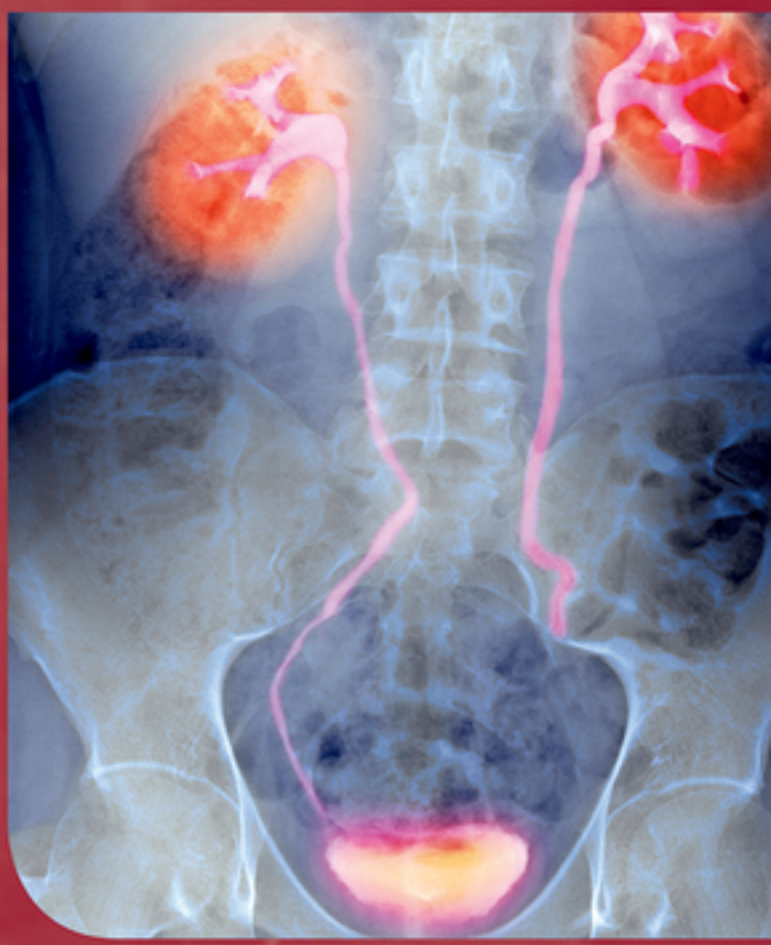
OXFORD TEXTBOOKS IN SURGERY

Oxford Textbook of Urological Surgery

Edited by
Freddie Hamdy
Ian Eardley



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Urological Surgery

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Edited by

Freddie C. Hamdy
Ian Eardley

Section Editors
James W. F. Catto
Christopher R. Chapple
Anthony R. Mundy
Rob Pickard
Rutger Ploeg
David John Ralph
John Reynard
David F. M. Thomas
Michael Weston

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Series Preface from Professor Sir Peter J. Morris

This is a new development in surgical publishing; the first two editions of the *Oxford Textbook of Surgery* are to be replaced by a series of specialty-specific textbooks in surgery. This change was precipitated by the ever-increasing size of a single textbook of surgery which embraced all specialties (the second edition of the *Oxford Textbook of Surgery* was three volumes), and a decision to adapt the textbooks to meet the needs of the audience; firstly, to suit the requirements of Higher Surgical trainees and, secondly, to make it available online.

Thus, we have produced a key book to deal with the fundamentals of surgery, such as Anatomy, Physiology, Biochemistry, Evaluation of Evidence, and so forth. Then there are to be separate volumes covering individual specialties, each appearing as an independent textbook and available on *Oxford Medicine Online*.

It is planned that each textbook in each specialty will be independent although there obviously will be an overlap between different specialties and, of course, the core book on *Fundamentals of Surgery* will underpin the required scientific knowledge and practice in each of the other specialties.

This ambitious programme will be spread over several years, and the use of the online platform will allow for regular updates of the different textbooks.

Each textbook will include the proposed requirements for training and learning as defined by the specialist committees (SACs) of surgery recognized by the four Colleges of Surgery in Great Britain and Ireland, and will continue to be applicable to a global audience.

This ambitious programme will be spread over several years, and the use of the online platform will allow for regular updates of the different textbooks.

When completed, the *Oxford Textbooks in Surgery* series will set standards for a long time to come.

Professor Sir Peter J. Morris
Nuffield Professor of Surgery Emeritus, and former Chairman of the Department of Surgery and Director of the Oxford Transplant Centre, University of Oxford and Oxford Radcliffe Hospitals, UK

Preface

Urology is a rich, diverse, and varied specialty. For certified urological surgeons, it is becoming increasingly challenging to remain updated in such a wide range of assorted conditions with expanding multidisciplinary treatment options, and it is doubly difficult for the trainee to understand what they need to know, and gain a comprehensive knowledge base which will equip them to become certified specialists.

The welcome initiative by Oxford University Press to create a series of specialty-specific textbooks mapped to the UK postgraduate surgical curricula has directly led to the production of this textbook. The urology curriculum describes the range of knowledge, skills, and behaviours that a trainee is expected to have acquired by the time that they are certified. We have taken the syllabus from within that urology curriculum in the United Kingdom and used it as the template for this textbook, which we hope will serve trainees and established colleagues across the world.

While the syllabus provides the basic architecture of urological surgery, the level of knowledge in each of the chapters goes beyond that which will be required for certification. The *Oxford Textbook of Urological Surgery* will be of value not only to trainees, but also to established urologists who wish to keep up-to-date with advances in urological care in one or more areas specific to their day-to-day practice.

We have recruited able expert section editors with an international reputation in their respective field, who led the development and composition of the varying components of this textbook. They, in turn, have relied on rich contributions from many national and international expert colleagues. The authors were specifically mandated to be concise as well as broadly comprehensive in covering their topic from the basics to the current limits of established knowledge, and to highlight areas of controversy, where they exist. Whereas detail may be lacking at times due to space constraints, the concepts and principles that direct modern urological practice are all included.

Urological science progresses continuously and the extent of knowledge described in this book is only a snapshot in time. However, with modern information technology allowing, we have asked all authors to provide frequent updates of their chapter at regular intervals for an exciting online version of the textbook, as well as future editions. Each chapter is accompanied by a long comprehensive reference list, as well as a short one for those interested in a specific theme.

We are confident that the *Oxford Textbook of Urological Surgery* will provide a novel, easy-to read, and useful source of knowledge and strong foundation both for the practising urologist and for trainees seeking to obtain entry into a wonderful specialty that we both continue to find challenging, fascinating, and enjoyable.

Freddie C. Hamdy
Nuffield Professor of Surgery and Professor of Urology,
Chairman, Nuffield Department of Surgical Sciences,
University of Oxford, Oxford OX3 7DQ,
Director of Surgery & Oncology,
Oxford University Hospitals NHS Foundation Trust,
United Kingdom

Ian Eardley
Consultant Urologist, St James's Hospital,
Leeds Teaching Hospitals NHS Trust,
Former Chairman Joint Committee on Surgical Training,
Vice-President, Royal College of Surgeons of England

Acknowledgements

Delivering a textbook is always an exciting challenge, which one paradoxically relishes and fears to take at the same time. The *Oxford Textbook of Urological Surgery* was no exception, and we are most grateful to our section editors and authors for their generous time and effort in providing such a rich and high-quality series of chapters. We thank Oxford University Press and its staff for helping us to deliver this textbook and for their patience during the lengthy preparation of the final manuscripts. We are particularly grateful to Sir Peter Morris whose vision was to map this series of textbooks to the United Kingdom's established training surgical curricula. We are both honoured to have been invited to deliver this important task, and proud to have completed it in this first edition. Finally, we are indebted to our families for their forbearance for the time that we have spent on this enterprise, most importantly our wives Bettina and Michelle.

Freddie C. Hamdy and Ian Eardley
Oxford and Leeds

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Abbreviations

AAST	American Association for the Surgery of Trauma
ABLC	amphotericin B-lipid complex
ABU	asymptomatic bacteriuria
ACE	angiotensin converting enzyme
ACOG	American Congress of Obstetricians and Gynecologists
ADEM	acute disseminated encephalomyelitis
ADH	antidiuretic hormone
ADPKD	autosomal dominant polycystic kidney disease
AFB	acid-fast bacilli
AHA	acetohydroxamic acid
AIDS	acquired immunodeficiency syndrome
AIS	Abbreviated Injury Scale
AKI	acute kidney injury
ALT	alanine aminotransferase
AMB	amphotericin B
APF	antiproliferative factor
AR	androgen receptor
ARHAI	Antimicrobial Resistance and Healthcare Associated Infection
ART	assisted reproductive techniques
AST	aspartate aminotransferase
ATN	acute tubular necrosis
AUA	American Urological Association
AUR	acute urinary retention
AUS	artificial urethral sphincter
BASICS	British Association for Immediate Care
BAUS	British Association of Urological Surgeons
BCG	Bacille Calmette-Guérin
BCI	bladder contractility index
BMA	bulbomembranous anastomosis
BMI	body mass index
BNC	bladder neck contracture
BOO	bladder outlet obstruction
BOOI	bladder outlet obstruction index
BOOP	bronchiolitis obliterans organizing pneumonia
BPE	benign prostatic enlargement
BPH	benign prostatic hyperplasia
BPO	benign prostatic obstruction
BPS	bladder pain syndrome
BRCA	breast cancer predisposition gene
BTX	botulinum toxin
BUO	bilateral ureteric obstruction
BVE	bladder voiding efficiency
BXO	balanitis xerotica obliterans
CAASB	catheter-associated asymptomatic bacteriuria
cAMP	cyclic adenosine monophosphate
CAUTI	catheter-associated urinary tract infection
CBT	cognitive behavioural therapy
CCD	charge-coupled device
CCU	camera control unit
CDC	disease control and prevention
CDI	clostridium difficile infection
CGH	comparative genomic hybridization
CIPO	chronic idiopathic pseudo-obstruction
cGMP	cyclic guanosine monophosphate
CIS	carcinoma in situ
CISC	clean intermittent self-catheterization
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CNF1	cytotoxic necrotizing factor 1
CNS	central nervous system
COLA	cystine, ornithine, lysine, and arginine
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
CPPS	chronic pelvic pain syndrome
CRP	C-reactive protein
CRPC	castration-resistant prostate cancer
CSU	catheter specimen of urine
CT	computed tomography
CTU	CT urography
CUR	chronic urinary retention
DBD	donation after brain death
DBU	double balloon urethrography
DCD	donation after circulatory death
DCS	damage control surgery
DEC	diethylcarbamazine
DGF	delayed graft function
DIT	doxazosin, ibuprofen, and thiocolchicoside
DMSO	dimethylsulphoxide
DRE	digital rectal examination
DSD	disorders of sex development

