy for distal ureteric calculi is unnecessary.[5,6] Many urologists will place a stent after ureteroscopy for proximal ureteric stones.

Do stents cause obstruction?

In normal kidneys, stents cause a significant and substantial increase in intrarenal pressure, which persists for up to 3 weeks.[7] (This can be prevented by placing a urethral catheter.)

Do stents aid stone passage?

Ureteric peristalsis requires coaptation of the wall of the ureter proximal to the bolus of urine to be transmitted down the length of the ureter. JJ stents paralyse ureteric peristalsis. In dogs, the amplitude of each peristaltic wave (measured by an intraluminal ureteric balloon) falls (from 50 to 15mmHg) and the frequency of ureteric peristalsis falls (from 11 to 3 waves/min). Peristalsis takes several weeks to recover. 3mm ball bearings placed within a non-stented dog ureter take 7 days to pass compared with 24 days in a stented ureter.

Are stents able to relieve obstruction due to extrinsic compression of a ureter?

Stents are less effective at relieving obstruction due to extrinsic obstruction by, for example, tumour or retroperitoneal obstruction.[8] They are much more effective for relieving obstruction by an intrinsic problem (e.g. a stone). Placement of two stents may provide more effective drainage (figure-of-eight configuration may produce more space around the stents for drainage).

For acute, ureteric stone obstruction with a fever, should I place a JJ stent or a nephrostomy?

In theory, one might imagine that a nephrostomy is better than a JJ stent—it can be done under local anaesthetic (JJ stent insertion may require general anaesthesia); it lowers the pressure in the renal pelvis to 0 or a negative value whereas a JJ stent results in a persistently positive pressure, it is less likely to be blocked by thick pus, and it allows easier subsequent imaging (contrast can be injected down the ureter—a nephrostogram—to determine if the stone has passed). A randomized trial of 42 patients with obstructing, infected stones (temperature >38°C and/or WBC >17 000/mm^3) showed J stenting (6 or 7 Ch J stent with a Foley bladder catheter) and nephrostomy drainage (8 Ch) to be equally effective in terms of time to normalization of temperature and white count (approximately 2–3 days) and in-hospital stay. As a consequence, the EAU/AUA Nephrolithiasis Guideline Panel[10] recommends that the system of drainage of the obstructed, infected kidney is left to the discretion of the urologist.

1 Al-Awadi KA, Abdul Halim H, Kehinde EO, Al-Tawheed A (1999) Steinstrasse: a comparison of incidence with and without J stenting and the effect of J stenting on subsequent management. *BJU Int* **84:**618–21.

2 Preminger GM, Tiselius HG, Assimos DG, *et al.* (2007) 2007 Guideline for the management of ureteral calculi, joint EAU/AUA Nephrolithiasis Guideline Panel. *J Urol* **178**:2418–34.

3 Djaladat H, Tajik P, Payandemehr P, Alehashemi S (2007) Ureteral catheterization in uncomplicated ureterolithotripsy: a randomized, controlled trial. *Eur Urol* **52:**836–41.

4 Joshi HB, Stainthorpe A, MacDonagh RP, *et al.* (2003) Indwelling ureteral stents: evaluation of symptoms, quality of life and utility. *J Urol* **169**:1065–9.

5 Srivastava A, Gupta R, Kumar A, Kapoor R, Mandhani A (2003) Routine stenting after ureteroscopy for distal ureteral calculi is unnecessary: results of a randomized controlled trial. *J Endourol* **17**:871–4.

6 Netto Jr NR, Ikonomidis J, Zillo C (2001) Routine ureteral stenting after ureteroscopy for ureteral lithiasis: is it really necessary? *J Urol* **166:**1252–4.

7 Ramsay JW, Payne SR, Gosling PT, Whitfield HN, Wickham JE, Levison DA (1985) The effects of double J stenting on obstructed ureters. An experimental and clinical study. *Br J Urol* **57**:630–4.

8 Docimo SG (1989) High failure rate of indwelling ureteral stents in patients with extrinsic obstruction: experience at two institutions. *J Urol* **142**:277–9.

9 Pearle MS, Pierce HL, Miller GL, *et al* (1998) Optimal method of urgent decompression of the collecting system for obstruction and infection due to ureteral calculi. *J Urol* **160**:1260–4.

10 Preminger GM, Tiselius HG, Assimos DG, *et al.* (2007) 2007 Guideline for the management of ureteral calculi Joint EAU/AUA Nephrolithiasis Guideline Panel. *J Urol* **178**:2418–34.

Lasers in urological surgery

Light amplification by stimulated emission of radiation.

Photons are emitted when an atom is stimulated by an external energy source and its electrons, having been so excited, revert to their steady state. In a laser, the light is coherent (all the photons are in phase with one another), collimated (the photons travel parallel to each other), and of the same wavelength (monochromatic). The light energy is thus 'concentrated', allowing delivery of high energy at a desired target.

The holmium:YAG laser is currently the principal urological laser. It has a wavelength of 2140nm and is highly absorbed by water and, therefore, by tissues which are composed mainly of water. The majority of the holmium laser energy is absorbed superficially, resulting in a superficial cutting or ablation effect. The depth of the thermal effect is no greater than 1mm. The holmium:YAG laser produces a cavitation bubble that generates only a weak shock wave as it expands and collapses. Holmium laser lithotripsy occurs primarily through a photothermal mechanism that causes stone vaporization.

Uses of the holmium:YAG laser

- Laser lithotripsy (ureteric stones, small intrarenal stones, bladder stones).
- Resection of the prostate (holmium laser prostatectomy).
- Division of urethral strictures.
- Division of ureteric strictures, including PUJO.
- Ablation of small bladder, ureteric, and intrarenal TCCs.

Advantages

- The holmium laser energy is delivered via a laser fibre (Fig. 17.12) which is thin enough to allow its use down a flexible instrument without affecting the deflection of that instrument and can, therefore, gain access to otherwise inaccessible parts of the kidney.
- Zone of thermal injury adjacent to the tip of the laser fibre is limited to no more than 1mm; the laser can safely be fired at a distance of 1mm from the wall of the ureter.
- Can be used for all stone types.
- Minimal stone migration effect because of minimal shock wave generation.

Disadvantages

- High cost.
- Produces a dust cloud during stone fragmentation, which temporarily obscures the view.
- Can irreparably damage endoscopes if inadvertently fired near or within the scope.
- Relatively slow stone fragmentation—the laser fibre must be 'painted' over the surface of the stone to vaporize it.

Greenlight PVP for TURP

The 80 or 120W KTP laser is used for photoselective vaporization of the prostate. The laser is green (hence, the name 'greenlight' laser) and is absorbed by haemoglobin, generating a heating effect which causes vaporization of targeted tissue.

The procedure is done under general or spinal anaesthetic.

Advantages

Saline is used for irrigation (therefore, no risk of TUR syndrome).

Disadvantages

No tissue for histological examination.

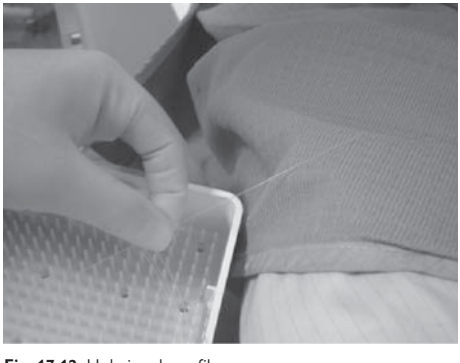

Fig. 17.12 Holmium laser fibre.

Diathermy

Diathermy is the coagulation or cutting of tissues through heat.

Monopolar diathermy

When an electric current passes between two contacts on the body, there is an increase in temperature in the tissues through which the current flows. This increase in temperature depends on the volume of tissue through which the current passes, the resistance of the tissues, and the strength of the current. The stronger the current, the greater the rise in temperature. If one contact is made large, the heat is dissipated over a wide area and the rise of temperature is insignificant. This is the earth or neutral electrode and under this, the rise in temperature is only 1 or 2°C. The working electrode or diathermy loop is thin so that the current density is maximal and, therefore, so is the heating effect.

When a direct current is switched on or off, nerves are stimulated and muscles will twitch. If the switching on and off is rapid enough, there is the sustained contraction familiar to the physiology class as the 'tetanic contraction'. If a high frequency alternating current is used (300kHz to 5MHz), there is no time for the cell membranes of nerve or muscle to become depolarized and nerves and muscles are not stimulated (they are stimulated at lower frequencies).

The effect of the diathermy current on the tissues depends on the heat that is generated under the diathermy loop. At relatively low temperatures, coagulation and distortion of small blood vessels occurs. If the current is increased to raise the temperature further, water within cells vaporizes and the cells explode. This explosive vaporization literally cuts the tissues apart.

Bipolar diathermy

Bipolar diathermy involves the passage of electrical current between two electrodes on the same hand piece. It is inherently safer than monopolar diathermy since the current does not pass through the patient and diathermy burns cannot, therefore, occur.

Potential problems with diathermy

The diathermy isn't working

- Do not increase the current.
- Check that the irrigating fluid is glycine (sodium chloride conducts electricity causing the diathermy to short-circuit).
- Check that the diathermy plate is making good contact with the skin of the patient.
- Check that the lead is undamaged.
- Check that the resectoscope loop is securely fixed to the contact.

Modern diathermy machines have warning circuits which sound an alarm when there is imperfect contact between the earth plate and the patient.

Diathermy burns

If current returns to earth through a small contact rather than the broad area of the earth pad, then the tissues through which the current passes will be heated just like those under the cutting loop. If the pad is making good contact, the current will find it easier to run to earth through the pad and no harm will arise, even when there is accidental contact with some metal object. The real danger arises when the diathermy pad is not making good contact with the patient. It may not be plugged in or its wire may be broken. Under these circumstances, the current must find its way to earth somehow and any contact may then become the site of a dangerous rise in temperature.

Pacemakers and implantable cardioverter defibrillators (ICDs) and the use of diathermy

See Box 17.2 for diathermy problems and their prevention.

Box 17.2 Pacemakers, ICDs, and diathermy: problems and their prevention

Diathermy can cause electrical interference of a pacemaker or ICD, leading to inhibition, triggering of electrical output from the device, reprogramming, asynchronous pacing, damage to the circuitry of the device, or triggering of defibrillator discharge. An electrical current can also be induced in the pacemaker or ICD leads, which can, in turn, cause tissue heating, leading to myocardial damage.

- **Pacemaker inhibition:** the high frequency of diathermy current may simulate the electrical activity of myocardial contraction so the pacemaker can be inhibited. If the patient is pacemaker-dependent, the heart may stop.
- **Phantom reprogramming:** the diathermy current may also simulate the radiofrequency impulse by which the pacemaker can be reprogrammed to different settings. The pacemaker may then start to function in an entirely different mode.
  - **The internal mechanism of the pacemaker:** may be damaged by the diathermy current if this is applied close to the pacemaker.
  - **Ventricular fibrillation:** if the diathermy current is channelled along the pacemaker lead, ventricular fibrillation may be induced.
  - **Myocardial damage:** another potential effect of channelling of the diathermy current along the pacemaker lead is burning of the myocardium at the tip of the pacemaker lead. This can subsequently result in ineffective pacing.

It was formerly recommended that a magnet was placed over the pacemaker to overcome pacemaker inhibition and to make the pacemaker function at a fixed rate. This can, however, result in phantom reprogramming. For demand pacemakers, it is better to programme the pacemaker to a fixed rate (as opposed to demand pacing) for the duration of the operation. Consult the patient's cardiologist for advice.

Other precautions

- The patient plate should be sited so that the current path does not go right through the pacemaker. Ensure that the indifferent plate is correctly applied as an improper connection can cause grounding of the diathermy current through the ECG monitoring leads and this can affect pacemaker function. The indifferent plate should be placed as close as possible to the pacemaker (e.g. over the thigh or buttock).
- The diathermy machine should be placed well away from the pacemaker and should certainly not be used within 15cm of it.
- The heartbeat should be continually monitored and a defibrillator and external pacemaker should be at hand.
- Try to use short bursts of diathermy at the lowest effective output
- Use bipolar diathermy in preference to monopolar (not practical for many urological procedures where the only form of diathermy that can be used is monopolar).

- Give antibiotic prophylaxis (as for patients with artificial heart valves).
- Because the pacemaker-driven heart will not respond to fluid overload in the normal way, the resection should be as quick as possible and fluid overload should be avoided.

Further reading

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Medicines and Healthcare Products Regulatory Agency (2006) Guidelines for the perioperative management of patients with implantable cardioverter defibrillators, where the use of diathermy is anticipated [online]. Available from: http://www.mhra.gov.uk.

Salukhe TV, Dob D, Sutton R (2004) Pacemakers and defibrillators: anaesthetic implications. *Br J Anaesth* **93:**95–104.

Sterilization of urological equipment

Techniques for sterilization

Autoclaving: modern cystoscopes and resectoscopes, including components such as light leads, are autoclavable. Standard autoclave regimens heat the instruments to 121°C for 15min or 134°C for 3min.

Chemical sterilization: this involves soaking instruments in an aqueous solution of chlorine dioxide (Tristel), an aldehyde-free chemical (there has been a move away from formaldehyde because of health and environmental concerns). Chlorine dioxide solutions kill bacteria, viruses (including HIV and hepatitis B and C), spores, and mycobacteria.

Cameras cannot be autoclaved. Use a camera sleeve or sterilize camera between cases in solutions such as Tristel.

Sterilization and prion diseases

Variant CJD (vCJD) is a neurodegenerative disease caused by a prion protein (PRP). Other examples of neurodegenerative prion diseases include classic CJD, kuru, sheep scrapie, and bovine spongiform encephalopathy (BSE). Variant CJD and BSE are caused by the same prion strain and represent a classic example of cross-species transmission of a prion disease.

There has been much recent concern about the potential for transmission of vCJD between patients via contaminated surgical instruments. Classic CJD may be transmitted by neurosurgical and other types of surgical instruments because normal hospital sterilization procedures do not completely inactivate prions.[1] It is not possible at present to quantify the risks of transmission of prion diseases by surgical instruments. To date, iatrogenic CJD remains rare, with 267 cases having been reported worldwide up to 2000.[2]

The risk of transmission of CJD may be higher with procedures performed on organs containing lymphoreticular tissue, such as tonsillectomy and adenoidectomy, because vCJD targets these tissues and is found in high concentrations there. For this reason, there was a move towards the use of disposable, once-only-use instruments for procedures such as tonsillectomy. However, these instruments have been associated with a higher post-operative haemorrhage rate[3] and as a consequence, ENT departments in the UK are no longer obliged to use disposable instruments.

In the UK, the Advisory Committee on Dangerous Pathogens and Spongiform Encephalopathy[4] provides advice on appropriate methods of cleaning and sterilization of surgical instruments. Prions are particularly resistant to conventional chemical (ethylene oxide, formaldehyde, and chlorine dioxide) and standard autoclave regimens, and dried blood or tissue remaining on an instrument could harbour prions that will not then be killed by the sterilization process. Once proteinaceous material such as blood or tissue has dried on an instrument, it is very difficult to

subsequently be sure that the instrument has been sterilized. Sterilization should include:

- **Pre-sterilization cleaning:** initial low temperature washing (<35°C) with detergents and an ultrasonic cleaning system removes and prevents coagulation of prion proteins—sonic cleaners essentially 'shake' attached material from the instrument.
- **Hot wash.**
- **Air drying.**
- **Thermal sterilization:** longer autoclave cycles at 134–137°C for at least 18min (or six successive cycles with holding times of 3min) or 1h at conventional autoclave temperatures may result in a substantial reduction in the level of contamination with prions.

The latest models of pre-sterilization cleaning devices—automated thermal washer disinfectors—perform all of these cleaning tasks within one unit.

Enzymatic proteolytic inactivation methods are under development.

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Telescopes and light sources in urological endoscopy

There are three types of modern urological telescopes—rigid, semi-rigid, and flexible. These endoscopes may be used for inspection of the urethra and bladder (cystoscourethroscopes—usually simply called cystoscopes), the ureter and collecting system of the kidney (ureteroscopes and ureterorenoscopes), and via a percutaneous access track, the kidney (nephroscopes). The light sources and image transmission systems are based on the innovative work of Professor Harold Hopkins from the University of Reading.

The Hopkins rod-lens system

Introduced by Professor Harold Hopkins in 1959. The great advance in telescope design was the development of the rod-lens telescope which replaced the conventional system of glass lens with rods of glass,separated by thin air spaces which, essentially, were air lenses (Fig. 17.13). By changing the majority of the light transmission medium from air to glass, the quantity of light that could be transmitted was doubled. The rods of glass were also easier to handle during manufacture and therefore, their optical quality was greater.