DTPA	diethyltetrapenta-acetic acid
DVIU	direct vision internal urethrotomy
EAU	European Association of Urology
EBRT	external beam radiotherapy
ED	erectile dysfunction
EEJ	electroejaculation
eGFR	estimated glomerular filtration rate
EHL	electrohydraulic lithotripsy
ELPAT	Ethical, Legal, and Psychosocial Aspects of Transplantation
EMT	epithelial–mesenchymal transition
eNOS	endothelial nitric oxide synthase
EORTC	European Organisation for Research and Treatment of Cancer
EPS	expressed prostatic secretion
ESBL	extended spectrum beta-lactamase
ESRD	end-stage renal disease
ESWL	extracorporeal shock wave lithotripsy
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAST	focused assessment with sonography for trauma
FDA	US Food and Drug Administration
FG	Fournier's gangrene
FGF	fibroblast growth factor
FGSI	Fournier's Gangrene Severity Index
FNAC	fine needle aspiration cytology
FSH	follicle-stimulatuing hormone
FTSG	full-thickness skin graft
f-URS	flexible ureterorenoscopy
FVC	frequency volume chart
GAG	glucosamine glycan layer
GCS	Glasgow Coma Scale
GFR	glomerular filtration rate
GI	gastrointestinal
GRE	glycopeptide-resistant enterococci
GuF	genitourinary fistulae
GWAS	genome-wide association studies
H&E	haematoxylin and eosin
HAI	healthcare-associated infections
HALDN	hand-assisted laparoscopic donor nephrectomy
HARP	hand-assisted retroperitoneoscopic donor nephrectomy
HA-UTI	hospital-acquired urinary tract infection
HAV	Hepatitis A virus
HBD	heart-beating donation
HCAI	healthcare-associated infections
HES	Hospital Episodes Statistics
HG-NMIBC	high-grade non-muscle invasive bladder cancer
HGPIN	high-grade prostatic intraepithelial neoplasia
HIFU	high-intensity focused ultrasound
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HlyA	α-haemolysin
HPCR	high-pressure chronic retention
HPV	human papilloma virus
HRPC	hormone-refractory prostate cancer
HRQoL	health-related quality of life
HSV	herpes simplex virus
IBC	intracellular bacterial communities
IC	interstitial cells
ICC	interstitial cells of Cajal
ICIQ	International Consultation on Incontinence Questionnaire
ICP	intracranial pressure
ICS	International Continence Society
ICSI	intracytoplasmic sperm injection
ICU-VS	International Consultation on Incontinence Vaginal Symptoms questionnaire
IDO	idiopathic detrusor overactive
IL-1	interleukin
INH	isoniazid
iNOS	inducible nitric oxide synthase
INR	international normalized ratio
IPP	leak point pressures
IPP	intravesical prostatic protrusion
IPSS	International Prostate Symptom Score
ISC	intermittent self-catheterization
ISD	intrinsic sphincter deficiency
ISS	Injury Severity Score
IUI	intrauterine insemination
IVF	*in vitro* fertilization
IVP	intravenous pyelography
IVU	intravenous urography
JGA	juxtaglomerular apparatus
KTx	kidney transplantation
KTXs	kidney transplants
KUB	kidney, ureter, and bladder
L-AMB	liposomal amphotericin B
LFT	liver function test
LESS	laparoendoscopic single site surgery
LGV	lymphogranuloma venereum
LH	lutenizing hormone
LPCR	low-pressure chronic retention
LPS	lipopolysaccharide
LRP	laparoscopic radical prostatectomy
LSCS	low segment caesarian section
LUT	lower urinary tract
LUTD	lower urinary tract dysfunction
LUTS	lower urinary tract symptoms
MAG3	mercaptoactyl-triglycine
MAP	magnesium ammonium phosphate
MCUG	micturating cystourethrogram
MDRD	modification of diet in renal disease
MDR-TB	multidrug-resistant tuberculosis
MET	medical expulsive therapy
MHRA	Medicines & Healthcare products Regulatory Agency (UK)
MIC	minimum inhibitory concentration
MRHA	mannose-resistant haemagglutination
MLCK	myosin light chain kinase
MRI	magnetic resonance imaging
MRSA	methicillin-resistant Staphylococcus aureus
MRU	magnetic resonance urography
MSA	multiple system atrophy
MSHA	mannose-sensitive haemagglutination
MSM	men having sex with men
MSSU	midstream specimen of urine
MSU	midstream uine

MTOPS	medical therapy of prostatic symptoms
MUCP	maximum urethral closure pressure
MUI	mixed urinary incontinence
MUP	maximum urethral pressure
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
NAAT	nucleic acid amplification test
NA	noradrenaline
NADPH	nicotinamide adenine dinucleotide phosphate
NANC	non-adrenergic non-cholinergic
NBI	narrow band imaging
NCCN	National Comprehensive Cancer Network
NCCT	non-contrast computed tomography
NDO	neurogenic detrusor overactivity
NGS	next generation sequencing
NHBD	non-heart-beating donation
NIAID	National Institute for Allergy and Infectious Diseases
NICE	National Institute for Health and Care Excellence
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NIH-CPSI	National Institutes of Health Chronic Prostatitis Symptom Index
NMIBC	non-muscle invasive bladder cancer
NNIS	National Nosocomial Infections Surveillance
nNOS	neuronal nitric oxide synthase
NNRTI	non-nucleoside reverse transcriptase inhibitors
NO	nitric oxide
NOS	nitric oxide synthase
NOTES	natural orifice transluminal endoscopic surgery
NRTI	nucleoside reverse transcriptase inhibitors
NSAID	non-steroidal anti-inflammatory drug
OAB	overactive bladder
OABS	overactive bladder symptom syndrome
OCC	urothelial cell carcinoma
PAH	p-aminohippuric acid
PAI	pathogenicity islands
PAIR	puncture, aspiration, injection and reaspiration
PAMP	pathogen-associated molecular pattern
PAS	para-aminosalicylic acid
PBP	penicillin-binding protein
PCa	prostate cancer
PCN	percutaneous nephrostomy
PCNL	percutaneous nephrolithotomy
PCR	polymerase chain reaction
PD	peritoneal dialysis
PDD	photodynamic diagnosis
PDE-5	phosphodiesterase type 5
PDT	photodynamic therapy
PET	positron emission tomography
PFDI	Pelvic Floor Distress Inventory
PFS	pressure flow studies
PI	protease inhibitors
PID	pelvic inflammatory disease
PLUTO	percutaneous shunting in lower urinary tract obstruction
PMC	pontine micturition centre
PMD	post-micturition dribble
PN	pneumatic lithotripsy
PNE	percutaneous nerve evaluation
POP	pelvic organ prolapse
POPIQ	POP Impact Questionnaire
PPD	purified protein derivative
PPMT	pre- and post-massage test
PPS	sodium pentosan polysulphate
PSA	prostate-specific antigen
PSF	probability of stone formation
PTB	pulmonary tuberculosis
PTNS	percutaneous tibial nerve stimulation
PUJ	pelviureteric junction
PUJO	pelviureteric junction obstruction
PUV	posterior urethral valve disorder
PVR	post-void residual
PVS	penile vibratory stimulation
PZA	pyrazinamide
QoL	quality of life
RADN	robot-assisted laparoscopic donor nephrectomy
RALP	robotic-assisted laparoscopic prostatectomy
RARP	robotic-assisted laparoscopic radical prostatectomy
RBF	renal blood flow
RCC	renal cell carcinoma
RCT	randomized controlled trial
RI	resistive index
RIRS	retrograde intrarenal surgery
RNA	ribonucleic acid
RP	radical prostatectomy
RPF	renal plasma flow
RRP	robotic radical prostatectomy
RRt	renal replacement treatment
RTA	renal tubular acidosis
RTX	repeats in toxin
RUG	retrograde urethrogram
RVT	renal vein thrombosis
SAT	secreted autotransporter toxin
SCC	squamous cell cancer
SCI	spinal cord injury
SEER	Surveillance, Epidemiology, and End Results programme
SIRS	systemic inflammatory response syndrome
sGC	soluble guanylate cyclase
SJS	Stevens–Johnson syndrome
SLED	slow low-efficiency dialysis
SNARE	sensitive factor attachment protein receptor
SNM	sacral neuromodulation
SPC	suprapubic catheterization
STARR	stapled transanal rectal resection
STI	sexually transmitted infection
STSG	split-thickness skin graft
SUI	stress urinary incontinence
SVI	seminal vesicle invasion
SWL	shockwave lithotripsy
TCC	transitional cell carcinoma
TEAP	transurethral ethanol ablation of the prostate
TEN	toxic epidermal necrolysis
TENS	transcutaneous electrical nerve stimulation
TGF	transforming growth factor
TH	tyrosine hydroxylase