The angle of view of the telescope can be varied by placing a prism behind the objective lens. 0°, 12°, 30°,' and 70° scopes are available.

Lighting

Modern endoscopes (urological and those used to image the GI tract) use fibre optic light bundles to transmit light to the organ being inspected (developed by Karl Storz). Each glass fibre is coated with glass of a different refractive index so that light entering at one end is totally internally reflected and emerges at the other (Fig. 17.14). These fibre optic bundles can also be used for image (as well as light) transmission as long as the arrangement of the fibres at either end of the instrument is the same (coordinated fibre bundles are not required for simple light transmission). The fibre bundles are tightly bound together only at their end (for coordinated image transmission). In the middle, the bundles are not bound—this makes the instrument flexible (e.g. flexible cystoscope and flexible ureteroscope).

Digital image capture systems

Conventional analog camera systems have a 3-chip camera with separate sensors for red, green, and blue colours. They convert analog data into digital data for image storage and enhancement. Image distortion can reduce image quality (a 'spectrum' effect can occur—bands of red, green, and blue across the image). A recent innovation in scope design is chip miniaturization which allows these sensors to be placed at the tip of the flexible cystoscope or flexible ureteroscope so allowing a totally digital imaging system (as in a digital camera). The resolution and image quality is superior to analog systems.

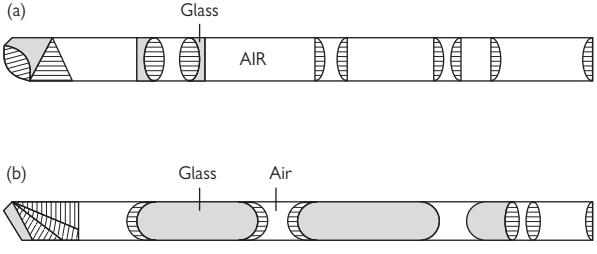

Fig. 17.13 (a) Diagram of conventional cystoscope. The glass lenses are held in place by metal spacers and separated by air spaces; (b) Rod-lens telescope with 'lenses' of air, separated by 'spaces' of glass, with no need for metal spacers. (Reproduced from Blandy J, Fowler C (1995) Urology. Oxford: Blackwell Science, pp. 3–5, with permission from Wiley Blackwell.)

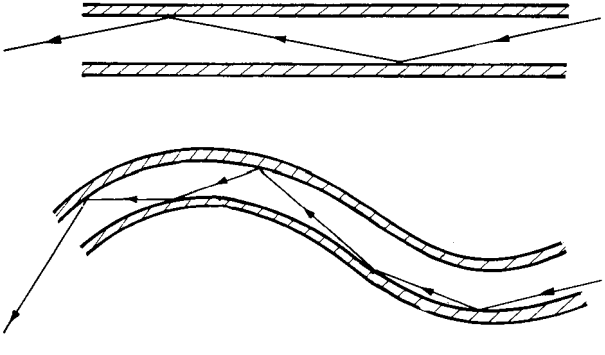

Fig. 17.14 Total internal reflection permits light to travel along a flexible glass fibre. (From Blandy and Fowler 1996, reproduced with permission from Wiley Blackwell.[2])

* In days gone by, when a tiny lamp at the end of the telescope was used for illumination, it was necessary to have a slightly angled line of vision, otherwise the light bulb got in the way of the view. The 30° scope is a throw back to this historical requirement.

Consent: general principles

Consent is required before you examine, treat, or care for a competent adult (a person aged 16 or more).

Think of obtaining consent as a *process* rather than an *event*. In order to give consent, a patient must understand the nature, purpose, and likely effects (outcomes, risks) of the treatment. From the information they receive, the patient must be able to weigh up the risks against benefits and so arrive at an informed choice. They must not be coerced into making a decision (e.g. by the doctor in a hurry). Giving the patient time to reach a decision is a good way of avoiding any accusation that they were pressured into a decision. To reiterate—think of consent as a process rather than an event.

Giving information and level of disclosure

How much information should you give? What options and risks should you mention? The adequacy of your consent will be judged against the Bolam test: 'A doctor is not guilty of negligence if he acted in accordance with a practice accepted by a responsible body of medical men skilled in that particular art'. (That body of medical men must be a competent and reasonable body and the opinion expressed must have a logical basis—the ***Bolitho*** modification of the ***Bolam*** defence.)

You have a duty to discuss the range of treatment options available (the alternatives), regardless of their cost, in a form the patient can understand and the side effects and risks that are relevant to the individual patient's circumstances.

A risk is defined as a material one (one that matters, one that is important) if a reasonable person in the patient's circumstances, if warned of that risk, would attach significance to it (e.g. loss of the tip of a little finger may be of little long-term consequence to many people, but for the concert pianist, it could be a disaster). In the words of Lord Scarman, disclosure is necessary:

' ... where the risk is such that in the court's view, a prudent person in the patient's situation would have regarded it as significant.'

Thus, the amount and type of information you give is different in every case. Just because there is a less than 1 in 100 chance of a particular risk materializing does not mean you need not warn about this particular risk:

'When one refers to a 'significant risk', it is not possible to talk in precise percentages.' (Lord Woolf in *Pearce vs United Bristol HA* 1996.)[1]

The obvious example is the need to warn of post-vasectomy pregnancy which occurs very infrequently (1 in 3000 cases). Failure to warn of such a risk would nowadays be regarded as substandard care.

Remember, it can be argued that the consent was not valid because the amount of information you gave was not enough or was in a form the patient could not understand.

Recording

Remember, record the consent discussion in the notes. If you do not record what you said, you might as well not bother saying it. If a patient later claims that they were not told of a particular risk or outcome, it will be difficult to refute this if your notes do not record what you said. Writing 'risks explained' is inadequate. When cases do come to court, this is usually several years after the events in question. You will have forgotten precisely what you said to the patient and it will not take much effort on the part of a barrister to suggest that you might not have said everything that you thought you said! If you give a written information sheet, record that you have done so and put a copy of the version you gave in the notes.

The consent form

The consent form is designed to record the patient's decision and to some extent, the discussions that took place during the consent process (although the space available for recording the discussion, even on the new NHS consent form, is limited). It is not proof that the patient was properly informed—that valid consent was obtained. Avoid, if possible, technical abbreviations such as TURBT. A patient could reasonably claim not to have understood what this was. Try to avoid standing over the patient waiting for them to sign the form. It is a good practice to leave the form with them and to return after a few minutes—they will feel less pressured and can ask further questions if they wish.

Children

Children aged less than 16 may give consent as long as they fully understand what is involved in the proposed examination or treatment (a parent cannot override the competent child's consent to treatment). However, a child cannot *refuse* consent to treatment (i.e. a parent can override a child's refusal to consent—the parent can consent on the child's behalf if the child refuses consent, although such situations are rare).

1 Pearce and another *v.* United Bristol Healthcare NHS Trust, 48 *BMLR* 118. 1996.

Cystoscopy

A basic skill of the urologist. Allows direct visual inspection of the urethra and bladder.

Indications

- Haematuria.
- Irritative LUTS (marked frequency and urgency) where intravesical pathology is suspected (e.g. carcinoma in situ, bladder stone).
- For bladder biopsy.
- Follow-up surveillance of patients with previously diagnosed and treated bladder cancer.
- Retrograde insertion of ureteric stents and removal.
- Cystoscopic removal of stones.

Technique

- Flexible cystoscopy: flexible cystoscope is easily passed down the urethra and into the bladder following instillation of lubricant gel (with or without local anaesthetic—a meta-analysis of nine RCTs showed no difference in pain control between lidocaine gel and plain gel lubrication).11 Principally diagnostic, but small biopsies can be taken with a flexible biopsy forceps, small tumours can be fulgurated (with a diathermy probe) or vaporized (with a laser fibre), and JJ stents can be inserted and removed using this type of cystoscope.
- Rigid cystoscopy: rigid metal instrument which can be passed under local anaesthetic in women (short urethra), but usually requires general anaesthetic. Preferred over flexible cystoscopy where deeper biopsies will be required or as an antecedent to TURBT or cystolitholapxy where it is anticipated that other pathology will be found (tumour, stone).

The flexible cystoscope uses fibre optics for illumination and image transmission. It can be deflected through 270°.

Common post-operative complications and their management

Mild burning discomfort and haematuria are common after both flexible and rigid cystoscopy. It usually resolves within hours. Bacteriuria after flexible cystoscopy occurs in about 8–9% of patients (4–5% have bacteriuria before cystoscopy) and this rate is reduced by prophylactic antibiotics (see Table 17.1).

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications of flexible cystoscopy

Warn the patient that if the cystoscopy is being done because of haematuria, it is possible that a bladder cancer may be found, which may require further treatment. You should specifically seek consent for biopsy (removal of tissue if an abnormality is found).

Common

- Mild burning or bleeding on passing urine for a short period after operation.
- Biopsy of an abnormal area in the bladder may be required.

Occasional

- Infection of bladder requiring antibiotics.

Rare

- Temporary insertion of a catheter.
- Delayed bleeding requiring removal of clots or further surgery.
- Injury to urethra causing delayed scar formation (a stricture).

Serious or frequently occurring complications of rigid cystoscopy

- As for flexible cystoscopy.
- The use of heat (diathermy) may be required to cauterize biopsy sites.
- Very rarely, perforation of the bladder can occur, requiring temporary insertion of a catheter or open surgical repair.

1 Patel AR, Jones JS, Babineau D (2008) Lidocaine 2% gel versus plain lubricating gel for pain reduction during flexible cystoscopy: a meta-analysis of prospective, randomized controlled trials. *J Urol* **179**:986–90.

Transurethral resection of the prostate (TURP)

Indications

- Bothersome LUTS which fail to respond to changes in lifestyle or medical therapy.
- Recurrent acute urinary retention.
- Renal impairment due to BOO (high-pressure ***chronic*** urinary retention).
- Recurrent haematuria due to BPE.
- Bladder stones due to prostatic obstruction.

Post-operative care

A 3-way catheter is left *in situ* after the operation, through which irrigation fluid (normal saline) is run to dilute the blood so that a clot will not form to block the catheter. The rate of inflow of the saline is adjusted to keep the outflow a pale pink rosé colour and as a rule, the rate of inflow can be cut down after about 20min. The irrigation is continued for 12–24h. The catheter is removed the day after (second post-operative day) if the urine has cleared to a normal colour (TWOC or trial of void (TOV)).

Common post-operative complications and their management

Blocked catheter post-TURP

Common

The catheter may become blocked with clot or a prostatic 'chip' which was inadvertently left in the bladder at the end of the operation.

- Apply a bladder syringe to the end of the catheter to try to dislodge the obstruction.
- If this fails, withdraw some irrigant into the syringe and flush the catheter.
- If this fails, change the catheter. The obstructing chip of prostate may be found stuck in one of the eyeholes of the catheter.
- Pass a new catheter on an introducer.

If the bladder has been allowed to become so full of clot that a simple bladder washout is unable to evacuate it all, return the patient to the theatre for clot evacuation.

Haemorrhage

Minor bleeding after TURP is common and will stop spontaneously. A simple system to allow communication between staff is to describe the colour of the urine draining through the catheter as the same as a rosé wine (minor haematuria), a dark red wine (moderate haematuria), or frank blood (bright red bleeding, suggesting serious haemorrhage). The rosé urine requires no action. Dark red urine should be managed by increasing the flow of irrigant and by applying gentle traction to the catheter (with the balloon inflated to 40–50mL), thereby pulling it onto the bladder neck or into the prostatic fossa to tamponade bleeding for 20min

or so. This will usually result in the urine clearing. An attempt at controlling heavier bleeding by these techniques may be tried, but at the same time, you should make preparations to return the patient to theatre because it is unlikely that bleeding of this degree will stop. The bleeding vessel(s), if seen, is controlled with diathermy. If bleeding persists, open surgical control is required—the prostatic capsule is opened, the bleeding vessels sutured, and the prostatic bed packed. Post-operative bleeding requiring a return to theatre occurs in 0.5% of cases.[1]

BAUS procedure-specific consent form—recommended discussion of adverse events

Serious or frequently occurring complications of TURP

- Temporary mild burning on passing urine, urinary frequency, haematuria.
- Retrograde ejaculation in 75% of patients.
- Failure of symptom resolution.
- Permanent inability to achieve an erection adequate for sexual activity.
- UTI requiring antibiotic therapy.
- Ten percent of patients require redo surgery for recurrent prostatic obstruction.
- Failure to pass urine after the post-operative catheter has been removed.
- In 10% of patients, prostate cancer is found on subsequent pathological examination of the resected tissue.
- Urethral stricture formation requiring subsequent treatment.
- Incontinence (loss of urinary control)—may be temporary or permanent.
- Absorption of irrigating fluid causing confusion and heart failure (TUR syndrome).
- Very rarely, perforation of the bladder requiring a temporary urinary catheter or open surgical repair.

Alternative therapy: observation, drugs, catheter, stent, laser prostatectomy, open operation.

1 Emberton M, Neal DE, Black N, *et al.* (1995) The National Prostatectomy Audit: the clinical management of patients during hospital admission. *Br J Urol* **75**:301–16.

Transurethral resection of bladder tumour (TURBT)

Indications

- Local control of non-muscle-invasive bladder cancer (i.e. stops bleeding tumours).
- **Staging of bladder cancer:** to determine whether the cancer is non-muscle-invasive or muscle-invasive so that subsequent treatment and appropriate follow-up can be arranged.

Post-operative care

A 2- or 3-way catheter is left *in situ* after the operation, depending on the size of the tumour and, therefore, on the likelihood that bleeding requiring irrigation will be required. As for TURP, normal saline is run through the catheter to dilute the blood so that a clot will not form to block the catheter. It is particularly important to avoid catheter blockage post-TURBT since this could lead to distension of the bladder already weakened by resection of a tumour. The period of irrigation is usually shorter than that required after TURP and for small tumours, the catheter may be removed the day after the TURBT. For larger tumours, remove it 2 days later.

Common operative and post-operative complications and their management

Bladder perforation during TURBT

Small perforations into the perivesical tissues (extraperitoneal) are not uncommon when resecting small tumours of the bladder and so long as you have secured good haemostasis and all the irrigating fluid is being recovered, no additional steps are required, except that perhaps one should leave the catheter in for 4 rather than 2 days.

Intraperitoneal perforations (through the wall of the bladder, through the peritoneum, and into the peritoneal cavity) are uncommon, but far more serious.

Is it an extraperitoneal or intraperitoneal perforation? Establishing this can be difficult. Both can cause marked distension of the lower abdomen—an intraperitoneal perforation by allowing escape of irrigating solution directly into the abdominal cavity and an extraperitoneal perforation by expanding the retroperitoneal space, with fluid then diffusing directly into the peritoneal cavity. The fact that a suspected intraperitoneal perforation was actually extraperitoneal becomes apparent only at laparotomy when no hole can be found in the peritoneum overlying the bladder (the peritoneum over the bladder is *not* breached in an extraperitoneal perforation).

When there is no abdominal distension, the volume of extravasated fluid is likely to be low and if the perforation is small, it is reasonable to manage the case conservatively. Achieve haemostasis and pass a catheter. Make frequent post-operative assessments of the patient's vital signs and abdomen (worsening abdominal pain, distension, and tenderness suggest the need for laparotomy).

Where there is marked abdominal distension, whether the perforation is extraperitoneal or intraperitoneal, explore the abdomen, principally to drain the large amount of fluid (which can compromise respiration in an elderly patient) by splinting the diaphragm, but also to check that loops of bowel adjacent to the site of perforation have not been injured at the same time. Failing to make the diagnosis of an intraperitoneal perforation, particularly if the bowel has been injured, is a worse situation to be in than performing a laparotomy for a suspected intraperitoneal perforation, but then finding that the perforation was 'only' extraperitoneal.

Open bladder repair

Pfannenstiel incision or lower midline abdominal incision, open the bladder, evacuate the clot, control bleeding, and repair the hole. Open the peritoneum and inspect small and large bowel for perforations. Leave a urethral catheter and a drain in place.

Blocked catheter post-TURBT

The catheter may become blocked with clot. Use the same technique for unblocking it as for TURP, but avoid vigorous washouts of the bladder because of the risk of bladder perforation.

Haemorrhage

Minor bleeding after TURBT is common and will stop spontaneously. The only 'technique' for controlling it is to ensure that an adequate flow of irrigant is maintained (to dilute the blood and thereby, preventing clots from forming). If bleeding persists, return the patient to theatre for endoscopic control.

TUR syndrome

Uncommon after TURBT unless the tumour is large and the resection, therefore, long.