THP	Tamm-Horsfall protein
TIN	testicular intraepithelial neoplasia
TIR	Toll/interleukin receptor
TLR	Toll-like receptor
TNM	tumour-node metastases system
TRUS	transrectal ultrasonography
TUR	transurethral resection
TURB	transurethral resection of the bladder
TURBT	transurethral resection of a bladder tumour
TURP	transurethral resection of prostate
TUU	transureteroureterostomy
TWOC	trial without catheter
UBC	urothelial bladder cancer
UD	urethral diverticula
UDIF	urothelium-derived inhibitory factor
UDT	undescended testis
UE	ureteroscopic endopyelotomy
UGTB	urogenital tuberculosis
UI	urinary incontinence
UICC	Union for International Cancer Control
UK	United Kingdom
UL	ultrasonic lithotripsy
UPEC	uropathogenic *Escherichia coli*
UPJ	ureteropelvic junction
UPOINT	urinary, psychosocial, organ specific, infection, neurological and muscle tenderness
UPOINTS	urinary, psychosocial, organ specific, infection, neurological and muscle tenderness, and sexual dysfunction
UPP	urethral pressure profiles
URS	ureteroscopy
UrVF	ureterovaginal fistula
USS	ultrasound scan
UTI	urinary tract infection
UTUC	upper urinary tract urothelial carcinoma
UUI	urgency urinary incontinence
UVF	urethrovaginal fistula
VAS	visual analogue scales
VCUG	voiding cystourethrography
VEGF	vascular endothelial growth factor
VHL	Von Hippel-Lindau
VIP	vasoactive intestinal polypeptide
VUA	vesicourethral anastomosis
VUF	vesicouterine fistula
VUR	vesicoureteric reflux
VVF	vesicovaginal fistula
WHO	World Health Organization
WIT	warm ischaemia time
XDR-TB	extensively drug-resistant tuberculosis

Contributors

Sally Ager, Leeds Teaching Hospital Trust, UK

Hashim Uddin Ahmed, Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, UK

Peter Albers, Department of Urology, University Clinic Düsseldorf Peter Albers, Urologische Klinik, Universitätsklinikum Düsseldorf, Germany

Ased Ali, Department of Urology, Mid Yorkshire Hospitals NHS Trust, UK

Ashraf Almatar, Department of Surgical Oncology, Division of Urology, Princess Margaret Hospital, Toronto, Ontario, Canada

Ines Teles Alves, Department of Urology, Erasmus MC, Rotterdam, the Netherlands

Akwasi Amoako, Department of Urology and Reproductive Medicine, Leeds Teaching Hospitals, Leeds, UK

Daniela E. Andrich, University College London Hospitals NHS Foundation Trust; London Bridge Hospital, both London, UK

Gastón M. Astroza, Duke University School of Medicine, Durham, NC, USA

Aditya Bagrodia, Department of Urology, The University of Texas Southwestern Medical Center, Dallas, USA & Urology Fellow, The David Solit Lab, Memorial Sloan Kettering Cancer Center, NY

Atul Bagul, Endocrine Surgery, Department of General Surgery, Sheffield Teaching Hospitals NHS Foundation Trust, UK

Saba Balasubramanian, Academic Surgical Oncology Unit, University of Sheffield, Royal Hallamshire Hospital, UK

Steve Ball, Department of Endocrinology, Central Manchester University Hospitals and Manchester Academic Health Science Centre, Manchester, UK

Roger Bayston, School of Medicine, University of Nottingham, UK

Mohammed Belal, University Hospitals Birmingham, Edgbaston, Birmingham, UK

Simone Bertz, Institute of Pathology, University Erlangen, Erlangen, Germany

Carlo Bettocchi, Institute of Urology, St. Peter's Hospital, UCH London, UK and University of Bari Aldo Morom, Italy

Anders Bjartell, Department of Urology, Skåne University Hospital, Lund University, Sweden

William Brant, University of Utah, Salt Lake City, Utah, USA

Alberto Briganti, Vita-Salute San Raffaele Hospital, Department of Urology, Milan, Italy

Maree Brinkman, Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Australia

Richard J. Bryant, The Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford, UK

Thomas Bschleipfer, Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig-University Giessen, Germany

Frank Buntin, Department of General Practice, Katholieke Universiteit Leuven, ACHG-KULeuven, Kapucijnenvoer, Leuven, Belgium

Max Burger, St Josef Medical Centre, Department of Urology of Regensburg University, Regensburg, Germany

Jeffrey A. Cadeddu, Department of Urology, UT Southwestern Medical Center, Dallas, Texas, USA

Fabio Calabrò, Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy

Peter Carroll, University of California, San Francisco, CA, USA

James W.F. Catto, Department of Oncology, The Medical School, Beech Hill Road, Sheffield, UK

Selim Cellek, Anglia Ruskin University, Faculty of Medical Science UK

Christopher R. Chapple, University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust, UK

Keith Chapple, Colorectal Surgical Unit, Sheffield Teaching Hospitals NHS Foundation Trust, UK

Liang Cheng, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Noel W. Clarke, The Christie and Salford Royal Hospitals NHS Trusts, Manchester, UK

Pierre Colin, Academic Department of Urology, CHRU Lille, Univ Lille Nord de France, Lille, France

Matthew Cooperberg, Departments of Urology and Epidemiology & Biostatistics, UCSF; Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

Eduardo Cortes, Department of Urogynaecology, Kingston Hospital NHS Foundation Trust, London, UK

David Cranston, The Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Peter Cuckow, Department of Paediatric Urology, Great Ormond Street Hospital NHS Trust, London, UK

Donna Daly, Department of Biomedical Science, University of Sheffield, UK

Ahmed A. Darwish, Ain Shams University, Cario, Egypt and Senior Clinical Fellow Pediatric Surgery and Urology, University Hospital of Wales, Cardiff, UK

Raj Das, Department of Radiology, St. George's Hospital and Medical School, London, UK

Johann De Bono, The Royal Marsden Foundation Trust, The Institute of Cancer Research, UK

Gert De Meerleer, University Hospital of Ghent, Department of Radiation Oncology, Ghent, Belgium

Louise Dickinson, Department of Urology, UCLH NHS Foundation Trust, London, UK

Thorsten Diemer, Pediatric Urology and Andrology, Justus-Liebig-University Giessen, Germany

Rosa Djajadiningrat, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Gert R. Dohle, Department of Urology, Erasmus University Medical Center, Rotterdam, the Netherlands

Frank J.M.F. Dor, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK

Marcus Drake, Bristol Urological Institute, School of Clinical Sciences, University of Bristol, UK

Ian Eardley, Leeds Teaching Hospital Trust, UK

Tim Eisen, Department of Oncology, Cambridge Biomedical Campus, Addenbrooke's Hospital, Cambridge University Health Partners, Cambridge, UK

Julie Ellis-Jones, University of the West of England; and Southmead Hospital, North Bristol Trust, Bristol, UK

Mark Emberton, Division of Surgery and Interventional Science University College London, UK

Stephen Faddegon, University of Texas Southwestern Medical Center, Dallas, USA

Magnus Fall, Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Sweden

Vincenzo Ficarra, O.L.V. Robotic Surgery Institute, Aalst, Belgium

Mikkel Fode, University of Copenhagen and Department of Urology, Herlev and Gentofte Hospital

Paolo Fornara, Faculty of Medicine, University Hospital, Halle (Saale), Germany

Clare Fowler, University College London, UK; the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Simon Freeman, Department of Radiology, Derriford Hospital, Plymouth, Devon, UK

Giulio Garaffa, St Peter's Andrology, University College London Hospitals, London, UK

Mary Garthwaite, James Cook University Hospital, Middlesborough, UK

Tarek P. Ghoneim, Academic Department of Urology, CHRU Lille, University Lille Nord de France, Lille, France

James A. Gilbert, OUH NHS Trust and Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford; and Oxford Kidney Unit, Oxford University Hospitals, UK

Inderbir Gill, University of Southern California, Los Angeles, USA

John Goepel, Sheffield Teaching Hospitals, Sheffield, UK

Zachariah G. Goldsmith, Department Urology, St. Luke's Center, USA

Paolo Gontero, University of Torino, Department of Surgival Sciences and Urology, Turin, Italy

Mieke Goossens, Department of General Practice, Katholieke Universiteit Leuven, ACHG-KULeuven, Kapucijnenvoer, Leuven, Belgium

Magnus Grabe, Department of Microbiology, Immunology and Glycobiology (MIG), Lund University, Sweden

Francesco Greco, Department of Urology and Mini-Invasive Centre, Romolo Hospital, Crotone, Italy

Basma Greef, Department of Oncology, Cambridge Biomedical Campus, Addenbrooke's Hospital, Cambridge University Health Partners, Cambridge, UK

Geoffrey I. Hackett, Consultant in Sexual Medicine, Heartlands Hospital, Birmingham, UK; Emeritus Professor of Men's Health and Diabetes, University of Bedfordshire, UK; occasional speaker for Bayer and v Besins Pharmaceuticals.