BAUS procedure-specific consent form—recommended discussion of adverse events

Serious or frequently occurring complications of TURBT

Common complications

- Mild burning on passing urine.
- Additional treatment (intravesical chemotherapy or immunotherapy) may be required to reduce the risk of future tumour recurrence.
- UTI.
- No guarantee of bladder cancer cure.
- Tumour recurrence is common.

Rare complications

- Delayed bleeding requiring removal of clots or further surgery.
- Damage to drainage tubes from kidney (ureters) requiring additional therapy.
- Development of a urethral stricture.
- Bladder perforation requiring a temporary urinary catheter or open surgical repair.

Alternative treatment: open removal of bladder; chemotherapy, radiation.

Optical urethrotomy

Indications

- Bulbar urethral stricture.
- Also used for penile urethral strictures.

Anaesthesia: regional or general.

Post-operative care

- Leave a catheter for 3–5 days (longer catheterization does not reduce long-term restricturing).
- Consider ISC for 3–6 months, starting several times daily, reducing to once or twice a week towards the end of this period.

Common post-operative complications and their management

- Septicaemia.
- Restricturing: is the most common long-term problem occurring after optical urethrotomy.

BAUS procedure-specific consent form—recommended discussion of adverse events

Common

- Mild burning on passing urine for short periods of time after operation.
- Temporary insertion of a catheter.
- Need for self-catheterization to keep the narrowing from closing down again.

Occasional

- Infection of bladder requiring antibiotics.
- Permission for telescopic removal/biopsy of bladder abnormality/stone, if found.
- Recurrence of stricture necessitating further procedures or repeat incision.

Rare: decrease in quality of erections, requiring treatment.

Alternative therapy: observation, urethral dilatation, open (non-telescopic) repair of stricture.

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Circumcision

Indications

- Phimosis.
- Recurrent paraphimosis.
- Penile cancer confined to the foreskin.
- Lesions on the foreskin of uncertain histological nature.

Contraindications

- In neonates—hypospadias, chordee with hypospadias, microphallus.
- In all patients—bleeding diatheses.

Circumcision in HIV prevention

Male circumcision has a significant protective effect against HIV infection.[1,2] This is thought to be due to the presence of large numbers of HIV-binding target cells being present on the inner layer of the prepuce compared to the glans and outer prepuce (which is lined by squamous epithelium).

Clearly, mass circumcision programmes in Africa and other high risk areas would be a huge task. In addition, concerns have been expressed that this beneficial effect will be negated by increased behaviour that increases HIV risk (e.g. a drop in condom use, a rise in sexual partners).

Anaesthesia: local or general.

Post-operative care

A non-adhesive dressing may be applied to the end of the penis, but this is difficult to keep on for more than an hour or two and is unnecessary. Warn the patient that the penis may be bruised and swollen after the operation, but that this resolves spontaneously over a week or two. Sexual intercourse or masturbation should be avoided until the absorbable skin sutures have dissolved.

Common post-operative complications and their management

You might think that circumcision is about as simple an operation as you can get, but it can cause both the patient (or, in the case of little boys, their parents) and you considerable concern if the cosmetic result is not what was expected or if 'complications' occur about which the patient was not warned. As with any procedure, it should be performed with care and with the potential complications always in mind so that steps can be taken to avoid these. If complications do occur, manage them appropriately.

Haemorrhage

Most frequently occurs from the frenular artery on the ventral surface of the penis. If local pressure does not stop the bleeding (and if it is from the frenular artery, it usually won't), return the patient to theatre and, either under ring block local anaesthesia or general anaesthesia, suture ligature the bleeding vessel. Be careful not to place the suture through the urethra!

Necrosis of the skin of the shaft of the penis

In most cases of suspected skin necrosis, there is none. Not infrequently, a crust of coagulated blood develops around the circumference of the penis after circumcision. As blood oxidizes, it turns black and this appearance can be mistaken for necrosis of the end of the penis. Reassurance of the patient (and the referring doctor!) is all that is needed. If necrosis has occurred because, for example, adrenaline was used in the local anaesthetic, wait for the necrotic tissue to demarcate before assessing the extent of the problem. The penis has a superb blood supply and has remarkable healing characteristics.

Separation of the skin of the coronal sulcus from the shaft skin

If limited to a small area, this will heal spontaneously. If a larger circumference of the wound has 'dehisced', resuture in theatre.

Wound infection: rare.

Urethrocutaneous fistula: due to haemostatic sutures (placed to control bleeding from the frenular) passing through the urethra, the wound later breaking down.

Urethral damage: due to a stitch placed through the urethra as the frenular artery is suture ligatured.

Excessive removal of skin

Re-epithelialization can occur if the defect between the glans and the shaft skin is not too great. If the defect is too great, the end result will be a buried penis—the glans retracts towards the skin at the base of the penis.

BAUS procedure-specific consent form—recommended discussion of adverse events

Serious or frequently occurring complications of circumcision

- Bleeding of the wound, occasionally needing a further procedure.
- Infection of incision requiring further treatment.
- Permanent altered sensation of the penis.
- Persistence of absorbable stitches after 3–4 weeks, requiring removal.
- Scar tenderness, rarely long-term.
- You may not be completely cosmetically satisfied.
- Occasional need for removal of excessive skin at a later date.
- Permission for biopsy of abnormal area of glans if malignancy is a concern.

Alternative therapy: drugs to relieve inflammation, leave uncircumcised.

1 Bailey RC, Moses S, Parker CB, *et al.* (2007) Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet* **369**:643–56.

2 Gray RH, Kigozi G, Serwadda D, *et al.* (2007) Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* **369**:657–66.

Hydrocele and epididymal cyst removal

Hydrocele repair (removal)

Indications: primary (idiopathic) hydrocele repair; not indicated for secondary hydrocele repair.

Anaesthesia: local or general.

Techniques

- **Lord's plication technique:** for small- to medium-sized hydroceles (minimal interference with surrounding scrotal tissues, which minimizes the risk of post-operative haematoma).
- **Jaboulay procedure:** for large hydroceles; excision of hydrocele sac.

Hydrocele aspiration

Strict attention to asepsis is vital since the introduction of infection into a closed space could lead to abscess formation. Avoid superficial blood vessels (if you hit them, a large haematoma can result).

Post-operative care: nothing specific.

Post-operative complications and their management

- **Scrotal swelling:** resolves spontaneously.
- **Haematoma formation:** if it is large, surgical drainage is best performed as spontaneous resolution may take many weeks. It can be difficult to identify the bleeding vessel. Leave a small drain to prevent reaccumulation of the haematoma.
- **Hydrocele recurrence.**

Epididymal cyst removal (spermatocelectomy)

- Avoid in young men who wish to maintain fertility since epididymal obstruction can occur.
- An alternative to surgical removal is aspiration, though recurrence is usual.

BAUS procedure-specific consent form: recommended discussion of adverse events

Hydrocele removal

Occasional

- Recurrence of fluid collection can occur.
- Collection of blood around the testes that resolves slowly or requires surgical removal.
- Possible infection of incision or testis requiring further treatment.

Alternative therapy

- Observation.
- Removal of fluid with a needle.

Epididymal cyst removal

Occasional

- Recurrence of fluid collection can occur.
- Collection of blood around the testes that resolves slowly or requires surgical removal.
- Possible infection of incision or testis requiring further treatment.

Rare

- Scarring can damage the epididymis causing subfertility.

Alternative therapy: observation, removal of fluid with a needle.

Nesbit's procedure

Penile straightening procedure for correcting penile curvature. Wait for at least 6 months after the patient has experienced no more pain and wait for the penile curvature to stabilize (there is no point in repairing the curvature if it is still progressing).

Indications: Peyronie's disease.

Anaesthesia: local or general.

Post-operative care: avoid intercourse for 2 months. Oedema can be managed with cold compresses.

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications

Common

- Some shortening of the penis.
- Possible dissatisfaction with the cosmetic or functional result.
- Temporary swelling and bruising of the penis and scrotum.

Occasional

- Circumcision is sometimes required as part of the procedure.
- There is no guarantee of total correction of the bend.
- **Bleeding or infection:** may require further treatment.

Rare

- Impotence or difficulty maintaining an erection.
- Nerve injury with temporary or permanent numbness of penis.

Alternative treatment: observation, drugs, other surgical procedures.

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Vasectomy and vasovasostomy

Vasectomy

This is the removal of a section of the vas deferens from each side with the aim of achieving infertility.

Indications: a method of birth control.

Anaesthesia: local or general.

Post-operative care and common post-operative complications and their management

Post-operative haematoma can occur. If large, evacuation may be required. Infection can occur, but is usually superficial. Two semen samples are required, usually at 10 and 12 weeks post-vasectomy, before unprotected intercourse can take place. Viable sperm can remain distal to the site of vasectomy (in the distal vas deferens or seminal vesicles) for some weeks after vasectomy and even longer. Occasionally, a persistently positive semen analysis is an indication that the vas was not correctly identified at the time of surgery and has not been ligated (or very rarely, that there were two vas deferens on one side). The potential for fertility remains in those with positive semen analysis and re-exploration is indicated. Warn the patient that the vas deferens can later recanalize, thereby restoring fertility.

Sperm granuloma: a hard, pea-sized lump in the region of the cut ends of the vas, forming as a result of an inflammatory response to sperm leaking out of the proximal cut end of the vas. It can be a cause of persistent pain in which case, it may have to be excised or evacuated and the vas cauterized or re-ligated.

Vasovasostomy

Vasectomy reversal.

Anaesthesia: this tends to be done under general or spinal anaesthesia as it takes far longer than a vasectomy.

Post-operative care and common post-operative complications and their management

Much the same as for vasectomy. The patient should avoid sexual intercourse for 2 weeks or so.

Vasectomy: BAUS procedure-specific consent form—recommended discussion of adverse events

Serious or frequently occurring complications

Common

- Irreversible.
- Small amount of scrotal bruising.
- Two semen samples are required before unprotected intercourse, both of which must show no spermatozoa.

Occasional

- Bleeding requiring further surgery or bruising.

Rare

- Inflammation or infection of testis or epididymis, requiring antibiotics.
- Rejoining of vas ends, resulting in fertility and pregnancy (1 in 2000).
- Chronic testicular pain (5%) or sperm granuloma.

Alternative treatment: other forms of contraception (male or female).

Vasovasostomy: BAUS procedure-specific consent form—recommended discussion of adverse events

Serious or frequently occurring complications

Common

- Small amount of scrotal bruising.
- No guarantee that sperm will return to semen.
- Sperm may return, but pregnancy not always achieved.
- If storing sperm, check that appropriate forms have been filled out.

Occasional

- Bleeding requiring further surgery

Rare

- Inflammation or infection of testes or epididymis, requiring antibiotics.
- Chronic testicular pain (5%) or sperm granuloma.

Alternative therapy: IVF, sperm aspiration, ICSI.

Orchidectomy

Indications

Two types—radical orchidectomy and simple orchidectomy.

Radical (inguinal) orchidectomy

For excision of testicular cancer. This approach is used for three reasons.

- To allow ligation of the testicular lymphatics as high as possible as they pass in the spermatic cord and through the internal inguinal ring, thereby removing any cancer cells which might have started to metastasize along the cord.
- To allow cross-clamping of the cord prior to manipulation of the testis which, theoretically at least, could promote dissemination of cancer cells along the lymphatics. (In reality, this probably doesn't occur.)
- To prevent the potential for dissemination of tumour cells into the lymphatics that drain the scrotal skin that could occur if a scrotal approach is used. These lymphatics drain to inguinal nodes. Thus, direct spread of tumour to scrotal skin and 'violation' of another lymphatic field (the groin nodes) are avoided. Historically, this was important because the only adjuvant therapy for metastatic disease was radiotherapy. The morbidity of groin and scrotal irradiation was not inconsiderable (severe skin reactions to radiotherapy, irradiation of femoral artery and nerve).

Obtain serum markers before surgery (α-fetoprotein, βHCG, and lactic acid dehydrogenase (LDH)) and get a CXR. For full staging CT scan, wait till after surgery. If the contralateral testis has been removed or is small, offer sperm storage—there is usually time to do this. Warn the patient that, very occasionally, what appears clinically and on ultrasound to be a malignant testis tumour turns out to be a benign tumour on subsequent histological examination.

Simple orchidectomy

For hormonal control of advanced prostate cancer. Done via a scrotal incision, with ligation and division of the cord and complete removal of the testis and epididymis. Alternatively, a subcapsular orchidectomy may be done, where the tunica of the testis is incised and the seminiferous tubules contained within are excised. There is the potential with this approach to leave a small number of Leydig cells which can continue to produce testosterone.

Anaesthesia: local, regional, general. Few men will require or opt for local.

Post-operative care and common post-operative complications and their management

For both simple and radical orchidectomy: scrotal haematoma. Drain it if large or enlarging or if there are signs of infection (fever, discharge of pus from the wound).

For radical orchidectomy: damage to the ilioinguinal nerve, leading to an area of loss of sensation overlying the scrotum.

Orchidectomy ± testicular implant: BAUS procedure-specific consent form—recommended discussion of adverse events

Serious or frequently occurring complications

Occasional

- Cancer, if found, may not be cured by orchidectomy alone.
- There may be a need for additional surgery, radiotherapy, or chemotherapy.
- Loss of future fertility.
- Biopsy of contralateral testis may be required if an abnormality is found (small testis or history of maldescent).

Rare

- On pathological examination, cancer may not be found or the pathologic diagnosis may be uncertain.
- Infection of incision may occur, requiring further treatment and possibly removal of implant if this has been inserted.
- Pain requiring removal of implant.
- Cosmetic expectation not always met.
- Implant may lie higher in the scrotum than the normal testis did.
- A palpable stitch may be felt at one end of the implant.
- Long-term risks of silicone implants are not known.

Urological incisions

Midline, transperitoneal

Indications: access to peritoneal cavity and pelvis for radical nephrectomy, cystectomy, reconstructive procedures, etc.

Technique

Divide skin, subcutaneous fat. Divide fascia in midline. Find the midline between the rectus muscles. Dissect the muscles free from the underlying peritoneum. Place two clips on either side of the midline, pinch between the two to ensure no bowel has been trapped, elevate the clips, and divide between them with a knife. Extend the incision in the peritoneum up and down, ensuring no bowel is in the way.

Closure: use a non-absorbable (e.g. nylon) or very slowly absorbable (e.g. PDS) suture, using Jenkins rule to reduce the risk of dehiscence (suture length 4 times wound length).

Specific complications: dehiscence (classically around day 10 post-operatively and preceded by pink serous discharge, then sudden herniation of a bowel through incision).

Lower midline, extraperitoneal

Indications: access to pelvis (e.g. radical prostatectomy, colposuspension).

Technique: divide skin, subcutaneous fat. Divide fascia in midline. Find the midline between the rectus muscles and dissect the muscles free from the underlying peritoneum. If you make a hole in it, repair the defect with vicryl. Divide the fascia posterior to the rectus muscles in the midline, so exposing the extravesical space.

Closure: as for midline, transperitoneal.

Pfannenstiel

Indications: access to pelvis (e.g. colposuspension, open prostatectomy, open cystolithotomy).

Technique: divide the skin 2cm above the pubis and the tissues down to the rectus sheath which is cut in an arc, avoiding the inguinal canal. Apply clips to the top flap (and afterwards the bottom flap) and use a combination of scissors and your fingers to separate the rectus muscle from the sheath. For maximum exposure, you must elevate the anterior rectus sheath from the recti cranially to just below the umbilicus and caudally to the pubis. Take care to diathermy a perforating branch of the inferior epigastric artery on each side. Apply two Babock's forceps to the inferior belly of the rectus on either side of the midline. Elevate and cut in the midline, the lower part of the fascia (transversalis fascia) between the recti. Separate the recti in the midline (do not divide them).

Closure: tack the divided transversalis fascia together and then close the transversely divided rectus sheath with vicryl.

Supra-12th rib incision

Indications: access to kidneys, renal pelvis, upper ureter.

Technique: make the incision over the tip of the 12th rib through skin and subcutaneous fascia. Palpate the tip of the 12th rib. Make a 3cm cut with diathermy through the muscle (latissimus dorsi) overlying the tip of the 12th rib so you come down onto the tip of the 12th rib and then cut anterior to the tip of the 12th rib, down through external and internal oblique, transversus abdominis, to Gerota's fascia, and the perirenal fat. Sweep anteriorly with a finger to push the peritoneum and intraperitoneal organs out of harm's way. Cut the muscles overlying the rib, cutting centrally along the length of the rib, in so doing avoiding the pleura. Cut with scissors along the top edge of the rib to free the intercostal muscle from the rib—beware the pleura! Insert a Gillie's forceps between the pleura and overlying intercostal muscle and divide the muscle fibres, so protecting the pleura. Dissect fibres of the diaphragm away from the inner surface of the 12th rib—as you do so, the pleura will rise upwards with the detached diaphragmatic fibres out of harm's way. At the posterior end of the incision, feel for the sharp edge of the costovertebral ligament. Insert heavy scissors, with the blades just open on the top of the rib (to avoid the XIth intercostal nerve), and divide the costovertebral ligament. You should now be on top of Gerota's fascia.