Simon Harrison, Department of Urology, Pinderfields Hospital, Wakefield, UK

Alice Hartley, Freeman Hospital, Newcastle upon Tyne, UK

Arndt Hartmann, Institute of Pathology, Erlangen University Hospital, Erlangen, Germany; Department of Pathology, Friedrich-Alexander University Medical Centre, Erlangen, Germany

Robert P. Hartman, Department of Radiology, Mayo Clinic School of Medicine, Mayo Clinic, Rochester, MN, USA

Hashim Hashim, Bristol Urological Institute, Southmead Hospital, Bristol, UK

Richard J. Haynes, Clinical Trial Service Unit, Oxford, UK

Susan Heenan, Department of Radiology, St. George's Hospital and Medical School, London, UK

Axel Heidenreich, Department of Urology, RWTH University Aachen, Germany

John Henderson, Churchill Hospital, Oxford

Dennis A. Hesselink, Department of Internal Medicine, Division of Nephrology and Renal Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

Christiaan F. Heyns, Formally of Department of Surgical Sciences, Division of Urology, Stellenbosch University, South Africa

Simon Horenblas, Department of Urology, the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Peter Howells, Department of Medical Physics, Leeds General Infirmary, Leeds Teaching Hospitals Trust, Leeds, UK

Kim Hutton, Department of Paediatric Surgery, University Hospital of Wales, Cardiff, UK

Muhammad Waqas Iqbal, Duke University Medical Centre, Durham, North Carolina

Mariam Jafri, School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, Medical and Molecular Genetics, University of Birmingham, UK

Guido Jenster, Department of Urology, Erasmus MC, Rotterdam, the Netherlands

Michael Jewett, Department of Surgical Oncology, Division of Urology, Princess Margaret Hospital, Toronto, Ontario, Canada

Ghalib Jibara, Urology Resident, Division of Urology, Department of Surgery, Duke University Hospital, Durham, NC, USA

Steven Joniau, University Hospital of Leuven, Department of Urology, Leuven, Belgium

Ates Kadioglu, Department of Urology, Medical Faculty of Istanbul, Istanbul University, Turkey

Sajid Kalathil, Department of Diabetes and Endocrine, University of Newcastle, International Centre for Life, Newcastle upon Tyne

R. Jeffrey Karnes, Mayo Clinic, Department of Urology, Rochester, USA

Oliver Kayes, Department of Urology and Reproductive Medicine, Leeds Teaching Hospitals, Leeds, UK

Akira Kawashima, Department of Radiology, Mayo Clinic School of Medicine, Mayo Clinic, Scottsdale, AZ, USA

Steven Kennish, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, UK

Stephen Keoghane, Portsmouth Hospitals NHS Trust, UK

Timothy J. Key, Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, UK

Jeannette Kathrin Kraft, Clarendon Wing Radiology Department, Leeds General Infirmary, Leeds Teaching Hospitals Trust, Leeds, UK

Jeff A. Lafranca, Department of Surgery, division of Transplant Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

Stephen M. Larsen, Rush University Medical Center, Chicago, IL, USA

Andrew J. LeRoy, Department of Radiology, Mayo Clinic School of Medicine, Mayo Clinic, Rochester, MN, USA

Laurence A. Levine, Rush University Medical Center, Chicago, IL, USA

Hans Lilja, Departments of Laboratory Medicine, Surgery, and Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK; Department of Translational Medicine, Lund University, Malmö, Sweden

Michael E. Lipkin, Duke University Medical Center, Department of Surgery, Division of Urology, Durham, NC, USA

Antonio Lopez-Beltran, Anatomical Pathology Unit, Department of Surgery, Faculty of Medicine and Nursing, University of Cordoba, Cordoba, Spain & Department of Pathology, Champalimaud Clinical Center, Lisbon, Portugal

Yair Lotan, Department of Urology, The University of Texas Southwestern Medical Center, Dallas, USA

Eamonn Maher, School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, Medical and Molecular Genetics, University of Birmingham, UK

Altaf Mangera, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK

Roy Mano, Institute of Urology, Rabin Medical Center, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Roman Mayr, St Josef Medical Centre, Department of Urology of Regensburg University, Regensburg, Germany

Roberta Mazzucchelli, Università Politecnica delle Marche, Italy

Emma J. McCarty, Department of Genitourinary Medicine, Royal Victoria Hospital, Belfast, UK

Chris G. McMahon, Australian Center for Sexual Health, Sydney, Australia

Richard P. Meijer, Department of Urology, University Medical Centre Utrecht, Utrecht, the Netherlands

Rodolfo Montironi, Section of Pathological Anatomy, Polytechnic University of the Marche Region (Ancona), School of Medicine, United Hospitals, Ancona, Italy

Roland Morley, Imperial College NHS Trust, London, UK

Alexander Mottrie, O.L.V. Robotic Surgery Institute, Aalst, Belgium

Deborah Mukherji, The Royal Marsden Foundation Trust, UK, American University of Beirut Medical Center, Riad El-Solh, Beirut, Lebanon

Anthony R. Mundy, Institute of Urology, University College Hospital, UCLH NHS Foundation Trust Headquarters, London

Asif Muneer, Department of Urology and NIHR Biomedical Research Centre, University College London Hospital, UK

Andreas Neisius, Department of Urology, University Medical Center, Johannes Gutenberg University, Mainz, Germany

Giacomo Novara, University of Padua, Padua, Italy

David Noyes, Consultant in Orthopaedic Trauma Surgery, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Tim O'Brien, Guys and St Thomas' Hospital, London, UK

Chris A. O'Callaghan, Nuffield Department of Medicine, University of Oxford, UK

Ephrem Olweny, Departments of Urology, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ

Aurelius Omlin, The Royal Marsden Foundation Trust, The Institute of Cancer Research, UK

Nadir Osman, Department of Urology, Royal Hallamshire Hospital, Sheffield, UK

Jalesh Panicker, University College London; The National Hospital for Neurology and Neurosurgery; UCL Institute of Neurology, all in London, UK

Amit Patel, Consultant in Urology, Guys and St Thomas' Hospital, London, UK

Nilay Patel, The Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Uday Patel, Department of Radiology, St. George's Hospital and Medical School, London, UK

Carmel Pezaro, The Royal Marsden Foundation Trust, The Institute of Cancer Research, UK

Adrian Pilatz, Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig-University Giessen, Germany

Hartmut Porst, Private Urological/Andrological Practice, Hamburg, Germany

Glenn M. Preminger, Department of Urologic Surgery, Duke University Medical Center, Durham, NC, USA

Alison J. Price, Cancer Epidemiology Unit, University of Oxford, UK

Samarpit Rai, Division of Urology, University of Miami Miller School of Medicine, Miami, USA

David John Ralph, St Peter's Andrology, University College London Hospitals, London, UK

Ashok Daya Ram, Consultant Paediatric and Neonatal Surgeon, Department of Paediatric Surgery, Norfolk and Norwich University Hospital, Norwich, UK

Yacov Reisman, Urologist, Amstelland Hospital, Laan van de Helende Meesters 8, Amstelveen, the Netherlands

John Reynard, Nuffield Department of Surgical Sciences, University of Oxford, UK

Morgan Roupret, Academic Department of Urology of la Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Faculté de Médecine Pierre et Marie Curie, University Paris VI, Paris, France

Antonino Saccà, Department of Urology, Ospedali Riuniti di Bergamo, Bergamo, Italy

Arun Sahai, Department of Urology, Guy's Hospital, Guy's and St Thomas' NHS Trust, King's Health Partners, London, UK

Neveen Said, Department of Radiation Oncology, University of Virginia, USA

Emre Salabaş, Department of Urology, Medical Faculty of Istanbul, Istanbul University, Turkey

Andrea Salonia, University Vita-Salute San Raffaele-Department of Urology, Milan, Italy

Salvatore Sansalone, Department of Urology, School of Medicine Tor Vergata University of Rome, Rome, Italy

Matteo Santoni, Medical Oncology, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I, GM Lancisi, G Salesi, Ancona, Italy

Charles D. Scales, David Geffen School of Medicine, UCLA

Marina Scarpelli, Università Politecnica delle Marche, Italy

Fritz H. Schröder, Department of Urology, Erasmus University Rotterdam, the Netherlands

Edward Sharples, Oxford University Hospitals NHS Trust, UK

Graham Sleat, Specialty Registar, Trauma & Orthopaedics, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Jens Sonksen, University of Copenhagen and Department of Urology, Herlev and Gentofte Hospital

Martin Spahn, Inselspital, Department of Urology, Bern, Switzerland

Mark Speakman, Department of Urology, Taunton and Somerset Hospital, Taunton, UK

Marco Spilotros, Institute of Urology, St. Peter's Hospital, UCH London, UK

Roly Squire, Leeds Children's Hospital, Leeds, UK

Henrik Steinbrecher, Department of Paediatric Surgery, Southampton University Hospital, Southampton, UK

Cora N. Sternberg, Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy

Mark Sullivan, The Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Eugene Teoh, Department of Radiology, Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford, and Department of Oncology, University of Oxford, UK

George Thalmann, Department of Urology, University of Bern, Inselspital, Switzerland

Dan Theodorescu, University of Colorado, Comprehensive Cancer Center, Aurora, Colorado, USA

Nikesh Thiruchelvam, Department of Urology, Addenbrookes Hospital, Cambridge, UK; Cambridge University Hospitals NHS Trust, UK

David F.M. Thomas, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Page Toby, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

Jan Trapman, Erasmus MC, Rotterdam, the Netherlands

Benjamin W. Turney, Department of Urology, Nuffield Department of Surgical Sciences, The Churchill Hospital, Oxford, UK

David Ulmert, Molecular Pharmacology and Chemistry Program, Memorial Sloan-Kettering Cancer Center, NY, USA, and Department of Surgery (Urology), Skåne University Hospital, Malmö, Sweden

Siska Van Bruwaene, University Hospital of Leuven, Department of Urology, Leuven, Belgium

Bas W.G. Van Rhijn, Department of Surgical Oncology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital

Sobhan Vinjamuri, Department of Nuclear Medicine, Royal Liverpool University Hospital, Liverpool, UK

Florian M.E. Wagenlehner, Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig-University Giessen, Germany