Specific complications

- **Damage to the pleura:** if you make a hole in the pleura, repair it at the end of the operation. Pass a small bore catheter (e.g. Jacques) through the hole, close all the muscle layers, inflate the lung, and then before closing the skin, remove the catheter.

Complications common to all incisions

Hernia, wound infection, chronic wound pain.

JJ stent insertion

Preparation

Can be done under sedation or general anaesthetic, using either a rigid or flexible cystoscope. The latter is particularly useful for patients who are not fit enough for a general anaesthetic. The technique described is that used with the flexible cystoscope, but this is essentially the same if using a rigid scope.

With sedation

Oral ciprofloxacin 250mg; lidocaine gel for urethral anaesthesia and lubrication; sedoanalgesia (diazemuls 2.5–10mg IV, pethidine 50–100mg IV). Monitor pulse and oxygen saturation with a pulse oximeter.

Technique

A flexible cystoscope is passed into the bladder and rotated through 180°. This allows greater deviation of the end of the cystoscope and makes identification of the ureteric orifice easier. A 0.9mm hydrophilic guidewire (Terumo Corporation, Japan) is passed into the ureter under direct vision. The guidewire is manipulated into the renal pelvis using C-arm digital fluoroscopy. The cystoscope is placed close to the ureteric orifice and its position, relative to bony landmarks in the pelvis, is recorded by frame-grabbing a fluoroscopic image. The flexible cystoscope is then removed and a 4 Ch ureteric catheter is passed over the guidewire into the renal pelvis. A small quantity of non-ionic contrast medium is injected into the renal collecting system to outline its position and to dilate it. The Terumo guidewire is replaced with an ultra-stiff guidewire (Cook UK Ltd, Letchworth, UK) and the 4 Ch ureteric catheter is removed. We use a variety of stent sizes, depending on the patient's size (6–8 Ch, 20–26cm; Boston Scientific Ltd, St Albans, UK). The stent is advanced to the renal pelvis under fluoroscopic control, using a 'pusher' (a hollow tube inserted over the guidewire), checking that the lower end of the stent is not inadvertently pushed up the ureter by checking the position of the ureteric orifice on the previously frame-grabbed image. The guidewire is then removed while the pusher holds the stent in position (so that the stent is not pulled out along with the wire).

Further reading

Hellawell GO, Cowan NC, Holt SJ, Mutch SJ (2002) A radiation perspective for treating loin pain in pregnancy by double-pigtail stents. *BJU Int* **90**:801–8.

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Nephrectomy and nephro-ureterectomy

Indications for nephrectomy

- Renal cell cancer.
- Non-functioning kidney containing a staghorn calculus.
- Persistent haemorrhage following renal trauma.

Indications for nephro-ureterectomy

Transitional carcinoma of the renal pelvis and/or ureter.

Anaesthesia: general.

Post-operative care

Nephrectomy

Cardiovascular status and urine output should be carefully monitored in the immediate post-operative period. Haemorrhage from the renal pedicle or for left-sided nephrectomy, the spleen, is rare, but will present with an increasing tachycardia, cool peripheries, falling urine output, and eventually a drop in BP. A drain is usually not left in place, but if it is, there may be excessive drainage of blood from the drain. However, do not be lulled into a false sense of security by the absence of drainage—this does not mean that haemorrhage is not occurring as the drain may be blocked, but haemorrhage may be ongoing.

For nephrectomy via a posterolateral (rib-based) incision, watch for pneumothorax. Arrange a CXR on return from the recovery room. Arrange routine chest physiotherapy to reduce the risk of chest infection. Regular chest examination is important, looking specifically for pneumothorax and pleural effusion.

Mobilize the patient as quickly as possible to reduce the risk of DVT and PE.

Nephro-ureterectomy

Where the ureter has been excised from the bladder, a urethral catheter is left in place at the end of the procedure to allow the hole in the bladder to heal. This is usually removed 10–14 days after surgery.

Common post-operative complications and their management

- **Haemorrhage:** see *Nephrectomy*.
- **Wound infection:** rare. If superficial, treat with antibiotics. If an underlying collection of pus is suspected, open the wound to allow free drainage and pack the wound daily.
- **Pancreatic injury:** rare, but would be indicated by excessive drainage of fluid from the drain, if present, which will have a high amylase level. If no drain is present, an abdominal collection will develop which may be manifested by a prolonged ileus.

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications of nephrectomy/nephro-ureterectomy

Simple nephrectomy

- **Common.**
  - Temporary insertion of a bladder catheter.
  - Occasional insertion of a wound drain.
- **Occasional.**
  - Bleeding requiring further surgery or transfusion.
  - Entry into lung, requiring temporary insertion of a drainage tube.
- **Rare.**
  - Involvement or injury to nearby structures—blood vessels, spleen, lung, liver, pancreas, bowel, requiring further extensive surgery.
  - Infection, pain, or hernia of incision, requiring further treatment.
  - Anaesthetic or cardiovascular problems, possibly requiring intensive care admission (including chest infection, PE, stroke, DVT, heart attack).
- **Alternative therapy:** observation, laparoscopic approach.

Radical nephrectomy

As above plus:

- **Occasional.**
  - Need for further therapy for cancer.
- **Rare.**
  - May be an abnormality other than cancer on microscopic analysis.
- **Alternative therapy:** observation, embolization, immunotherapy, laparoscopic approach.

Nephro-ureterectomy

As above.

Radical prostatectomy

Indications: localized prostate cancer.

Anaesthesia: general or regional.

Post-operative care

Mobilize as quickly as possible and continue subcutaneous heparin and AK-TEDS until discharge to reduce the risk of DVT and PE. Remove the drains when drainage is minimal. If there is persistent leak of fluid from the drains, send a sample for urea and creatinine and if it is urine, get a cystogram to determine the size of the leak at the vesicourethral junction. Urethral catheters are left *in situ* post-radical prostatectomy for a variable time, depending on the surgeon who performs the operation. Some surgeons leave a catheter for 3 weeks and others for just 1 week.

Common post-operative complications and their management

Haemorrhage

Managed in the usual way (transfusion; return to theatre where bleeding persists or where there is cardiovascular compromise).

Ureteric obstruction

Usually results from oedema of the bladder, obstructing the ureteric orifices. Retrograde ureteric catheterization is rarely possible (this would require urethral catheter removal and it is difficult to see the ureteric orifices because of the oedema). Arrange placement of percutaneous nephrostomies.

Lymphocele

Drain by radiologically assisted drain placement. If the lymphocele recurs after drain removal, create a window from the lymph collection into the peritoneal cavity so the lymph drains into the peritoneum from which it is absorbed.

Displaced catheter post-radical prostatectomy

If the catheter falls out a week after surgery, the patient may well void successfully and in this situation, no further action needs be taken. If, however, the catheter inadvertently falls out the day after surgery, gently attempt to replace it with a 12 Ch catheter which has been well lubricated. If this fails, pass a flexible cystoscope under local anaesthetic, into the bulbar urethra and attempt to pass a guidewire into the bladder, over which a catheter can then safely be passed. If this is not possible, another option is to hope that the patient voids spontaneously and does not leak urine at the site of the anastomosis. An ascending urethrogram may provide reassurance that there is no leak of contrast and that the anastomosis is watertight. If there is a leak or the patient is unable to void, a suprapubic catheter can be placed (percutaneously or under general anaesthetic via an open cystostomy).

Faecal fistula

Due to rectal injury, either recognized and repaired at the time of surgery and later breaking down or not immediately recognized. Formal closure is often required.

Contracture at the vesicourethral anastomosis

Gentle dilatation may be tried. If the stricture recurs, instruct the patient on ISC in an attempt to keep the stricture open. If this fails, bladder neck incision may be tried.

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications of radical prostatectomy

Common

- Temporary insertion of a bladder catheter and wound drain.
- High chance of impotence due to unavoidable nerve damage.
- No semen is produced during orgasm, causing subfertility.

Occasional

- Blood loss, requiring transfusion or repeat surgery.
- Urinary incontinence—temporary or permanent, requiring pads or further surgery.
- Discovery that cancer cells are already outside the prostate, needing observation or further treatment at a later date if required, including radiotherapy or hormonal therapy.

Rare

- Anaesthetic or cardiovascular problems possibly requiring intensive care admission (including chest infection, PE, stroke, DVT, heart attack).
- Pain, infection, or hernia in area of incision.
- Rectal injury, very rarely needing temporary colostomy.

Alternative therapy: watchful waiting, radiotherapy, brachytherapy, hormonal therapy, and perineal or laparoscopic removal.

Radical cystectomy

Indications

- Muscle-invasive bladder cancer.
- Adenocarcinoma of bladder (radioresistant).
- Squamous carcinoma of bladder (relatively radioresistant).
- Non-muscle-invasive TCC bladder, which has failed to respond to intravesical chemotherapy or immunotherapy.
- Recurrent TCC bladder post radiotherapy.

Combined with urethrectomy if:

- Multiple bladder tumours.
- Involvement of bladder neck or prostatic urethra.

Anaesthesia: general.

Post-operative care and common post-operative complications and their management

Monitor cardiovascular status, urine output, and respiratory status carefully in the first 48h. Routine chest physiotherapy is started early in the post-operative period to reduce the chance of chest infection. Mobilize the patient as early as possible to minimize the risk of DVT and PE. Drains are removed when they stop draining. Some surgeons prefer to leave them for a week or so so that late leaks (urine, intestinal contents) will drain via the drain track and not cause peritonitis. Try to remove the nasogastric tube, if used, as soon as possible to assist respiration and reduce the risks of chest infection. The patient usually starts to resume their diet within a week or so. If the ileus is prolonged, start parenteral nutrition.

Haemorrhage: persistent bleeding that fails to respond to transfusion should be managed by re-exploration.

Wound dehiscence: requires resuturing under general anaesthetic.

Ileus: common. Usually resolves spontaneously within a few days.

Small bowel obstruction

From herniation of small bowel through the mesenteric defect created at the junction between the two bowel ends. Continue nasogastric aspiration. The obstruction will usually resolve spontaneously. Re-operation is occasionally required where the obstruction persists or where there are signs of bowel ischaemia.

Leakage from the intestinal anastomosis

Leading to:

- **Peritonitis:** requiring re-operation and repair or refashioning of the anastomosis.
- **An enterocutaneous fistula:** bowel contents leak from the intestine and through a fistulous track onto the skin. If low-volume leak (<500mL/24h), will usually heal spontaneously. Normal (enteral) nutrition may be maintained until the fistula closes (which usually occurs within a matter of days or a few weeks). If high-volume, spontaneous closure is less likely and re-operation to close the fistula may be required.

Pelvic abscess

Formal surgical (open) exploration of the pelvis is indicated with drainage of the abscess and careful inspection to see if the underlying cause is a rectal injury, in which case a defunctioning colostomy should be performed.

Partial cystectomy

Indications

Primary, solitary bladder tumours at a site that allows 2cm of normal tissue around it to be removed in a bladder that will have adequate capacity and compliance after operation. There should be:

- No prior history of bladder cancer.
- No carcinoma in situ.
- A solitary muscle-invasive tumour located well away from the ureteral orifices, which includes 2cm of normal surrounding bladder.

High-grade tumours should not be excluded if these criteria are met. The lesions most commonly amenable to partial cystectomy are G2 or G3 TCCs or adenocarcinomas located on the posterior wall or dome.

Contraindications

Associated carcinoma *in situ*, deeply invasive tumours, tumours at the bladder base (i.e. near the ureteric orifices).

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications of radical cystectomy

See also consent for ileal conduit if this is the planned form of urinary diversion.

Common

- Temporary insertion of a nasal tube, drain, and stent.
- High chance of impotence (lack of erections) due to unavoidable nerve damage.
- No semen is produced during orgasm (dry orgasm), causing subfertility.
- Blood loss, requiring transfusion or repeat surgery.
- In women, pain or difficulty with sexual intercourse due to narrowing or shortening of vagina and need for removal of uterus and ovaries (causing premature menopause in those who have not reached menopause).

Occasional

- Cancer may not be cured with surgery alone.
- Need to remove penile urinary pipe as part of procedure.

Rare

- Infection or hernia of incision, requiring further treatment.
- Anaesthetic or cardiovascular problems, possibly requiring intensive care admission (including chest infection, PE, stroke, DVT, heart attack).
- Decreased renal function with time.

Very rarely

- Rectal injury, very rarely needing temporary colostomy.
- Diarrhoea due to shortened bowel, vitamin deficiency requiring treatment.
- Bowel and urine leak, requiring re-operation.
- Scarring of bowel or ureters, requiring operation in the future.
- Scarring, narrowing, or hernia formation around stomal opening, requiring revision.

Alternative treatment: radiotherapy, neobladder formation, rather than ileal conduit urinary diversion.

Formation of neo-bladder with bowel

Common: need to perform ISC if bladder fails to empty.

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Ileal conduit

Indications

- For urinary diversion following radical cystectomy.
- Intractable incontinence for which anti-incontinence surgery has failed or is not appropriate.

Post-operative care and common post-operative complications and their management

Oliguria or anuria: try a fluid challenge.

Wound infection: treat with antibiotics and wound care. Open the superficial layers of the wound to release pus.

Wound dehiscence: rare. Requires resuturing in theatre under general anaesthetic.

Ileus: common. Usually resolves spontaneously within a few days.

Small bowel obstruction: from herniation of small bowel through the mesenteric defect created at the junction between the two bowel ends. Continue nasogastric aspiration. The obstruction will usually resolve spontaneously. Re-operation is occasionally required where the obstruction persists or where there are signs of bowel ischaemia.

Leakage from the intestinal anastomosis:
Leading to:

- **Peritonitis:** requiring re-operation and repair or refashioning of the anastomosis.
- **An enterocutaneous fistula:** bowel contents leak from the intestine and through a fistulous track onto the skin. If low-volume leak (<500mL/24h), will usually heal spontaneously. Normal (enteral) nutrition may be maintained until the fistula closes (which usually occurs within a matter of days or a few weeks). If high-volume, spontaneous closure is less likely and re-operation to close the fistula may be required.

Leakage from the uretero-ileal junction
May be suspected because of a persistently high output of fluid from the drain. Test this for urea. Urine will have a higher urea and creatinine concentration than serum. If the fluid is lymph, the urea and creatinine concentration will be the same as that of serum. Arrange a loopgram (conduitogram). This will confirm the leak. Place a soft, small catheter (12 Ch) into the conduit to encourage antegrade flow of urine and assist healing of the uretero-ileal anastomosis. If the leakage continues, arrange bilateral nephrostomies to divert the flow of urine away from the area and encourage wound healing.

Occasionally, a uretero-ileal leak will present as a urinoma (this causes a persistent ileus). Radiologically assisted drain insertion can result in a dramatic resolution of the ileus, with subsequent healing of the uretero-ileal leak.

Hyperchloraemic acidosis
May be associated with obstruction of the stoma at its distal end or from infrequent emptying of the stoma back (leading to back pressure on the conduit). Catheterize the stoma—this relieves the obstruction. In the long term, the conduit may have to be surgically shortened.

Acute pyelonephritis
Due to the presence of reflux combined with bacteriuria.

Stomal stenosis
The distal (cutaneous) end of the stoma may become narrowed, usually as a result of ischaemia to the distal part of the conduit. Revision surgery is required if this stenosis causes obstruction, leading to recurrent UTIs or back pressure on the kidneys.

Parastomal hernia formation
Around the site through which the conduit passes, through the fascia of the anterior abdominal wall. Many hernias can be left alone. The indications for repairing a hernia are:
- Bowel obstruction.
- Pain.
- Difficulty with applying the stoma bag (distortion of the skin around the stoma by the hernia can lead to frequent bag detachment).

Repair the hernia defect by placing mesh over the hernia site, via an incision sited as far as possible from the stoma itself, so as to reduce the risk of wound infection.

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications of ileal conduit formation
Common
- Temporary drain, stents, or nasal tube.
- Urinary infections, occasionally requiring antibiotics.

Occasional
- Diarrhoea due to shortened bowel.
- Blood loss, requiring transfusion or repeat surgery.
- Infection or hernia of incision, requiring further treatment.

Rare
- Bowel and urine leakage from anastomosis, requiring re-operation.
- Scarring to bowel or ureters, requiring operation in future.
- Scarring, narrowing, or hernia formation around urine opening, requiring revision.
- Decreased renal function with time.

Alternative treatment: catheters, continent diversion of urine.

Percutaneous nephrolithotomy (PCNL)

Indications

- Stones >3cm in diameter.
- Stones that have failed ESWL and/or an attempt at flexible ureteroscopy and laser treatment.
- Staghorn calculi.

Preoperative preparation

- CT scan to assist planning the track position and to identify a retrorenal colon.[1]
- Stop aspirin 10 days prior to surgery.
- Culture urine (so appropriate antibiotic prophylaxis can be given).
- Cross-match 2 units of blood.
- Start IV antibiotics the afternoon before surgery to reduce the chance of septicaemia (many of the stones treated by PCNL are infection stones). If urine is culture-negative, use 1.5g IV cefuroxime tds and once daily IV gentamicin (3mg/kg). Routine antibiotic prophylaxis also reduces the incidence of post-operative UTI.[2]

Post-operative management

Once the stone has been removed, a nephrostomy tube is left *in situ* for several days (Fig. 17.15). This drains urine in the post-operative period and tamponades bleeding from the track. So-called 'tubeless' PCNL (no nephrostomy tube, although a J stent is often inserted, which has a certain morbidity) can be used in select patients (no infection—therefore, not suitable for infection staghorn stones). Less requirement for post-operative analgesia and earlier discharge has been reported.

Complications of PCNL and their management

Bleeding

Some bleeding is inevitable, but that severe enough to threaten life is uncommon. In most cases, it is venous in origin and stops following placement of a nephrostomy tube (which compresses bleeding veins in the track). If bleeding persists, clamp the tube for 10min. If bleeding continues despite this, arrange urgent angiography, looking for an arteriovenous fistula or pseudoaneurysm, both of which will require selective renal artery embolization (required in 1% of PCNLs)[3] or open exposure of kidney to control bleeding by suture ligation, partial nephrectomy, or nephrectomy.

Septicaemia

Occurs in 1–2% of cases. Incidence is reduced by prophylactic antibiotics. Track damage. Essentially minimal. Cortical loss from track is estimated to be <0.2% of total renal cortex in animal studies.[4]

Colonic perforation

The colon is usually lateral or anterolateral to the kidney and is, therefore, not usually at risk of injury unless a very lateral approach is made. The colon is retrorenal in 2% of individuals (more commonly in thin females with little retroperitoneal fat).[1] The perforation usually occurs in

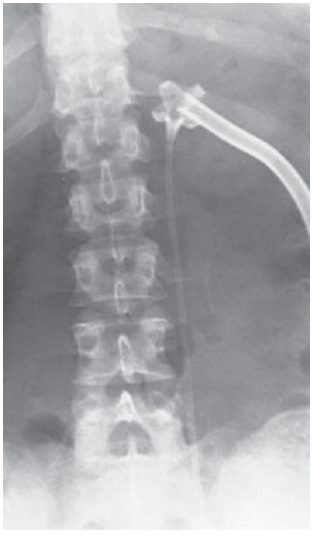

Fig. 17.15 A Malecot catheter which has wide drainage eyeholes and an extension at the distal end, which passes down the ureter to prevent fragments of stone from passing down the ureter.

an extraperitoneal part of the colon and is managed by JJ stent placement and withdrawal of the nephrostomy tube into the lumen of the colon to encourage drainage of bowel contents away from that of the urine, thereby encouraging healing without development of a fistula between bowel and kidney. A radiological contrast study a week or so later confirms that the colon has healed and that there is no leak of contrast from the bowel into the renal collecting system.

Damage to the liver or spleen: very rare in the absence of splenomegaly or hepatomegaly.

Damage to the lung and pleura, leading to pneumomothorax or pleural effusion: can occur with supra-12th rib puncture.

Nephrocutaneous fistula

When the nephrostomy tube is removed from the kidney, a few days after surgery, the 1cm incision usually closes within a few hours to a day or so. Occasionally, urine continues to drain percutaneously for a few days and a small 'stoma' bag must be worn. In the majority of such cases, the urine leak will stop spontaneously, but if it fails to do so after a week or so, place a JJ stent to encourage antegrade drainage of urine.

Outcomes

For small stones, the stone-free rate after PCNL is in the order of 90–95%. For staghorn stones, the stone-free rate of PCNL, when combined with post-operative ESWL for residual stone fragments, is in the order of 80–85%.

BAUS procedure-specific consent form—recommended discussion of adverse events

Serious or frequently occurring complications of PCNL

Common

- Temporary insertion of a bladder catheter and ureteric stent/kidney tube, needing later removal.
- Transient haematuria.
- Transient temperature.

Occasional

- More than one puncture site may be required.
- No guarantee of removal of all stones and need for further operations.
- Recurrence of stones.

Rare

- Severe kidney bleeding requiring transfusion, embolization, or, at last resort, surgical removal of kidney.
- Damage to lung, bowel, spleen, liver, requiring surgical intervention.
- Kidney damage or infection, needing further treatment.
- Over absorption of irrigating fluids into blood system, causing strain on heart function.

Alternative treatment: external shock wave treatments, open surgical removal of stones, observation.

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2 Inglis JA, Tolly DA (1988) Antibiotic prophylaxis at the time of percutaneous stone surgery. *J Endourol* **2**:59–62.

3 Martin X (2000) Severe bleeding after nephrolithotomy: results of hyperselective embolisation. *Eur Urol* **37**:136–9.

4 Clayman J (1987) Percutaneous nephrostomy: Assessment of renal damage associated with semi-rigid (24F) and balloon (36F) dilation. *J Urol* **138**:203–6.

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Ureteroscopes and ureteroscopy

The instruments

Two types of ureteroscope in common use—the semi-rigid ureteroscope and the flexible ureteroscope.

Semi-rigid ureteroscopes

Have high-density fibre optic bundles for light ('non-coherently' arranged) and image transmission ('coherently' arranged to maintain image quality). For equivalent light and image transmission using glass rod lenses, thicker lenses are required than with fibre optic bundles. As a consequence, semi-rigid ureteroscopes can be made smaller while maintaining the size of the instrument channel. In addition, the instrument can be bent by several degrees without the image being distorted.

The working tip of most current models is in the order of 7–8 Ch, with the proximal end of the scope being in the order of 11–12 Ch. There is usually at least one working channel of at least 3.4 Ch.

Flexible ureteroscopes

The fibre optic bundles in flexible ureteroscopes are the same as those in semi-rigid scopes, only of smaller diameter. Thus, image quality and light transmission are not as good as with semi-rigid scopes, but are usually adequate.

The working tip of most current models is in the order of 7–8 Ch, with the proximal end of the scope being in the order of 9–10 Ch. There is usually at least one working channel of at least 3.6 Ch.

The great advantage of the flexible ureteroscope over the semi-rigid variety is the ability to perform controlled deflection of the end of the scope (active deflection). Behind the actively deflecting tip of the scope is a segment of the scope which is more flexible than the rest of the shaft. This section is able to undergo passive deflection—when the tip is fully actively deflected by advancing the scope further, this flexible segment allows even more deflection. Flexible ureteroscopes have recently been developed which have two actively deflecting segments.

Flexible ureteroscopes are intrinsically more intricate and are, therefore, less durable than semi-rigid scopes.

Ureteroscopic irrigation systems

Normal saline is used (high-pressure irrigation with glycine or water would lead to fluid absorption from pyelolymphatic or venous backflow). Irrigation by gravity pressurization alone (the fluid bag suspended above the patient without any applied pressure) will produce flow that is inadequate for visualization because the long, fine bore irrigation channels of modern ureteroscopes are inherently high resistance. Several methods are available—hand-inflated pressure bags, foot pumps, and hand-operated syringe pumps. Whatever system is chosen, use the minimal flow required to allow a safe view so as to avoid flushing the stone out of the ureter and into the kidney, from where you may not be able to retrieve it.

Ureteric dilatation

Some surgeons do, others don't. Those who don't argue that dilatation is unnecessary in the era of modern, small-calibre ureteroscopes. Those who do cite a higher chance of being able to pass the ureteroscope all the way up to the kidney. Ureteric dilatation may be helpful where multiple passes of the ureteroscope up and down the ureter are going to be required for stone removal (alternatively, use a ureteric access sheath). Some surgeons prefer to place two guidewires into the ureter, one to pass the ureteroscope over ('railroading') and the other to act as a safety wire so that access to the kidney is always possible if difficulties are encountered. The second guidewire is most easily placed via a dual lumen catheter which has a second channel through which the second guidewire can be easily passed into the ureter without requiring repeat cystoscopy. This dual lumen catheter has the added function of gently dilating the ureteric orifice to about 10 Ch. There is probably no long-term harm done to the ureter as a consequence of dilatation.[1]

Ureteric access sheaths, which have outer diameters from 10 to 14 Ch, may facilitate access to the ureter and are particularly useful if it is anticipated that the ureteroscope will have to be passed up and down the ureter on multiple occasions (to retrieve fragments of stone). In addition, they facilitate the outflow of irrigant fluid from the pelvis or the kidney, thereby maintaining the field of view and decreasing intrarenal pressures.

Patient position

The patient is positioned as flat as possible on the operating table to 'iron out' the natural curves of the ureter. A cystoscopy is performed with either a flexible or rigid instrument. A retrograde ureterogram can be done to outline pelvicalyceal anatomy. A guidewire is then passed into the renal pelvis. We use a Sensor guidewire (Microvasive, Boston Scientific) which has a 3cm long floppy, hydrophilic tip which can usually easily be negotiated up the ureter. The remaining length of the wire is rigid and covered in a smooth PTFE. Both properties aid passage of the ureteroscope.

Technique of flexible ureteroscopy and laser treatment for intrarenal stones

Flexible ureteroscopy and laser treatment can be performed with topical urethral local anaesthesia and sedation. However, trying to fragment a moving stone with the laser can be difficult and ideally, therefore, ureteroscopy is most easily done under general anaesthesia with endotracheal intubation (rather than a laryngeal mask) to allow short periods of suspension of respiration and so stop movement of the kidney and its contained stone.

Empty the bladder to prevent 'coiling' of the scope in the bladder. Pass the scope over a guidewire. This requires two people—the surgeon holds the shaft of the scope and the assistant applies tension to the guidewire to fix the latter in position without pulling it down. This allows the scope to progress easily up the ureter. The assistant also ensures that acute angulation of the scope where the handle meets the shaft does not occur. The flexible ureteroscope should slide easily up the ureter and into the renal pelvis.

With modern active secondary deflection ureteroscopes, access to most, if not all, parts of the renal collecting system is possible.

Laser lithotripsy

The main drawback of laser lithotripsy is the dust-cloud effect that occurs as the stone is fragmented. This temporarily obscures the view and must be washed away before the laser can safely be re-applied.

The use of stone baskets to retrieve stones after ureteroscopy

The aim of ureteroscopy (or flexible ureterorenoscopy) is to remove the ureteric (or renal) stone. It, therefore, seems intuitive to remove any large fragments—leaving them *in situ* runs the risk of ureteric colic post-ureteroscopy.

To stent or not to stent after ureteroscopy

JJ stent insertion does not increase stone-free rates and is, therefore, not required in 'routine' cases. A stent should be placed if:

- There has been ureteric injury (e.g. perforation—indicated by extravasation of contrast).
- There are residual stones that might obstruct the ureter.
- The patient has had a ureteric stricture that required dilatation.
- Solitary kidneys.

Routine stenting after ureteroscopy for distal ureteric calculi is unnecessary.[2] Many urologists will place a stent after ureteroscopy for proximal ureteric stones.

Complications of ureteroscopy

Septicaemia; ureteric perforation, requiring either a JJ stent or, very occasionally, a nephrostomy tube where JJ stent placement is not possible; ureteric stricture (<1%).

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications of ureteroscopy for treatment of ureteric stones

Common

- Mild burning or bleeding on passing urine for a short period after the operation.
- Temporary insertion of a bladder catheter may be required.
- Insertion of a stent may be required with a further procedure to remove it.
- Urinary infections, occasionally requiring antibiotics.

Occasional

- Inability to get stone or movement of stone back into kidney where it is not retrievable.
- Kidney damage or infection, requiring further treatment.
- Failure to pass scope if ureter is narrow.
- Recurrence of stones.

Rare

- Damage to ureter with need for open operation or placement of a nephrostomy tube into the kidney.

Alternative treatment: open surgery, shock wave therapy, or observation to allow spontaneous passage.

1 Garvin TJ, Clayman RV (1991) Balloon dilation of the ureter for ureteroscopy. *J Urol* **146**:742–5.

2 Srivastava A, Gupta R, Kumar A, Kapoor R, Mandhani A (2003) Routine stenting after ureteroscopy for distal ureteral calculi is unnecessary: results of a randomized controlled trial. *J Endourol* **17**:871.

Pyeloplasty

Indications: PUJ obstruction.

Anaesthesia: general.

Post-operative care

A JJ stent, bladder catheter, and a drain are left *in situ*. The bladder catheter serves to prevent reflux of urine up the ureter, which can lead to increased leakage of urine from the anastomosis site (reflux occurs because of the presence of the JJ stent). The drain is removed when the drain output is minimal. The stent is left in position for about 6 weeks.

Common post-operative complications and their management

Haemorrhage

Usually arising from the nephrostomy track (if a nephrostomy tube has been left in place—some surgeons leave a JJ stent and a perinephric drain, with no nephrostomy). Clamp the nephrostomy tube in an attempt to tamponade the bleeding. If the bleeding continues, consider angiography and embolization of the bleeding vessel if seen or exploration.

Urinary leak

This can occur within the first day or so. If a urethral catheter has not been left in place, catheterize the patient to minimize bladder pressure and, therefore, the chance of reflux which might be responsible for the leak. If the drainage persists for more than a few days, shorten the drain—if it is in contact with the suture line of the anastomosis, it can keep the anastomosis open, rather than letting it heal. If the leak continues, identify the site of the leak by either a nephrostogram (if a nephrostomy has been left *in situ*) or a cystogram (if a JJ stent is in place—contrast may reflux up the ureter and identify the site of leakage) or an IVU. Some form of additional drainage may help 'dry up' the leak (a JJ stent if only a nephrostomy has been left *in situ* or a nephrostomy if one is not already in place).

Obstruction at PUJ

This is uncommon and if it occurs, it is usually detected once all the tubes have been removed and a follow-up renogram has been done. If the patient had symptomatic PUJO, but remains asymptomatic, then no further treatment may be necessary. If they develop recurrent flank pain, re-operation may be necessary.

Acute pyelonephritis

Manage with antibiotics.

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications of pyeloplasty

Common

- Temporary insertion of a bladder catheter and wound drain.
- Further procedure to remove ureteric stent, usually a local anaesthetic.

Occasional

- Bleeding, requiring further surgery or transfusion.

Rare

- Recurrent kidney or bladder infections.
- Recurrence can occur, needing further surgery.

Very rarely

- Entry into lung cavity, requiring insertion of temporary drainage tube.
- Anaesthetic or cardiovascular problems, possibly requiring intensive care admission (including chest infection, PE, stroke, DVT, heart attack).
- Need to remove kidney at a later time because of damage caused by recurrent obstruction.
- Infection, pain, or hernia of incision, requiring further treatment.

Alternative therapy: observation, telescopic incision, dilation of area of narrowing, temporary placement of plastic tube through narrowing, laparoscopic repair.

Laparoscopic surgery

Virtually every urological procedure can be done laparoscopically. It is particularly suited to surgery in the retroperitoneum (nephrectomy for benign and malignant disease and for kidney donation at transplantation, pyeloplasty for PUJO), but it is also suited to pelvic surgery (lymph node biopsy, radical prostatectomy). Reconstructive surgery requiring laparoscopic suturing and using bowel is technically very challenging, but possible. Laparoscopic surgery offers the advantage over open surgery of:

- Reduced post-operative pain.
- Smaller scars.
- Less disturbance of bowel function (less post-operative ileus).
- Reduced recovery time and reduced hospital stay.

Contraindications to laparoscopic surgery

- Severe COPD (avoid use of CO2 for insufflation).
- Uncorrectable coagulopathy.
- Intestinal obstruction.
- Abdominal wall infection.
- Massive haemoperitoneum.
- Generalized peritonitis.
- Suspected malignant ascites.