Katherine E. Walton, Department of Microbiology, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

Wolfgang Weidner, Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig-University Giessen, Germany

Toby Wells, Department of Radiology, Derriford Hospital, Plymouth, Devon, UK

Sven Wenske, MD. Department of Urology, Columbia University Medical Center, College of Physicians & Surgeons, New York, NY, USA

Michael Weston, Leeds Teaching Hospitals NHS Trust, UK

Christian Winter, Department of Urology, University Clinic Düsseldorf Peter Albers, Urologische Klinik, Universitätsklinikum Düsseldorf, Germany

Han Hsi Wong, Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Björn Wullt, Department of Microbiology, Immunology and Glycobiology (MIG), Lund University, Sweden

Ofer Yossepowitch, Institute of Urology, Rabin Medical Center, Petah Tikva, Israel

Filiberto Zattoni, University of Padua, Padua, Italy

Maurice P. Zeegers, Nutrition and Translational Research in Metabolism (School NUTRIM), Maastricht University, the Netherlands; Care and Public Health Research Institute (School CAPHRI), Maastricht University, the Netherlands

Pascal Zehnder, Department of Urology, University of Bern, Inselspital, Switzerland

Alexandre R. Zlotta, Division of Urology, Mount Sinai Hospital, Toronto, Canada

SECTION 1

Inflammation

Section editor: Rob Pickard

CHAPTER 1.1

Pathogenesis of urinary tract infection

Ased Ali

Introduction to urinary tract infection

Urinary tract infection (UTI) is one of the most common bacterial infections to affect humans. Its incidence increases with age and the cumulative probability of a woman having had a UTI by the age of 50 is approximately 50%.[1] The normally sterile urinary tract is the site of an ongoing but complex interplay between an evolving pathogen and a highly developed host immune defence system, such that the pathogenesis of a UTI generally requires either greater virulence in the pathogen or deficient host defence. Typically, the process of infection begins with attachment of the uropathogen to the epithelial surface; it subsequently forms colonies, which then disseminate and invade through the urothelial tissue. This dissemination may be associated with ascent up the urinary tract, which may manifest symptomatically as cystitis (in the bladder) or pyelonephritis (in the kidney). Symptomatic infection indicates a powerful immune response and the interplay between pathogen and host will continue, influencing the extent and level of invasion, the duration of infection, and the degree of tissue damage.

An understanding of bacterial pathogenesis and anti-adherence defence mechanisms is important for clinicians so that appropriate strategies for the management and prevention of UTI are used. This section outlines current understanding of the pathogenesis of UTI, with particular emphasis on bacterial virulence and interaction with host defences, together with other factors which increase susceptibility to UTI.

Routes of infection

The ascending route is the commonest mode of infection of the urinary tract with most bacteria originating from the individual's own lower bowel and subsequently colonizing the periurethral tissue before ascending through the urethra and into the bladder.[2] Colonization of the periurethral mucosa with bowel flora is particularly problematic in females, where the shorter urethra provides a convenient conduit for invading pathogens and rapid entry to the lower urinary tract. Even small variations in perineal anatomy in females can increase susceptibility; for example, women with an anal to urethral distance of less than 4.5 cm are at increased risk of UTI.[3] These anatomical risks can be further increased by the influence of external agents such as spermicides, faecal contamination of the perineum, and the use of urethral catheters.[4,5]

Symptomatic UTI is usually confined to the bladder (cystitis), but in up to a half of cases there are signs indicating upper urinary tract involvement such as fever and loin pain.[6] Pyelonephritis is most frequently caused by the ascent of bacteria from the bladder up the ureter and into the renal pelvis, with subsequent invasion of the renal parenchyma through the collecting ducts and disruption of the renal tubules. Certain pathogenic bacterial virulence factors including P-fimbriae and endotoxins can enhance the ability of bacteria to ascend the urinary tract, as can host susceptibility factors such as pregnancy and ureteral obstruction, which inhibit peristalsis.

Haematogenous infection of the urinary tract is uncommon in normal individuals. However, patients with primary foci of infection elsewhere in the body involving *Staphylococcus aureus, Candida spp., Salmonella spp.*, and *Mycobacterium tuberculosis* can suffer secondary kidney infection. The risk of such infection is enhanced when urine drainage from the kidney is obstructed.[7] Infection via the lymphatic route is rare but can be caused by direct invasion of bacteria from adjacent organs in conditions that result in retroperitoneal sepsis and suppuration. The lymphatic route is not thought to play a significant role in the majority of UTIs.

Pathogenic bacterial virulence factors

The interplay between host and pathogen is at the heart of any UTI. Uropathogenic *Escherichia coli* (UPEC) strains for example encode a number of virulence factors, which enable the bacterial clone to colonize the urinary tract and persist in the face of host defences. In recent years, great advances have been made in the understanding of these virulence factors. Prior to their migration, these bacteria will typically have come from a commensal site, such as the bowel. The role of virulence factors is therefore critical in the understanding of how commensals at one site act as pathogens at another.

UPEC strains exhibit a high degree of genetic diversity facilitated by the possession of specialized virulence genes located on specific transferable genetic elements known as pathogenicity islands, which may be as large as 170 kb and can increase the size of the pathogen genome by about 20% over a commensal strain.[8,9] Virulence factors may be broadly divided into two groups according to whether or not they are involved in bacterial adhesion to host epithelium.

Adhesive virulence factors

The presentation of cell surface adhesive organelles (adhesins) by UPEC is one of the most significant determinants of pathogenicity. UPEC may express several adhesins that allow it to attach to urinary tract tissues and contribute to virulence in different ways which

include: directly triggering host and bacterial cell signalling pathways; facilitating the delivery of other bacterial products to host tissues; and promoting bacterial invasion.[10] The best characterized group of adhesins are the fimbriae.

Type I fimbriae

Type I fimbriae are the most commonly expressed fimbriae on *E. coli* (Fig. 1.1.1) and are composed of a helical rod with repeating FimA subunits that are bound to a distal tip structure containing the FimH adhesin.[11] Classically these fimbriae (also called type I pili) were shown to mediate haemagglutination of guinea pig erythrocytes[12] and the reaction could be inhibited by the addition of mannose; mannose-sensitive haemagglutination (MSHA).[13,14]

However, while type I fimbriae have been shown to function as virulence factors in animal models of UTI where they facilitate bacterial colonization, their function in human infection is less clear.[10,15–17] This uncertainty arises from the observation that type I fimbriae are expressed in both pathogenic and commensal strains[18,19]; furthermore, there is no significant difference in the Fim gene frequency between more or less virulent strains in the urinary tract.[20] In the mouse model, type I fimbriae bind to the urothelial mannosylated glycoproteins uroplakin Ia (UPIa) and Ib (UP1b) via the adhesin subunit FimH, located at the fimbrial tip.[21] Uroplakins are membrane proteins that are found on the luminal surface of the umbrella cells of bladder epithelium. Interaction between FimH and uroplakins stimulates signalling pathways involved in bacterial invasion and epithelial cell apoptosis and may also contribute to mucosal inflammation.[17,22–24] In humans, the main evidence for the role of type I fimbriae comes from the analysis of urinary bacterial isolates from patients with UTI, which were found to express mannose-sensitive adhesins.[25]

Murine studies show that after binding to the urothelial surface, bacteria with FimH adhesins are quickly internalized within the epithelium as a result of localized actin rearrangement and engulfment of the bound bacterium by the epithelial cell membrane.[26] Within the superficial urothelium, UPEC is able to establish a new niche as a mechanism to avoid host innate immune response.

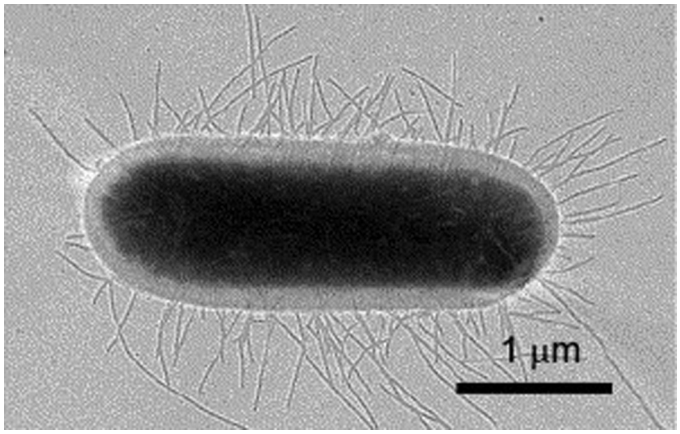

Fig. 1.1.1 Electron micrograph of a uropathogenic *E. coli* cell bearing type 1 fimbriae.

Within the epithelial cell, UPEC proliferates in the cytosol to form clusters known as intracellular bacterial communities (IBCs).[27] After six to eight hours, the morphology of the bacteria changes to an engulfing biofilm phenotype that further protects the uropathogen from the host immune response.[28] This process has yet to be demonstrated in human cells however.