Laparoscopic surgery is difficult or potentially hazardous in the morbidly obese (inadequate instrument length, decrease range of movement of instruments, higher pneumoperitoneum pressure required to lift the heavier anterior abdominal wall, excess intra-abdominal fat limiting the view); those with extensive previous abdominal or pelvic surgery (adhesions); previous peritonitis, leading to adhesion formation; in those with organomegaly; in the presence of ascites; in pregnancy; in patients with a diaphragmatic hernia; in those with aneurysms.

Potential complications unique to laparoscopic surgery

Gas embolism (potentially fatal), hypercarbia (acidosis affecting cardiac function, e.g. arrhythmias), post-operative abdominal crepitus (subcutaneous emphysema), pneumothorax, pneumomediastinum, pneumopericardium, barotraumas.

Bowel, vessel (aorta, common iliac vessels, IVC, anterior abdominal wall injury), and other viscus injury are not unique to laparoscopic surgery, but are a particular concern during port access. Perforation of small or large bowel is the most common trocar injury. Rarely, the bladder is perforated. Failure to progress with a laparoscopic approach or vessel injury with uncontrollable haemorrhage requires conversion to an open approach. Post-operatively, bowel may become entrapped in the trocar sites or there may be bleeding from the sheath site. An acute hydrocele can develop due to irrigation fluid accumulating in the scrotum. It resorbs spontaneously. Scrotal and abdominal wall bruising not uncommonly occurs.

BAUS procedure-specific consent forms

For all laparoscopic procedures

Common

- Temporary shoulder tip pain.
- Temporary abdominal bloating.
- Temporary insertion of a bladder catheter and wound drain.

Occasional

- Infection, pain, or hernia of incision, requiring further treatment.

Rare

- Bleeding, requiring conversion to open surgery or transfusion.
- Entry into lung cavity, requiring insertion of a temporary drainage tube.

Very rarely

- Recognized (and unrecognized) injury to organs or blood vessels, requiring conversion to open surgery or deferred open surgery.
- Anaesthetic or cardiovascular problems, possibly requiring intensive care admission (including chest infection, PE, stroke, DVT, heart attack).

Laparoscopic pyeloplasty

Common

- Further procedure to remove ureteric stent, usually under local anaesthesia.

Occasional

- Recurrence can occur, needing further surgery.
- Short-term success rates are similar to open surgery, but long-term results unknown.

Very rarely

- Need to remove kidney at a later time because of damage caused by recurrent obstruction.

Alternative therapy: observation, telescopic incision, dilation of area of narrowing, temporary placement of a plastic tube through narrowing, conventional open surgical approach.

Laparoscopic simple nephrectomy

Occasional

- Short-term success rates are similar to open surgery, but long-term results unknown.

Alternative therapy: observation and conventional open surgical approach.

Laparoscopic radical nephrectomy

Occasional

- Short-term success rates are similar to open surgery, but long-term results unknown.

Rare

- A histological abnormality other than cancer may be found.

Alternative therapy: observation, embolization, chemotherapy, immunotherapy, conventional open surgical approach.

Endoscopic cystolitholapaxy and (open) cystolithotomy

Indications

- **Endoscopic cystolitholapaxy:** generally indicated for small stones. The definition of 'small' is debatable. Many stones <4cm in diameter can be removed endoscopically, but the greater the number and size of the stones, the more inclined will the surgeon be to adopt an open approach. Having said this, if you anticipate that the patient is likely to develop recurrent stones and, therefore, will require multiple future procedures to remove them, then try to avoid open surgery because each redo open cystolithotomy will be more difficult (due to the presence of scar tissue).
- **Open cystolithotomy:** for stones >4cm in diameter and/or multiple stones (though some surgeons will be happy to 'take on' larger stones endoscopically); patients with urethral obstruction which precludes endoscopic access to bladder.

Anaesthesia: regional or general.

Post-operative care

A catheter is left in the bladder for a day or so since haematuria is common, particularly after fragmentation of large stones. Irrigation may be required if the haematuria is heavy.

Common post-operative complications and their management

Haematuria requiring bladder washout or return to theatre is rare.

Septicaemia: uncommon.

Bladder perforation: uncommon, but can occur with the use of stone 'punches' which grab the stone between powerful cutting jaws. Grasping the bladder wall in the jaws of the stone forceps or punch is easily done and can cause perforation.

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications of endoscopic cystolitholapxy

Common

- Mild burning or bleeding on passing urine for short periods after operation.
- Temporary insertion of a catheter.

Occasional

- Infection of bladder requiring antibiotics.
- Permission for removal/biopsy of bladder abnormality, if found.
- Recurrence of stones or residual stone fragments.

Rare

- Delayed bleeding, requiring removal of clots or further surgery.

- Injury to urethra, causing delayed scar formation.

Very rarely

- Perforation of bladder, requiring a temporary urinary catheter or return to theatre for open surgical repair.

Alternative therapy: open surgery, observation.

Scrotal exploration for torsion and orchidopexy

Indications: suspected testicular torsion.

Technique

A midline incision since this allows access to both sides so that they may both be 'fixed' within the scrotum. Untwist the testis and place in a warm, saline-soaked swab for 10min. If it remains black, remove it, having ligated the spermatic cord with a transfixion stitch of absorbable material. If it 'pinks up', fix it. If uncertain about its viability, make a small cut with the tip of a scalpel. If the testis bleeds actively, it should be salvaged (close the small wound with an absorbable suture). If not, it is dead and should be removed. Whatever you do, fix the other side.

Fixation technique

Some surgeons fix the testis within the scrotum with suture material, inserted at three points (3-point fixation). Some use absorbable sutures and others non-absorbable. Those who use the latter argue that absorbable sutures may disappear, exposing the patient to the risk of retorsion.[1] Those who use absorbable sutures argue that the fibrous reaction around the absorbable sutures prevents retorsion and argue that the patient may be able to feel non-absorbable sutures which can be uncomfortable. The sutures should pass through the tunica albuginea of the testis and then through the parietal layer of the tunica vaginalis lining the inner surface of the scrotum.

Others say the testis should be fixed within a dartos pouch,[2] arguing that suture fixation breaches the blood–testis barrier, exposing both testes to the risk of sympathetic orchidopathia (an autoimmune reaction caused by development of antibodies against the testis). For dartos pouch fixation, open the tunica vaginalis, bring the testis out, and untwist it. Develop a dartos pouch in the scrotum by holding the skin with forceps and dissecting with scissors between the skin and the underlying dartos muscle. Enlarge this space by inserting your two index fingers and pulling them apart. Place the testis in this pouch. Use a few absorbable sutures to attach the cord near the testis to the inside of the dartos pouch to prevent retorsion of the testes. The dartos may then be closed over the testis and the skin can be closed in a separate layer.

Post-operative care and potential complications and their management

As for all procedures involving scrotal exploration, a scrotal haematoma may result, which may have to be surgically drained.

BAUS procedure-specific consent form: recommended discussion of adverse events

Serious or frequently occurring complications of scrotal exploration

Common

- The testis may have to be removed if non-viable.

Occasional

- You may be able to feel the stitch used to fix the testis.
- Blood collection around the testes which slowly resolves or requires surgical removal.
- Possible infection of incision or testis, requiring further treatment.

Rare

- Loss of testicular size or atrophy in future if testis is saved.
- No guarantee of fertility.

Alternative therapy: observation—risks loss of testis and autoimmune reaction, leading to subfertility and loss of hormone production in remaining testis.

1 Kuntze JR (1985) Testicular torsion after orchidopexy. *J Urol* **134**:1209–10.

2 Frank JD (2002) Fixation of the testis. *Br J Urol Int* **89**:331–3.

Electromotive drug administration (EMDA)

EMDA is a non-invasive method of enhancing drug penetration across the bladder urothelium (and prostatic urethra), resulting in greater quantities of local drug being delivered to a greater tissue depth than is achievable by passive diffusion alone. It avoids many of the side effects seen with systemic administration.

Mechanism of action

EMDA uses an electric current to accelerate and actively transport ionized molecules into tissues. Drug administration can, therefore, be controlled by altering the electric current intensity. The two main electrokinetic principles are: ***iontophoresis*** (transport of ionized molecules into tissue by applying a current across a solution containing the ions, e.g. lidocaine) and ***electro-osmosis*** (transport of non-ionized solutes associated with the bulk transport of water, e.g. mitomycin C).

Applications in urology

- Local anaesthesia (LA) of the bladder (and prostatic urethra) prior to other procedures: flexible and rigid cystoscopy with biopsy and cystodiathermy, TURBT, BNI, TUIP, intravesical capsaicin therapy, and botulinum toxin-A injections.
- Intravesical mitomycin C therapy for TCC of the bladder.
- Intravesical oxybutynin therapy for OAB.
- Antibiotic administration (i.e. gentamicin) for infective recalcitrant cystitis.
- LA with anti-inflammatory drugs for cystodistention.

Method of EMDA LA

It can be performed as a day case or outpatient procedure. A CE-DAS® UROGENICS® catheter electrode* (Fig. 17.16) is inserted urethrally and the bladder emptied and irrigated with sterile water to remove any residual urine. A total of 150mL of 0.5% bupivacaine and 1.5mL (1.5mg) of 1/1000 epinephrine is instilled into the bladder. Two dispersive electrode pads are placed on the lower abdomen and both the electrode pads and the catheter are connected to the PHYSIONISER® generator* set to positive polarity, 25mA current strength, a pulsed current with rise rate 50μA/s for 23min. The catheter is then removed and endoscopy can proceed. EMDA LA is effective for 60min.

Contraindications to EMDA LA

Allergy to LA, significant haematuria, patients on monoamine oxidase inhibitors.

Relative contraindications

Active infection of lower genitourinary tract, protrusion of enlarged median lobe of prostate into the bladder, urethral stricture, bladder neck stenosis.

* Physion Srl, Medolla, Italy.

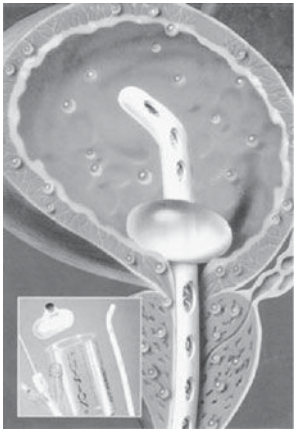

Fig. 17.16 EMDA in bladder and prostate using catheter electrode (Reproduced with permission from Physion S.r.l.)

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Chapter 18

Basic science and renal transplant

Basic physiology of bladder and urethra

Bladder

The bladder has an endothelial lining (urothelium) on a connective tissue base (lamina propria), surrounded by smooth muscle (detrusor), with outer connective tissue (adventitia). Urothelium consists of multilayered transitional epithelium, with numerous tight junctions that render it impermeable to water and solutes. Detrusor muscle is a homogeneous mass of smooth muscle bundles. C-kit antigen-positive 'interstitial cells' exist around detrusor bundles and in the suburothelium and play a role in modulating contractile behaviour of adjacent smooth muscle. The bladder base is known as the trigone—a triangular area with the two ureteric orifices and the internal urinary meatus forming the corners. Intravesical pressure during filling is low. The main excitatory motor input to the bladder is from the autonomic nervous system and is predominantly **parasympathetic innervation (S2–4)**. Preganglionic nerve fibres are conveyed to the bladder in the pelvic nerves and then synapse with cholinergic postganglionic nerve cells in the pelvic plexus and on the bladder, which, when activated, cause muscle contraction. **Sympathetic innervation (T10–L2)** plays a role in urine storage (see 📖 p. 592).

Urethra

The bladder neck (and posterior urethra) is normally closed during filling. It is composed of circular smooth muscle (with sympathetic innervation) and is also referred to as the internal sphincter. High pressure is generated at the midpoint of the urethra in women and at the level of the membranous urethra in men where the urethral wall is composed of a longitudinal and circular smooth muscle coat, surrounded by striated muscle (external urethral sphincter).

The striated part of the sphincter receives **motor innervation** from the somatic **pudendal nerve derived from (S2–4)** in a region in the sacral spinal cord called 'Onuf's nucleus'. It has voluntary control and acetylcholine (ACh) mediates contraction. The smooth muscle component of the sphincter has myogenic tone and receives excitatory and inhibitory innervation from the autonomic nervous system. Contraction is enhanced by sympathetic input (noradrenaline) and Ach. Inhibitory innervation is nitrergic (nitric oxide; see 📖 pp. 593–4).

Micturition

As the bladder fills, sensory afferent nerves respond to stretch in the bladder wall and send information about bladder filling to the central nervous system (CNS). During urine storage, the **pontine storage centre** mediates enhanced external urethral sphincter activity (so causing constriction of the sphincter). There is also somatic outflow via the pudendal nerve to the external striated sphincter muscle to cause contraction and sympathetic outflow to constrict the internal smooth muscle sphincter (bladder neck) and also inhibit ganglia in the bladder wall. At a socially acceptable time, the voiding reflex is activated (Fig. 18.1). Neurones in

the **periaqueductal grey (PAG) matter** in the pons trigger a switch to the **pontine micturition centre (PMC)** in the brainstem to activate the voiding reflex. Stimulation of detrusor smooth muscle by parasympathetic cholinergic nerves causes the bladder to contract. Simultaneous activation of nitrergic nerves reduces the intraurethral pressure. Inhibition of somatic input relaxes the external striated sphincter muscle and sympathetic inhibition causes coordinated bladder neck smooth muscle (internal sphincter) relaxation, resulting in bladder emptying (also see 📖 pp. 596–7).

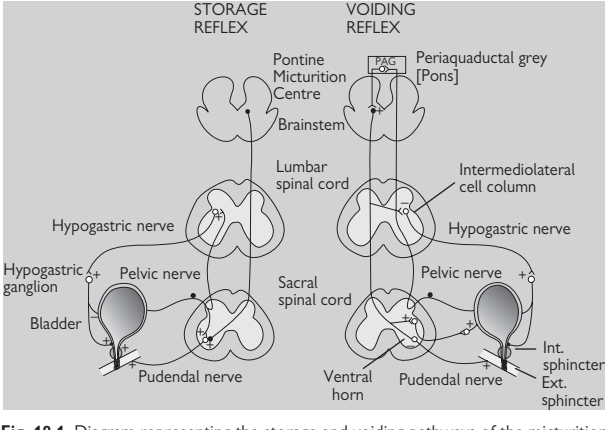


Fig. 18.1 Diagram representing the storage and voiding pathways of the micturition reflex. Micturition is stimulated by activity in the parasympathetic (pelvic) nerves and inhibited by activity in the sympathetic (hypogastric) nerves and pudendal nerves.

Basic renal anatomy

The kidneys and ureters lie within the retroperitoneum (behind the peritoneal cavity). The hila of the kidneys lie on the transpyloric plane (vertebral level L1). Each kidney is composed of a cortex surrounding the medulla which forms projections (papillae) that drain into cup-shaped epithelial-lined pouches called calyces. The calyx draining each papilla is known as a minor calyx and several minor calyces coalesce to form a major calyx, several of which drain into the central renal pelvis (Fig. 18.2). The renal artery, which arises from the aorta at vertebral level L1/2, branches to form interlobar arteries which in turn form arcuate arteries, and then cortical radial arteries from which the afferent arterioles are derived. Venous drainage occurs into the renal vein. There are two capillary networks in each kidney—a glomerular capillary network (lying within Bowman's capsule) which drains into a peritubular capillary network surrounding the tubules (proximal tubule, Loop of Henle, distal tubule, and collecting ducts).

Anatomical relations of the kidney

- Anterior relations of the right kidney are, from top to bottom, the adrenal (suprarenal) gland, liver, and hepatic flexure of the colon. Medially and anterior to the right renal pelvis is the second part of the duodenum. The anterior relations of the left kidney are, from top to bottom, the adrenal gland, stomach, spleen, and splenic flexure of the colon. Medially lies the tail of the pancreas.
- Posterior relations of both kidneys are, superiorly, the diaphragm and lower ribs, and inferiorly (from lateral to medial), transversus abdominis, quadratus lumborum, and psoas major muscles.

The nephron

Each kidney has 1 million functional units or nephrons (Fig. 18.3). These consist of a glomerular capillary network, surrounded by podocytes (epithelial cells) that project into Bowman's capsule which then drains into a tubular system. This includes a proximal convoluted tubule (PCT), Loop of Henle (LoH), distal convoluted tubule (DCT), collecting tubule (CT), and collecting duct (CD). Blood is delivered to the glomerular capillaries by an afferent arteriole and drained by an efferent arteriole. An ultrafiltrate of plasma is formed within the lumen of Bowman's capsule, driven by Starling forces across the glomerular capillaries. Reabsorption of salt and water occurs in the PCT, LoH, DCT, and CD, although the majority of glomerular filtrate is absorbed in the PCT (Table 18.1). LoH generates hypertonicity; its descending limb is only permeable to water whereas its ascending limb is only permeable to solutes. The role of the DCT is fine adjustment of the composition of urine by selective reabsorption or secretion of solutes.