The biofilm phenotype is characterized by decreased growth rate, allowing the formation of a biofilm matrix. This matrix is able to prevent attack from neutrophils and is also effective at preventing penetration by both host antimicrobials and external antibiotics. Animal models also suggest that bacteria at the edge of IBCs are able to detach and become motile again to re-enter the urine and then re-adhere to the superficial urothelium and reinvade cells to form further IBCs.[29] Ultimately, after a few days, possibly as a result of ongoing immune activity, the invasive bacteria enter a quiescent state, but may persist in a dormant state in IBCs before re-emerging later to cause recurrent infection.[27]

P-fimbriae

P-fimbriae (named from their interaction with P-blood group antigens) mediate haemagglutination of human erythrocytes that is not altered by mannose, which is thus termed mannose-resistant haemagglutination (MRHA). P-fimbriae are believed to play a key role in ascending UTI and pyelonephritis.[30,31] They are heteropolymeric fibres made up of various peptides encoded by the papA-K gene.[32] The adhesin PapG, at the tip of these fimbriae, recognizes kidney glycosphingolipids carrying the α-d-galactopyranosyl-(1–4)-β-d-galactopyranoside determinant on renal epithelia.[30,33,34] The attachment of P-fimbriae leads to the release of ceramide, which acts as an agonist of Toll-like receptor 4 (*TLR 4*), a receptor involved in activation of the innate immune response including antimicrobial peptide and cytokine production.[35] This then activates an inflammatory response cascade producing the symptoms of pyelonephritis.[16]

P-fimbriae may also work synergistically with type I fimbriae by enhancing early colonization of the tubular epithelium, while the latter mediates colonization of the tubular lumen by forming a biofilm. This colony then disrupts tubular filtration, leading to obstruction of nephron and the symptoms of pyelonephritis.[36] P-fimbriae have also been implicated as one of the key virulence factors involved in acute kidney dysfunction in renal transplant patients.[37]

Other adhesins

S-fimbriae and F1C fimbriae have also been shown to play a role in UTI. S-fimbriae bind to sialic acid residues via the SfaS adhesin; this facilitates bacterial dissemination within host tissues and is often associated with *E. coli* strains that cause sepsis, meningitis, and ascending UTIs.[10] F1C fimbriae bind to glycosphingolipids in renal epithelial cells and induce an interleukin-8 inflammatory response.[38] Fimbrial Dr and afimbrial Afa adhesins of *E. coli* are associated with recurrent UTI and UTI during pregnancy.[39–42] Murine models suggest that that Dr and Afa adhesins play a role in the development of chronic kidney infection.[43,44]

Non-adhesive virulence factors

UPEC, in common with other Gram-negative organisms, also has cell wall modifications, motility enhancements, and secreted toxins that further enhance pathogenicity.

Polysaccharides

The bacterial capsule and lipopolysaccharide (LPS) both act as virulence factors. The capsule is a polysaccharide covering for the bacteria that protect it from the host immune system's responses, particularly phagocytic engulfment and complement-mediated attack. Some capsular subtypes, such as K1 and K5 mimic components of host tissue, preventing effective immune response.[45]

LPS is a core component of the cell wall of Gram-negative bacteria, and in UPEC is an important activator of pro-inflammatory epithelial response via the induction of nitric oxide, as well as antimicrobial peptide and cytokine production.[46,47] However, the systemic immune response evoked by UPEC LPS may also have detrimental effects by causing acute kidney injury, particularly in renal transplant patients with UTI.[48,49]

Flagellum

Flagellum, the organelle made up of flagellin protein and responsible for bacterial motility plays a role in the virulence of many UPEC strains for both lower and upper urinary tract infection. Flagella activity may allow bacteria to ascend from the bladder and cause pyelonephritis. These UPEC strains may invade renal collecting duct cells through flagellin acting as an epithelial invasion through interaction with the *TLR 5* receptor.[50] Mice deficient in TLR5 are more susceptible to UPEC infection in both the bladder and the kidney, suggesting that flagellin may be involved in the original ascent into the bladder.[51]

Secreted factors

Secretion of toxins by UPEC and other Gram-negative bacteria is often responsible for inflammatory response and symptoms. The most significant toxin is a lipoprotein called α-haemolysin (HlyA) which is frequently associated with pyelonephritis and renal scarring.[52] α-haemolysin is a pore-forming toxin of the repeats in toxin (RTX) family that are common among Gram-negative pathogens.[53,54] At high concentrations it lyses erythrocytes and host cells, enabling bacteria to cross epithelial barriers, damage immune cells, and gain access to host iron stores.[45,55,56] At low concentrations, it can induce apoptosis of host immune cells and promote the exfoliation of bladder epithelial cells.[57,58] It can also affect intracellular calcium levels in renal epithelial cells, with consequent increases in IL-6 and IL-8 production.[59]

Cytotoxic necrotizing factor 1 (CNF1) is produced by around one-third of all pyelonephritis UPEC strains.[60] Experimental data suggest that CNF1 disrupts the epithelial cell membrane, allowing bacterial invasion.[61] In addition, it has been shown to interfere with polymorphonuclear phagocytosis and cause apoptosis of bladder epithelial cells, thus increasing bladder exfoliation and exposure of vulnerable underlying cells.[62,63]

Other secreted proteins include secreted autotransporter toxin (SAT) and Toll/interleukin (IL-1) receptor (TIR) domain-containing protein (Tcp). *In vitro*, SAT has toxic activity against bladder and kidney cells, suggesting a role in the early pathogenesis of UTI.[64] Recent work has found that Tcp is able to subvert epithelial Toll-like receptor (TLR) signalling, preventing early initiation of the innate immune response, thereby facilitating bacterial survival and kidney infection (Fig. 1.1.2).[65]

Host defences against uropathogenic *Escherichia coli* colonization of the urinary tract

The constant challenge of microbial invasion of the urinary tract epithelium from the host's own bowel has mobilized a variety of host defensive mechanisms to prevent bacterial colonization and survival. The first line of defence is aimed at preventing or limiting bacterial adherence to the epithelium. Once adhesion has occurred, further responses are activated.

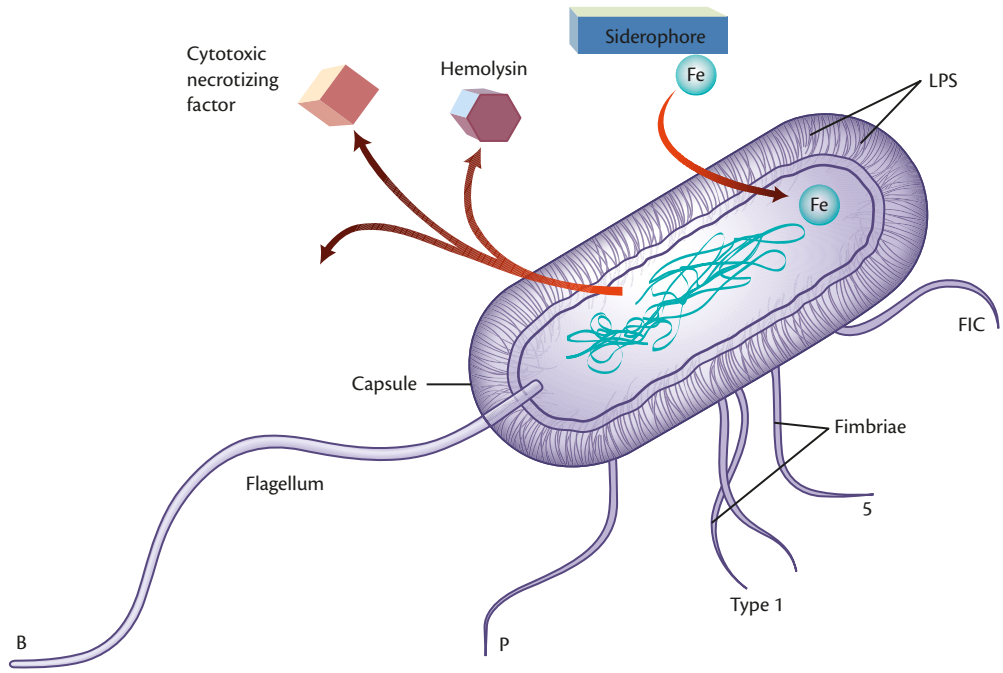

Fig 1.1.2 Diagram of a uropathogenic *E. coli* cell bearing type I fimbriae.

Constitutive defences

The normal urinary tract has a number of constitutive (continually present) physiological and immune defences to prevent or avert bacterial colonization. First is the 'washout' effect of urine flow. This rinses away loosely adherent or non-attached pathogens from the epithelial surface.[66] Adherence is further limited by the secretion of glucosamines by the urothelium, which form a protective layer on the luminal surface. The high urinary osmolality and low pH make it difficult for poorly adapted bacteria to survive.

Within the urine there are also a number of larger proteins, which have been identified as important in innate urinary immune defence. The most characterized is Tamm–Horsfall protein (THP), a glycoprotein secreted by the loop of Henlé epithelium present at high concentrations in the urine. THP acts as an anti-adhesive urinary factor by complexing with UPEC type I fimbriae, which is then cleared by voiding.[67] THP knockout mice have been shown to clear *E. coli* less rapidly and go on to develop chronic bladder wall inflammation suggestive of persistent infection.[68] Other renal epithelial proteins, such as lactoferrin and lipocalin also show antimicrobial activity through the sequestering of iron. Cathelicidin and defensins; small, highly cationic antimicrobial peptides, are also secreted by urothelium in response to pathogens.[47] These peptides work in a non-specific manner by attachment to the anionic phospholipids on the bacterial cell wall—disrupting their cell membrane, increasing cell permeability, and causing cell death.[69]

Activated responses

Bacteria that overcome these initial defences are able to have prolonged contact with the urothelium, resulting in the activation of further host immune defence mechanisms. These include epithelial exfoliation and the induction of a local and systemic inflammatory response.

Exfoliation of infected cells

One of the most notable observations of the host response during UTI is disruption of the epithelial barrier by the exfoliation of infected cells.[70,71] In the absence of infection, the urothelium is relatively quiescent, with the umbrella cell layer only renewed every few months. However, the normally repressed proliferation and differentiation processes are rapidly activated by the FimH component of fimbriae, resulting in an exfoliation mechanism that involves activation of caspases and cysteine proteases in a pathway similar to apoptosis.[72,73] Following activation of this pathway, there is potential for the umbrella cell layer to regenerate within 24 hours.