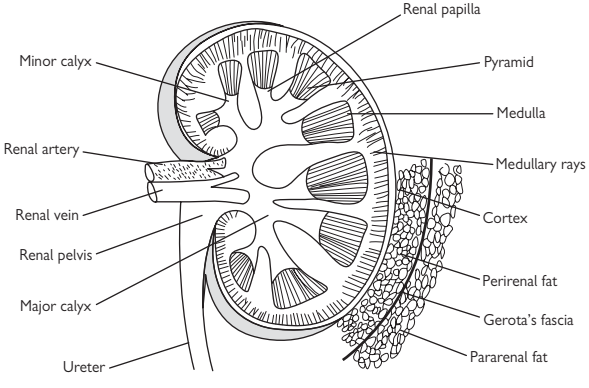
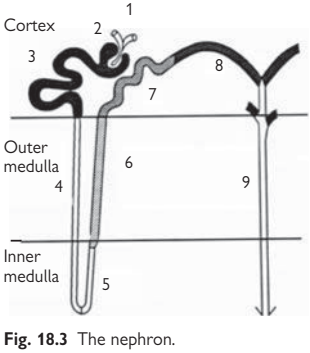


Fig. 18.2 Basic renal anatomy.



KEY:
1 Afferent and efferent arterioles of the glomerulus
2 Bowman's capsule
3 Proximal convoluted tubule
4 Loop of Henle (thin descending limb)
5 Loop of Henle (thin ascending limb)
6 Loop of Henle (thick ascending limb)
7 Distal convoluted tubule
8 Collecting tubule
9 Collecting duct

Fig. 18.3 The nephron.

Table 18.1 Solute and water reabsorption by different parts of the nephron

Solute	PCT	LoH	DCT	CD
Sodium	66%	25% (in TAL)	~5%	~5% under control of aldosterone
Potassium	Majority		Reabsorption by intercalated cells; secretion by principle cells	
Water	66% (by osmosis)			ADH ↑ permeability to water
Magnesium		80%	<5%	
Phosphate	90%			
Calcium	60% passive transport	20%	10% active transport	
Bicarbonate	Majority			
Glucose	Majority			
Amino acids	Majority			

PCT=proximal convoluted tubule; LoH=Loop of Henle; TAL=thick ascending limb (of Loop of Henle); DCT=distal convoluted tubule; CD=collection duct.

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Renal physiology: glomerular filtration and regulation of renal blood flow

Renal plasma clearance

Clearance is the volume of plasma that is completely cleared of solute by the kidney per minute. The clearance ratio for a substance indicates the amount of active reabsorption or excretion (i.e. ratio <1 = actively reabsorbed; >1 = actively excreted). Clearance of a substance from the plasma can be expressed mathematically as:

$$\text{Clearance} = \frac{U \times V}{P} (\text{mL/min})$$

$$\text{Clearance ratio} = \text{clearance} / \text{GFR}$$

where U is the concentration of a given substance in urine, P is its concentration in plasma, and V is the urine flow rate.

Glomerular filtration rate (GFR) (see also 📖 p. 38)

Glomerular filtration is driven by Starling forces: a hydrostatic pressure gradient between capillary and Bowman's capsule, which favours filtration, and colloid oncotic pressure which opposes filtration. ***GFR*** is the clearance for any substance which is ***freely filtered*** and is ***neither reabsorbed, secreted, nor metabolized by the kidney***. For such a substance, clearance is equivalent to GFR. Where a substance is both filtered at the glomerulus and secreted by the renal tubules, its clearance will be greater than GFR. Where a substance is filtered at the glomerulus, but reabsorbed by the renal tubules, its clearance will be less than GFR.

Clinically, GFR is estimated using creatinine and is ~125mL/min. Of note, serum creatinine is an insensitive marker of early renal impairment, as GFR needs to fall below 60–80mL/min before a rise in creatinine is seen.

GFR is directly related to renal plasma flow (RPF). Experimentally, GFR can be accurately calculated by measuring the clearance of inulin (a substance, which is freely filtered by the glomerulus and is neither secreted nor reabsorbed by the kidneys), using the equation:

$$\text{GFR} = \frac{U \times V}{P} \ (= 125 \text{ mL/min})$$

Thus, the volume of plasma from which in 1min the kidneys remove all inulin is equivalent to GFR. Factors affecting the GFR are:

- Rate of blood flow through the glomerulus.
- Permeability of glomerular capillary wall (K).
- Surface area of glomerular capillary bed (S).
- Differences in hydrostatic pressure between glomerular capillary lumen (P_{gc}) and Bowman's space (P_t).
- Differences in oncotic pressure between glomerular capillary (π_{gc}) and Bowman's space (π_t) (although autoregulation of blood flow tends

to keep GFR constant despite a varying range of incoming perfusion pressures).

This can be represented by the equation:

$$\text{GFR (single nephron)} = KS([P_{gc} - P_t] - [\pi_{gc} - \pi_t])$$

Normally about one-fifth (120mL/min) of the plasma that flows through the glomerular capillaries (600mL/min) is filtered (filtration fraction = GFR/RPF).

Renal blood flow (RBF)

The kidneys represent <0.5% of body weight, but they receive 25% of cardiac output (~1300mL/min through both kidneys; 650mL/min per kidney). Combined blood flow in the two renal veins is about 1299mL/min and the difference in flow rates represents the urine production rate (i.e. ~1mL/min).

Autoregulation of RBF

RBF is defined as the pressure difference between the renal artery and renal vein divided by the renal vascular resistance. The glomerular arterioles are the major determinants of vascular resistance. RBF remains essentially constant over a range of perfusion pressures (~80–180mmHg, i.e. RBF is autoregulated). Autoregulation requires no innervation and probably occurs via:

- **A myogenic mechanism**: increased pressure in the afferent arterioles causes them to contract, thereby preventing a change in RBF.
- **Tubuloglomerular feedback**: the flow rate of tubular fluid is sensed at the macula densa of the juxtaglomerular apparatus (JGA) and in some way, this controls flow through the glomerulus to which the JGA is opposed.

Other factors that influence RBF

Neural mechanisms

Sympathetic nerves innervate the glomerular arterioles. A reduction in circulating volume (such as blood loss) can stimulate sympathetic nerves, causing the release of noradrenaline (NA) (which acts on α1-adrenoceptors on the afferent arteriole) to cause vasoconstriction. This results in reduced RBF and GFR.

Endocrine and paracrine mechanisms

- Angiotensin II constricts efferent and afferent arterioles and reduces RBF.
- ADH, ATP, and endothelin all cause vasoconstriction and reduce RBF and GFR.
- Nitric oxide causes vasorelaxation and increases RBF.
- Atrial natriuretic peptide (ANP) causes afferent arteriole dilatation and increases RBF and GFR.

Renal physiology: regulation of water balance

Total body water (TBW) is 42L. It is contained in two major compartments—the intracellular fluid (ICF or the water inside cells) which accounts for 28L and the extracellular fluid (ECF or water outside of cells) representing 14L. ECF is further divided into interstitial fluid (ISF, 11L), transcellular fluid (1L), and plasma (3L). Hydrostatic and osmotic pressures influence movement between the compartments. Water is taken in from fluids, food, and from oxidation of food. Water is lost from urine, faeces, and insensible losses. Intake and losses usually balance (~2L/day) and TBW remains relatively constant. The role of the kidney is regulation of the volume and composition of ECF by constant adjustment of solutes and water to maintain a normal concentration.

ADH or vasopressin

ADH is secreted from the posterior pituitary in response to stimulus from changes in plasma osmolarity (detected by osmoreceptors in the hypothalamus) or changes in BP or volume (detected by baroreceptors in the left atrium, aortic arch, and carotid sinus). These changes also stimulate the thirst centre in the brain.

The action of ADH on the kidney:

- Increases CD permeability to water (via aquaporin water channel proteins) and urea.
- Increases LoH and collecting duct reabsorption of sodium chloride (NaCl).
- Vasoconstriction.

During conditions of water excess

Body fluids become hypotonic and ADH release and thirst are suppressed. In the absence of ADH, the CD is impermeable to water and a large volume of hypotonic urine is produced so restoring normal plasma osmolarity.

During conditions of water deficit

Body fluids are hypertonic and ADH secretion and thirst are stimulated. The CD becomes permeable, water is reabsorbed into the lumen, and a small volume of hypertonic urine is excreted.

The ability to concentration or dilute urine depends on the countercurrent multiplication system in the LoH. Essentially, a medullary concentration gradient is generated (partly by the active transport of NaCl), which provides the osmotic driving force for the reabsorption of water from the lumen of the collecting duct when ADH is present.

Children have a circadian rhythm in ADH secretion—high at night and low during the day. Adults essentially have a constant ADH secretion over a 24h period, with slight increases occurring around meal times. At these times, increased ADH secretion probably acts to prevent sudden increases in plasma osmolarity that would otherwise occur due to ingestion of solutes in a meal.

Renal physiology: regulation of sodium and potassium excretion

Sodium regulation

NaCl is the main determinant of ECF osmolality* and volume. Two-thirds of sodium (Na^+) is reabsorbed in the PCT by either primary active transport (Na^+-K^+-ATPase pump which transports Na^+ in and potassium (K^+) out) or by secondary active transport (specialized Na^+ channels allow Na^+ in and transfer of other solutes in and out of the cell).

Low-pressure receptors in the pulmonary vasculature and cardiac atria and high-pressure baroreceptors in the aortic arch and carotid sinus recognize changes in the circulating volume. Decreased blood volume triggers increased sympathetic nerve activity and stimulates ADH secretion, which results in reduced NaCl excretion. Conversely, when blood volumes are increased, sympathetic activity and ADH secretion are suppressed and NaCl excretion is enhanced (natriuresis). A variety of natriuretic peptides have been isolated which cause a natriuresis. Under physiological conditions, renal natriuretic peptide (urodilatin) is the most important of these. ANP, released after atrial distension, may influence sodium output under conditions of heart failure (acting to increase excretion of NaCl and water).

Renin–angiotensin–aldosterone system

Renin is an enzyme made and stored in the juxtaglomerular cells found in the walls of the afferent arteriole. Factors increasing renin secretion are:

- Reduced perfusion of afferent arteriole.
- Sympathetic nerve activity.
- Reduced Na^+ delivery to the macula densa.

Renin acts on angiotensin to create angiotensin I. This is converted to angiotensin II in the lungs by angiotensin-converting enzyme (ACE). Angiotensin II performs several functions which result in the retention of salt and water:

- Stimulates aldosterone secretion (resulting in NaCl reabsorption and promotes secretion of K^+ and H^+).
- Vasoconstriction of arterioles.
- Stimulates ADH secretion and thirst.
- Enhances NaCl reabsorption by the proximal tubule.

Potassium regulation

K^+ is critical for many cell functions. A large concentration gradient across cell membranes is maintained by Na^+-K^+-ATPase pump. Insulin and adrenaline also promote cellular uptake of K^+.

The majority of K^+ is reabsorbed in the PCT. The DCT can both reabsorb K^+ in cases of K^+ depletion (intercalated cells) and secrete it when there is K^+ excess (principal cells). It is also secreted by the CD. Overall, the kidney excretes up to 95% of K^+ ingested in the diet.

Factors promoting K^+ secretion include:

- Increased dietary K^+ (driven by the electrochemical gradient).
- Aldosterone.
- Increased rate of flow of tubular fluid.
- Metabolic alkalosis (acidosis exerts the opposite effect).

* Osmolality = mol/kg water; osmolarity = mol/L of solution.

Renal physiology: acid–base balance

The normal pH of ECF is 7.4 ([H^+] = 40nmol/L). Several mechanisms are in place to eliminate acid produced by the body and maintain body pH within a narrow range.

Buffering systems that limit [H^+] fluctuation in the blood

Buffer bases that take up H^+ ions in the body include:

Bicarbonate buffer system: $H^+ + HCO_3^- \leftrightarrows H_2CO_3 \leftrightarrows H_2O + CO_2$

Phosphate system: $H^+ + HPO_4^{2-} \leftrightarrows H_2PO_4^-$

Protein buffers: $H^+ + Protein^- \leftrightarrows HProtein$

The Henderson–Hasselbalch equation describes the relationship between pH and the concentration of conjugate acid and base.

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03\ pCO_2}$$

From this equation, it can be seen that alterations in bicarbonate (HCO_3^-) or CO_2 will affect pH. Metabolic acid—base disturbances relate to a change in HCO_3^- and respiratory acid—base disorders relate to alterations in CO_2.

Bicarbonate reabsorption along the nephron (Fig. 18.4)

Bicarbonate is the main buffer of ECF and is regulated by both the kidneys and lungs. Eighty-five percent is reabsorbed in the PCT. Carbonic acid is first produced from CO_2 and water (accelerated by carbonic anhydrase). The carbonic acid dissociates and an active ion pump (Na^+/H^+ antiporter) extrudes intracellular H^+ into the tubule lumen in exchange for Na^+. Secretion of H^+ ions favours a shift of the carbonic acid–bicarbonate equilibrium towards carbonic acid which is rapidly converted into CO_2 and water. CO_2 diffuses into the tubular cells down its diffusion gradient and is reformed into carbonic acid by intracellular carbonic anhydrase. The HCO_3^- formed by this reaction is exchanged for chloride and passes into the circulation. Essentially, with each H^+ ion that enters the kidney, a HCO_3^- ion enters the blood, which bolsters the buffering capacity of the ECF.

The remaining bicarbonate is absorbed in the DCT where cells actively secrete H^+ into the lumen via an ATP-dependent pump. The distal tubule is the main site that pumps H^+ into the urine to ensure the complete removal of HCO_3^-. Once the bicarbonate has gone, phosphate ions and ammonia buffer any remaining H^+ ions.

Abbreviations: H_2O = water; CA = carbonic anhydrase; Cl^- = chloride ion; CO_2 = carbon dioxide; HCO_3^- = bicarbonate; H_2CO_3 = carbonic acid; H^+ = hydrogen ion; HPO_4^{2-} = phosphate ions; $H_2PO_4^-$ = phosphoric acid; Na^+ = sodium ion; Pco_2 = partial pressure of CO_2.

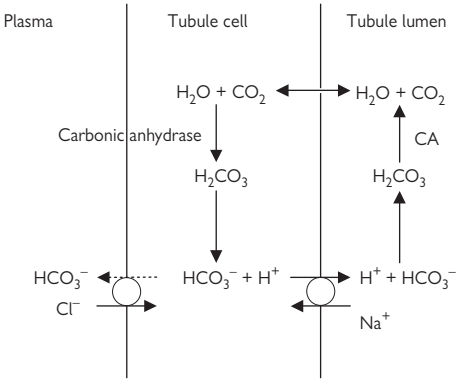

Fig. 18.4 Diagram showing bicarbonate reabsorption in the proximal convoluted tubule.

Renal replacement therapy

Indications for dialysis

- Chronic kidney disease (CKD) stage 5 (eGFR 10–15mL/min).
- Acute renal failure due to persistent hyperkalaemia, metabolic acidosis, fluid overload, symptomatic uraemia, sepsis, and multiorgan failure, drug or toxin poisoning.

Haemodialysis

Access: arteriovenous fistula (requires 8 weeks to mature).

Principles: the dialysis machine pumps blood and dialysate through a dialyser. Dialysate is composed of water, sodium, potassium, dextrose, calcium, chloride, magnesium, and bicarbonate or acetate (as a buffer). The fluids are on opposite sides of a semi-permeable membrane and pumped in opposite directions (countercurrent flow). Waste products of metabolism diffuse from blood to dialysate. Accumulated fluid is removed by convection of water and dissolved solutes (including proteins) down a pressure gradient (ultrafiltration). Heparin is used to prevent clotting.

Regimen: 4h sessions performed three times per week in a hospital-based dialysis unit or at home.

Complications: Anaemia, cardiovascular disease (hypertension, arrhythmias, MI, PVD, CVA), acquired renal cystic disease and renal tract cancers, renal osteodystrophy, neuropathy, erectile dysfunction. Fistula problems include thrombosis, stenosis, aneurysm, and infection.

Peritoneal dialysis

Access: Tenckhoff catheter which allows instillation of fluid into the peritoneum.

Principles: fluid and solute exchange occur between peritoneal capillary blood and dialysis solution using the peritoneum as the dialysis membrane. Small molecular weight solutes diffuse down a concentration gradient from the blood into the dialysate. Water movement is achieved by osmosis from the ECF compartment to the hypertonic peritoneal dialysate.