Experiments in which the exfoliation mechanism was dampened using a pan-caspase inhibitor showed greatly reduced bacterial expulsion from the bladder. This allowed intracellular bacteria to transfer from dying superficial cells to infect other cells.[74] In mouse studies, a mild exfoliation process in response to UPEC was more likely to result in biofilm formation that migrated into deeper layers.[27] Consequently, it is clear that rapid exfoliation is a key mechanism in the eradication of both attached and internalized bacteria from urothelium.

Inflammatory response

Successful bacterial adherence to urothelium triggers a variety of other innate immune responses. These are characterized by the production of a number of pro-inflammatory mediators, including cytokines and chemokines.[75–77] Bladder and kidney epithelial cells appear to be a major source of interleukin-6 (IL-6) and interleukin-8 (IL-8) after infection with UPEC, which are important in the development of local tissue damage.[78–79]

IL-6 possesses a variety of pro-inflammatory functions, including neutrophil recruitment and production of acute phase proteins.[80] IL-8 is also a potent neutrophil chemotactic agent. In humans, induction of IL-8 correlates with appearance of neutrophils in the urine.[75] Neutrophil recruitment to the site of infection has been shown to be critical for bacterial clearance from both the bladder and kidney, and their presence is a clinical diagnostic for UTI. Other immune competent cells, such as macrophages, eosinophils, and natural killer cells are also recruited and granulocytes synthesize nitric oxide, which can kill invading bacteria.[81]

Neutrophil migration to the site of infection is initiated by specific bacterial components, which activate pathogen-associated molecular pattern receptors (PAMPs) such as Toll-like receptors (TLRs).[82,83] This triggers a signalling pathway that initiates epithelial antimicrobial and wider inflammatory responses. The primary receptors expressed on urothelium are *TLR 2, 4*, and *5*. *TLR 2* is activated by peptidoglycan, part of the cell wall of bacteria. *TLR 4* and its co-receptors (CD14 and MD2) recognize bacterial LPS and *TLR 5* is activated by flagellin. Bacteria can evade these responses by expressing virulence factors such as Tcp to inhibit some *TLR*-activated pathways.[65,84] The importance of these early interactions between bacterium and epithelial cell has been further highlighted by the effect of gene polymorphisms. In mice, polymorphisms of the *TLR 4* gene are associated with reduced sensitivity to LPS, absence of neutrophil recruitment, and delayed clearance of bacteria from the urinary tract.[85] Recently, it was also observed that infected mouse urothelial cells were over time able to expel intracellular *E. coli* via a *TLR 4*-initiated and cyclic AMP-mediated mechanism.[86] In humans, a *TLR 4* polymorphism has been shown to increase susceptibility to septic shock and Gram-negative bacteraemia.[87] Other studies have suggested a role for reduced *TLR 4* expression in promoting a clinically beneficial tolerance state in asymptomatic bacteriuria, rather than a more harmful situation of severe disease.[88] In population studies of women with recurrent cystitis, a *TLR 5* stop-codon polymorphism is associated with increased UTI susceptibility.[89]

Antibody response

Due to the relatively short duration of most UTI and the constantly evolving expression profile of invading bacteria, adaptive immunity is not thought to play a significant role in host defence. However, in ascending infections of longer duration, the adaptive immune response is activated with the production of high-affinity antibodies by B and T lymphocytes. In pyelonephritis, there is serum and kidney immunoglobulin synthesis with antibodies targeting type I and P-fimbriae detectable in serum, and in IgG and SIgA antibodies in the urine.[90] Local synthesis of these antibodies enhances opsonization and reduces adherence of *E. coli*.[91] These findings have encouraged attempts to create vaccines against fimbrial components of UPEC to reduce colonization and ascending infections in susceptible female patients.[92]

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CHAPTER 1.2

Antimicrobial agents

Katherine E. Walton and Sally Ager

Introduction to antimicrobial agents

Urinary tract infections (UTIs) are common and they are experienced more frequently by women than men.[1] It is estimated that up to half of all women will have at least one UTI during their lifetime.[1] Healthcare-associated infections (HCAI) are recognized as important, potentially preventable causes of morbidity, mortality, and healthcare costs. In a recent prevalence survey, UTIs were the second commonest type of HCAI in English hospitals.[2] *Escherichia coli* is the commonest cause of UTI[3] and the urinary tract is the commonest source for *E. coli* bacteraemia (Fig. 1.2.1).[4]

Important risk factors for the development of UTI include sex, age, structural and functional abnormalities of the urinary tract, and catheterization or urinary tract instrumentation. Safe urological practice therefore relies on an understanding of the prevention and management of UTI, including judicious antimicrobial prescribing.

Antimicrobial agents are substances that kill or inhibit the growth of microorganisms, such as bacteria, fungi, or protozoa. Antibacterial agents affect bacteria. Strictly speaking, the term 'antibiotic' refers to antimicrobials produced by a microorganism, thus excluding synthetic antibacterials, although the terms 'antibiotic', 'antibacterial', and 'antimicrobial' are often used interchangeably.

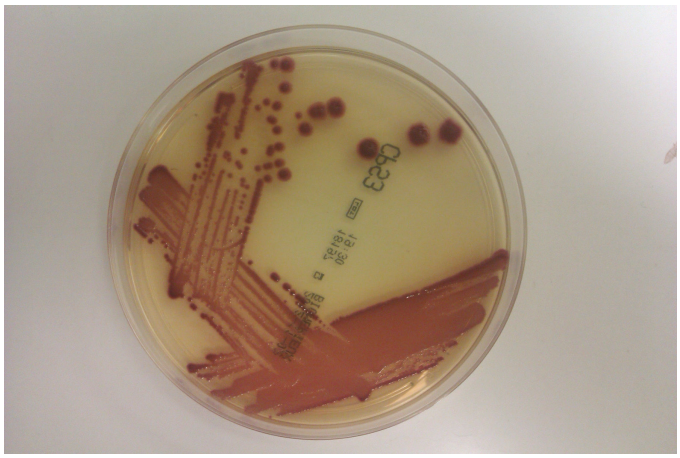

Fig. 1.2.1 *Escherichia coli (E. coli)* growing on chromogenic agar. *E. coli* is the commonest cause of urinary tract infections. Chromogenic media may be used in the laboratory to aid identification of potential uropathogens.
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Indications for antimicrobial prescribing

Antimicrobial agents are prescribed for the following reasons:

- Empirical therapy
- Directed therapy
- Prophylaxis

Empirical therapy

Antimicrobials are given based on the most likely causative organism(s) and local resistance patterns, before confirmation of the pathogen's identity. Empirical therapy is required for severe or life-threatening infection; it is important that appropriate, broad-spectrum antibiotics are started quickly, ideally within one hour of the presumptive diagnosis. Whenever possible, relevant diagnostic specimens should be collected prior to starting antimicrobial therapy (Fig. 1.2.2).

Directed therapy

Wherever possible, empirical therapy using broad-spectrum agents should be de-escalated to directed therapy using narrow spectrum antimicrobials once the identity and sensitivities of the pathogen are known. For less severe infections, particularly if the diagnosis is uncertain, it may be appropriate to await culture and sensitivity results before prescribing directed therapy, facilitating targeted treatment with narrow spectrum antimicrobials.

Prophylaxis

Prophylactic antimicrobials are given in circumstances where the risk or consequences of an infection are sufficiently severe to justify preventative action. It should be noted that the use of antibiotics is only part of a range of infection prevention measures.

Surgical prophylaxis

Antimicrobial prophylaxis is recommended for surgical procedures with a recognized risk of infection; generally, clean-contaminated or contaminated operations, and clean surgery involving implantation of prosthetic material.[5–7] Opening of the urinary tract is considered clean-contaminated surgery.[8] Local guidelines are based on the likely organisms associated with the procedure and local antimicrobial susceptibility patterns. Where possible, narrow spectrum agents should be chosen. Many guidelines advise avoidance of agents such as cephalosporins, quinolones, and clindamycin to minimize the risk of *Clostridium difficile* infection.[9]

In order to achieve maximum serum concentration during the procedure, intravenous antimicrobial prophylaxis should be

administered at induction of anaesthesia or within 30–60 minutes before the operation starts.[5–8] Single-dose prophylaxis is usually adequate. A second dose may be indicated for significant intraoperative blood loss (more than 1.5 L) or prolonged operations.[5,6,8] Oral agents with good bioavailability can be considered but this may be less reliable and logistically more difficult to administer at the appropriate time.[6,7]

There is good evidence supporting antibacterial prophylaxis for transurethral resection of prostate (TURP) and transrectal prostate biopsy but there have been few studies for other urologic interventions.[10] Nevertheless, antimicrobial prophylaxis is currently recommended for a number of invasive urological procedures (see Table 1.2.1).[6–8,11]

Post-exposure prophylaxis

Post-exposure prophylaxis may be advised for contacts of certain communicable diseases in order to prevent transmission of the infection, for example meningococcal meningitis, pertussis, and tuberculosis.[11]

Prophylaxis of special patient groups

Antibacterial prophylaxis may also be recommended for certain individuals with factors that put them at higher risk for specific infections. For example, asplenic patients may receive phenoxymethylpenicillin in order to prevent pneumococcal infection.[11]

Prophylactic antibacterials may sometimes be prescribed for specific individuals in an attempt to prevent recurrent UTIs, for example in children with vesicoureteric reflux. Prophylaxis should generally only be considered following a risk assessment if other approaches are not possible. Long-term low-dose therapy is administered, basing the choice of agent on previous urinary culture and sensitivity results. Nitrofurantoin or trimethoprim may be considered as options.[11] Long-term antibiotic exposure may result in adverse drug effects and the development of antimicrobial resistance.