Regimen: continuous ambulatory dialysis (CAPD) involves continuous dialysis using 3–5 exchanges per day of fluid, performed at home. Automated peritoneal dialysis (APD) allows fast instillation and drainage of large volumes of fluid if more intense dialysis is needed or for dialysis overnight.

Contraindications: bowel adhesions, obesity, inoperable hernias, stoma.

Complications: as for haemodialysis and also catheter infection, peritonitis, membrane (peritoneal) failure, hernia.

Haemofiltration

Access: intravascular (tunneled) catheters, placed in femoral or internal jugular veins.

Principle: removal of solutes with water is achieved by convection down a pressure gradient. It does not require dialysate. Large volumes of filtrate are removed and need to be replaced during this process. This is a controlled and slow process, avoiding large intravascular fluid shifts and minimizing electrolyte disturbances, arrhythmias, and hypotension. It is particularly useful for the haemodynamically compromised patients with acute renal failure. Anticoagulation is required.

Regimen: blood is filtered continuously across a highly permeable synthetic membrane.

Complications: similar, but lower, incidence than for haemodialysis. Includes thrombosis of catheter or access vein, bleeding or clotting, sepsis, fluid overload, alkalosis, hypotension.

Haemodiafiltration

This describes the combination of dialysis and ultrafiltration (diffusion and convection removal of solutes).

Renal transplant: recipient

Indications for transplant

End-stage renal disease.

Contraindication to renal transplant

- Active malignancy is a contraindication to receiving immunotherapy. Generally should remain cancer-free for 2y before transplantation can be considered. Higher risk tumours, including melanoma, breast, colorectal carcinoma, must be disease-free for longer (5y). Lower risk tumours of the skin (basal and squamous cell carcinoma) can undergo transplantation immediately after treatment.
- Active infection (bacterial and viral, including hepatitis B and C, HIV, CMV, and TB).
- Severe vasculitis.
- Significant cardiovascular disease (including recent MI).
- Active systemic lupus erythematosus (SLE).
- Primary hyperoxaluria (requires combined renal and liver transplant).
- Untreated psychological disorders, IV drug use, or alcohol excess.

Genitourinary tract assessment

- USS of kidneys, ureters, and bladder.
- Urine analysis and cultures.
- Urodynamic studies for LUTS (if clinically indicated).

Preoperative assessment

- History: including cause and length of time of renal failure, previous interventions for renal impairment, and previous transplants. Coexisting conditions such as diabetes mellitus (which might require pancreatic transplant). Symptoms of voiding dysfunction which will require treatment before transplant.
- Physical examination.
- Cardiology workup: stress test and ECG.
- Bloods: FBC, U & E, LFT, glucose, calcium, magnesium, clotting, viral serology (HIV, hepatitis, CMV, syphilis, EBV, HTLA).
- ABO blood group.
- Tissue typing for HLA-A, B, and DR phenotypes.
- Blood cross-match to detect preformed antibodies. Recipient's sera are mixed with donor lymphocytes. Recipient antibodies will bind to and lyse donor cells if the cross-match is positive.

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Renal transplant: donor

Types of donor

- **Cadaveric (heart beating)**: brainstem-dead* donor with supported ventilation and circulation.
- **Cadaveric (non-heart beating)**: rapid retrieval is required to minimize ischaemia from these patients without active circulation.
- **Living-related**.
- **Live unrelated**: donation must comply with regulations set by the Unrelated Live Transplant Regulatory Authority (ULTRA).

Absolute contraindications

- Active malignancy.
- History of metastatic cancer or cancer with a higher recurrence risk (i.e. lymphoma).
- Significant cardiac disease (previous MI, coronary artery bypass graft (CABG), angina).
- Diabetes, hypertension, significant pulmonary or vascular disease.
- Active systemic renal disease, i.e. SLE.
- HIV or other active infection.
- BMI >35.
- Coercion.
- Inability to give consent.
- IV drug or alcohol abuse.
- Pregnancy.

Assessment of donor

- History: including family history of disorders such as glomerulonephropathies, PCKD, SLE). Clinical and psychological evaluation in living donors, BP check.
- Bloods: FBC, U&E, cholesterol, glucose, clotting.
- ABO and HLA compatibility: Kidneys should be allocated to the recipient with the lowest number of HLA mismatches.
- Viral serology (hepatitis B and C, HIV, CMV, EBV, syphilis, TB): Establish any family history of high-risk renal disease or prion disease (Creutzfeldt–Jacob).
- eGFR (24h urine collection or EDTA in living donors).
- ECG and CXR.
- Renal imaging to assess donor anatomy, choose the kidney (leave the donor with the better kidney), and plan technique.

Living donors

- Higher success rates than deceased donors and shortens waiting times.
- Long-term follow-up of donor is recommended for surveillance of hypertension or renal impairment.
- Full informed consent should be taken. Risks of nephrectomy include: hypertension, chronic renal failure, mortality (<0.03%).

* Brainstem death: requires two sets of test by two doctors (registered for >5y). The criteria include absence of: corneal reflex, cranial nerve motor function, vestibulo-ocular reflex, cough and gag reflex. Pupils are fixed and unresponsive, no spontaneous movement, and apnoea off ventilator ($PaCO_2$ >6.7kPa)

Transplant surgery and complications

Technique for donor removal

The kidney, ureter, vena cava, aorta, and renal vessels may be taken en bloc from a cadaveric donor. Transport mediums include University of Wisconsin preservation solution (with glutathione and adenosine) with the graft, then packed in ice. Living donor kidney and ureter may be harvested via a laparoscopic or open approach.

Surgery

The renal graft is most commonly placed into the iliac fossa and the vessels anastomosed to the external iliac vein and artery (alternatives include common iliac vessels). An extravesical ureteric reimplantation is performed and a ureteric stent inserted.

Immunosuppression after renal transplantation

Immunosuppression is used as prophylaxis against graft rejection. Agents utilized include:

- **Calcineurin inhibitors** (CNI), cyclosporin or tacrolimus, which inhibit IL-2 production. Blood level monitoring is required.
- **Mycophenolate** (MPA).
- **Corticosteroid** (prednisolone or methylprednisolone).
- Azathioprine, an antimetabolite producing bone marrow suppression.
- mTOR.
- Antithymocyte globulin (ATG), a polyclonal antibody which can lyse human leucocytes.
- OKT3, a monoclonal antibody directed against T lymphocytes.
- Rapamycin, an mTOR inhibitor, involved in IL-2 downregulation.

Common regimens include CNI, MPA, and corticosteroid. Steroids can be stopped at 3–12 post-surgery for patients on combination of CNI and MPA. Azathioprine is an alternative to MPA in low-risk patients. The consent process should include the need for long-term immunosuppression and explanation of the related side effects (increased risk of malignancy, infection, diabetes, hypertension, tremor, renal and liver problems, osteoporosis, etc.).

Post-operative management

- Monitor fluid balance with input and output charts and daily weights.
- Radionuclide renal scan to assess graft blood flow and exclude extravasation.
- Removal of catheter at 7 days if no extravasation.
- Antiplatelet inhibitors (aspirin, dipyridamole).
- Antibacterial and antifungal prophylaxis.
- **Avoid** NSAIDs and ACE inhibitors.
- Be wary of drug interaction and alter doses of drugs accordingly.

Complications

Graft dysfunction can occur early or late and may be due to medical or surgical causes.

Rejection

This manifests as renal function deterioration (oliguria, rising creatinine, hypertension, and proteinuria). Patients may be asymptomatic, have systemic symptoms (fever), or local symptoms, including graft tenderness or swelling. Investigate with percutaneous renal biopsy.

- **Hyperacute rejection** (intraoperatively or within days): due to preformed antibodies to allograft MHC. Treatment is graft removal.
- **Accelerated rejection** (within first week): due to cellular presensitization. Treatment is intensive antirejection treatment, with temporary dialysis support.
- **Acute allograft rejection** (occurs in the first 3 months): affects around 20–30% (90% respond to steroids). Classified as **acute cellular rejection (ACR)** which is T-cell-mediated or **acute humoral rejection (AHR)** which is antibody-mediated. **ACR**: treat with a steroid bolus. If this fails, employ intensified immunosuppression, conversion to tacrolimus, and T-cell-depleting agents. **AHR**: steroid bolus, conversion to tacrolimus, and IV immunoglobulin treatment.
- **Chronic allograft rejection** (months to years): is multifactorial and affects around 30%. Treatment options include conversion from CNI to mTOR inhibitor, or CNI reduction with MPA ± steroid cover.

Other

- Post-transplant malignancy. Most affect the skin (40%) or lymphatic system (11%).
- Graft loss due to recurrence of original renal disease.
- Urinary tract: urinary leak, ureteric stricture/obstruction, fistula, stones, perinephric collections (lymphocele, haematoma, urinoma, abscess).
- Vascular complications: renal artery stenosis or thrombosis, renal vein thrombosis, pseudoaneurysm, A–V fistula, atheromatous vascular disease.
- Drug toxicity.
- Infection.
- Diabetes (thought to be due to the use of corticosteroids and tacrolimus).
- Hypertension.

Outcomes

Recipient death rate at 12 months is 5%. Graft survival rate is >85% at 1y, 60–70% at 5y, and 40–50% at 10y. The best results are with living donors.

Long-term follow-up

Review every 6–12 months. Monitor renal function, immunosuppression, and side effects. Monitor cholesterol (may be raised due to cyclosporine or rapamycin). Diabetes control may be difficult due to steroids. Perform surveillance for the development of malignancy.

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Urological eponyms

Alcock's canal: canal for the internal pudendal vessels and nerve in the ischiorectal fossa.
Benjamin Alcock (b 1801). Professor of Anatomy, Physiology, and Pathology (1837) at the Apothecaries Hall in Dublin.

Anderson–Hynes pyeloplasty: dismembered pyeloplasty for PUJO.
James Anderson and Wilfred Hynes. Surgeons, Sheffield United Hospitals.

BCG (Bacille Calmette–Guérin): attenuated TB bacillus used for immunotherapy of carcinoma *in situ* of bladder.
Leon Charles Albert Calmette (1863–1933). A pupil of Pasteur in Paris, later becoming first director of Pasteur Institute.
Camille Guérin (b 1872). A veterinary surgeon at the Calmette Institute in Lille who, along with Calmette, developed BCG vaccine.

Bonney's test: elevation of bladder neck during vaginal examination reduces leakage of urine during coughing (used to diagnose stress incontinence).
William Bonney (1872–1953). Studied at Barts and Middlesex Hospitals. On the staff of Royal Masonic Hospital and Chelsea Hospital for Women. A highly skilled surgeon with an international reputation.

Bowman's capsule: epithelial-lined 'cup' surrounding the glomerulus in the kidney.
Sir William Paget Bowman (1816–1892). Surgeon to Birmingham General Hospital. Elected FRS in 1841. FRCS 1844. Won the Royal Medal of the Royal Society for his description of the Malpighian body of the kidney. He proposed the theory of urine production by filtration of plasma. Described as the father of histology. In 1846 became surgeon to Moorfields Eye Hospital. An early proponent of the ophthalmoscope and the first in England to treat glaucoma by iridectomy (1862).

Camper's fascia: superficial layer of superficial fascia (fat) of abdomen and inguinal region.
Pieter Camper (1722–1789). Physician and anatomist in Leyden, The Netherlands.

Charrière system: system of measurement for 'sizing' catheters and stents.
Joseph Charrière (1803–1876). Surgical instrument maker in Paris.

Clutton's sounds: metal probes for dilating the urethra (originally used for 'sounding' for bladder stones).
Henry Clutton (1850–1909). Surgeon to St.Thomas's Hospital, London.

Colles fascia: superficial fascia of the perineum.
Abraham Colles (1773–1843). Professor of Anatomy and Surgery in Dublin.

Denonvilliers fascia: rectovesical fascia.
Charles Denonvilliers (1808–1872). Professor of Anatomy, Paris and later Professor of Surgery.

Dormia basket: basket for extracting stones from the ureter.
Enrico Dormia. Assistant Professor of Surgery, Milan.

Douglas, Pouch of: rectouterine pouch (in females), rectovesical pouch (in males).
James Douglas (1675–1742). Anatomist. Physician to the Queen.

Foley catheter: balloon catheter, designed to be self-retaining.

Foley pyeloplasty
Frederic Foley (1891–1966). Urologist, St Paul's, Minnesota.

Fournier's gangrene: fulminating gangrene of external genitalia and lower abdominal wall.
Jean Fournier (1832–1914). Professor of Dermatology, Hôpital St Louis, Paris. Also recognized the association between syphilis and tabes dorsalis.

Gerota's fascia: the renal fascia.
Dumitru Gerota (1867–1939). Professor of Surgery, University of Budapest.

(Loop of) Henle: U-shaped segment of the nephron between the proximal and distal convoluted tubules.
Friedrich Henle (1809–1885). Professor of Anatomy, Zurich and Göttingen.

von Hippel–Lindau syndrome: syndrome of multiple renal cancers.
Eugen von Hippel (1867–1939). Ophthalmologist in Berlin.
Arvid Lindau (b 1892). Swedish pathologist.

Hunner's ulcer: ulcer in bladder in interstitial cystitis.
Guy Hunner (1868–1957). Professor of Gynaecology, Johns Hopkins.

Jaboulay procedure: operation for hydrocele repair (excision of hydrocele sac).
Mathieu Jaboulay (1860–1913). Professor of Surgery, Lyon.

Klinefelter's syndrome: male hypogonadism with XXY chromosome complement.
Harry Klinefelter (b 1912). Associate Professor of Medicine, Johns Hopkins.

Kockerization of the duodenum: mobilization of the 2nd part of the duodenum. Used to expose the inferior vena cava and right renal vein during radical nephrectomy.
Emil Kocker (1841–1917). Professor of Surgery, Berne University. A founder of modern surgery. Won the Nobel Prize in 1909 for work on the physiology, pathology, and surgery of the thyroid gland.

Lahey forceps: curved forceps used during surgery.
Frank Lahey (1880–1953). Head of Surgery, Lahey Clinic, Boston.

Langenbeck retractor: commonly used retractor during surgery.
Bernard von Langenbeck (1810–1887). Professor of Surgery, Kiel and Berlin. A great teacher and surgeon.

Leydig cells: interstitial cells of the testis.
Franz von Leydig (1821–1908). Professor of Histology, Würtzburg, Tübingen, Bonn.

Malécot catheter: large bore catheter, used for drainage of kidney following PCNL.
Achille Malécot (b 1852). Surgeon in Paris.

Millin's prostatectomy: retropubic open prostatectomy.
Terence Millin (d 1980). Irish surgeon, trained in Dublin. Surgeon at Middlesex and Guy's Hospitals and later, Westminster Hospital. Became President of the British Association of Urological Surgeons and then President of the Royal College of Surgeons of Ireland.

Peyronie's disease: fibrosis of shaft of penis, causing a bend of the penis during erection.
François Peyronie (1678–1747). Surgeon to Louis XV in Paris.

Pfannenstiel incision: suprapubic incision used for surgery to the bladder and uterus.
Hermann Pfannenstiel (1862–1909). Gynaecologist from Breslau.

(Cave of) Retzius: prevesical space.
Andreas Retzius (1796–1860). Professor of Anatomy and Physiology at the Karolinska Institute, Stockholm.

Santorini's plexus: plexus of veins on the ventral surface of the prostate.
Giandomenico Santorini (1681–1738). Professor of Anatomy and Medicine in Venice. Wrote a great work on anatomy, *Observationes anatomicae*, published in Venice in 1724.

Scarpa's fascia: deep layer of the superficial fascia of the abdominal wall.
Antonio Scarpa (1747–1832). Professor of Anatomy in Modena and Pavia.

Sertoli cells: supportive cells of testicular epithelium.
Entrico Sertoli (1842–1910). Professor of Experimental Physiology, Milan.

Trendelenburg position: head down operating position.
Friedrich Trendelenburg (1844–1924). Langenbeck's assistant in Berlin and was then Professor of Surgery at Rostock, Bonn, and then Leipzig.

Weigert's law: inverse position of ectopic ureter (the ureter of the upper moiety of a duplex system) drains distally into the bladder (or below into the urethra), whereas the lower pole ureter drains into a proximal position in the bladder.
Carl Weigert (1845–1904). German pathologist.

Wilms' tumour: nephroblastoma of kidney.
Max Wilms (1867–1918). Surgical assistant to Trandeleburg in Leipzig and subsequently Professor of Surgery in Leipzig. Later, Professor of Surgery in Basle and Heidelberg.

Young's prostatectomy: perineal prostatectomy.
Hugh Hampton Young (1870–1945). Professor of Urology, John Hopkins School of Medicine.

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