Principles of antimicrobial prescribing

Antimicrobial stewardship

Careful consideration must be given before antimicrobial agents are prescribed. They may cause allergic or other adverse reactions, and harm an individual's normal protective microbial flora.[12] Broad-spectrum antibacterial use is associated with the acquisition of resistant organisms such as extended spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria[13,14] or methicillin-resistant *Staphylococcus aureus* (MRSA)[15–18] and the development of *Clostridium difficile* infection (CDI).[9,19–22] Adverse effects can be minimized by the introduction of antimicrobial stewardship programmes such as 'Start smart—then focus'.[23] Antibacterial drugs should not be prescribed unless there is an accepted prophylactic indication or clinical evidence of a bacterial infection requiring treatment. At the same time, patients with severe or life-threatening infections must receive prompt treatment with appropriate, often

Table 1.2.1 Prophylaxis for urological procedures

Procedure	Antibiotic prophylaxis recommended?			Likely pathogens
	EAU	AUA	SIGN	
Transurethral resection of prostate	Yes	Yes	Yes	Enterobacteriaceae and enterococci
Transrectal biopsy of prostate	Yes	Yes	Yes	Enterobacteriaceae and enterococci, possibly anaerobes
Transurethral resection of bladder tumour	No[1]	Yes	No	Enterobacteriaceae and enterococci
Percutaneous nephrolithotomy	Yes	Yes	Yes/No[2]	Enterobacteriaceae, enterococci, and staphylococci
Ureteroscopy for stone removal/fragmentation	Yes/No[3]	Yes	Yes	Enterobacteriaceae, enterococci, and staphylococci
Shock wave lithotripsy	Yes/No[4]	Yes	Yes	Enterobacteriaceae and enterococci
Cystoscopy/urodynamic investigation	No[5]	Yes/No[6]	No[5]	Enterobacteriaceae, enterococci, and staphylococci
Clean open or laparoscopic procedures (urinary tract not opened, e.g. nephrectomy)	No[5]	No[5]	No[7]	Skin organisms, catheter-associated organisms
Clean-contaminated procedures (urinary or gastrointestinal tracts opened, e.g. pyeloplasty, vaginal surgery, cystectomy)	Yes	Yes	Yes	Enterobacteriaceae, enterococci, and staphylococci
Implantation of prosthetic device	Yes	Yes	Yes	Enterobacteriaceae, enterococci, and skin organisms (e.g. staphylococci)
Contaminated open procedures (use of bowel segments)	Yes	Yes	Yes	Enterobacteriaceae, enterococci anaerobes, and skin organisms (e.g. staphylococci)

EAU = European Association of Urology; SIGN = Scottish Intercollegiate Guidelines Network; AUA = American Urological Association.

1: Consider in cases with high risk factors for UTI and for large necrotic tumours; 2: Recommended for stones 20 mm or greater or with pelvicalyceal dilation (one week preoperative fluoroquinolone recommended); 3: Recommended for proximal/impacted stone. Not recommended for uncomplicated distal stone (but consider in high-risk patients); 4: Not recommended for uncomplicated cases. Recommended in cases complicated by stent or nephrostomy catheter; 5: Consider in patients with high risk factors (bacteriuria, indwelling catheters, history of urogenital infection/abnormalities, immunosuppressed/post-transplant patients, diabetes mellitus, long inpatient stay, poor nutritional status, smoking, recent hospitalization, coexistent infection at other sites, older age, obesity); 6: Not if negative urine culture pre-procedure; 7: In children.

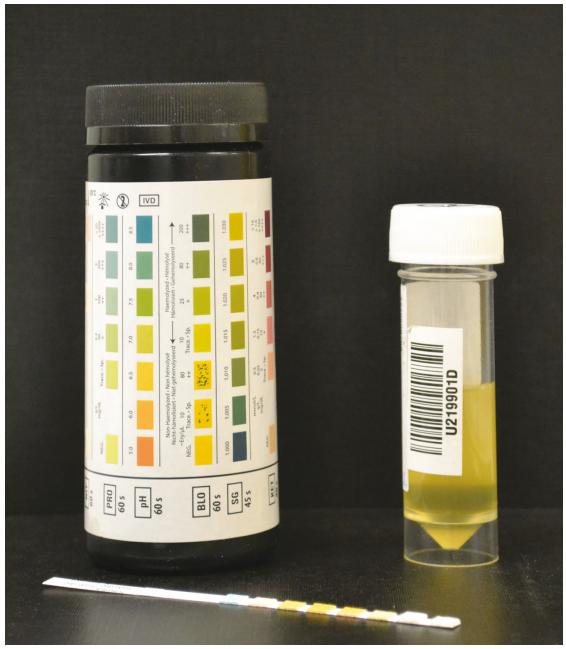

Fig. 1.2.2 Specimen of urine and urine test strip. Near-patient testing of urine samples, including analysis for the presence of leucocyte esterase, nitrites, protein, and blood, may be carried out using urine reagent strips (dipsticks) to give an early indication of the likelihood of urinary infection.
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broad-spectrum agents. If indicated, the choice of antimicrobial agent should normally be directed by local or national evidence-based guidelines and, whenever possible, diagnostic specimens should first be collected. Antimicrobial prescriptions should be accompanied by a clear record of the clinical indication, route of administration, duration, and review date. Oral administration is generally preferred, however, if intravenous antimicrobial treatment is required, it should be switched to oral medication as soon as this is safe. The duration of therapy depends on the type and nature of the infection and the clinical response to treatment. Local guidelines should specify standard durations for specific infections and courses should generally be kept to the minimum consistent with safety. Regular review of clinical progress and microbiology results facilitates the de-escalation of therapy, allowing patients who were initially commenced on broad-spectrum agents to be switched to targeted treatment with narrower spectrum antimicrobials. There should be regular review of local antimicrobial guidelines and audit of adherence to the key principles of judicious antimicrobial prescribing.

Antimicrobial choice

Local antimicrobial guidelines should be evidence-based and refer to available national guidelines.[23] Antibacterial choice will depend on the site and severity of the infection, the likely pathogens, and their local antimicrobial resistance patterns. Patient factors should also be considered, including age, clinical status, special factors such as pregnancy or immunosuppression, co-morbidities, allergies, medication which may result in potential drug interactions, previous microbiology results, and antimicrobial treatment history.

Important antimicrobial characteristics include the drug's spectrum of activity, routes of administration, potential side effects, and cost. Pharmacokinetics is the study of the effects of the body on a drug, including absorption, distribution, metabolism, and elimination, while pharmacodynamics is the study of the effect of the drug on the patient. Both factors help to determine optimal dosing regimens. Some antibacterial agents, such as the beta-lactams, are able to kill bacteria (bactericidal), while others only inhibit replication (bacteriostatic), for example sulphonamides. This may be a consideration when choosing therapy. The minimum inhibitory concentration (MIC) provides an assessment of an individual antibacterial agent's activity against a particular organism. Antimicrobials may show time-dependent or concentration-dependent killing. Dosing regimens that expose bacteria to drug concentrations above their MIC for as long as possible are preferred for time-dependent killing (e.g. penicillin therapy). To optimize concentration-dependent killing, peak serum concentrations should exceed the MIC of the target bacterium. This is important for aminoglycoside treatment.

Combination therapy

Treatment with a single antimicrobial agent is generally preferred, however, combination therapy is sometimes indicated. It may provide a broad spectrum of activity for mixed infections or be used for severe infections in immunocompromized patients, empirical treatment of life-threatening infections, or treatment of serious, deep-seated infections, such as prosthetic valve endocarditis. Combination therapy is also indicated for a few specific infections, such as tuberculosis, to prevent the development of resistant bacterial clones.[11]

Therapeutic drug monitoring

Measurement of serum concentration is advisable for some antimicrobials in order to minimize toxicity or determine whether effective concentrations have been achieved.[24] This is particularly important for drugs with a narrow therapeutic index, such as aminoglycosides, where the therapeutic band between effective and toxic concentrations is narrow. The correct timing of the sample is important: pre-dose (trough) concentrations are usually measured, although post-dose (peak) levels may sometime be helpful. Therapeutic drug monitoring is required for courses of parenteral gentamicin and vancomycin as well as other, less frequently used agents.[11,25] Local guidelines should be followed and the advice of a clinical microbiologist or other infection specialist sought in cases of uncertainty.

Prescribing for special patient groups

Patient factors are important when prescribing antimicrobial agents. Examples of special considerations for certain patient groups are given below:

Children

The pharmacokinetics and pharmacodynamics of drugs are often different in children. There may be a greater risk of adverse effects, particularly in the neonate, as a result of reduced drug clearance and different tissue sensitivities to toxins. Certain antimicrobial agents such as tetracyclines are contraindicated in children, while others should be used with caution (e.g. ciprofloxacin). When prescribing for children, the doses of antimicrobial agents must be carefully calculated.[26]

Pregnancy and breast feeding

A risk assessment should be carried out before drugs are prescribed during pregnancy as there may be the potential for teratogenicity or other harmful effects on the embryo or foetus. For example, tetracyclines, quinolones, and aminoglycosides should be avoided throughout pregnancy, trimethoprim should be avoided during the first trimester, and nitrofurantoin should be avoided at term.[11]

It is important to check whether individual antimicrobial agents may be safely prescribed to a breast-feeding mother. Some antimicrobial agents appear only as trace amounts in breast milk, while others reach higher concentrations and are therefore likely to be transmitted to the breast-feeding infant.[11]

The elderly

Serum and tissue concentrations may be increased in the elderly as a result of pharmacokinetic changes, such as reduced renal clearance. Older patients may have several co-morbidities and may also take multiple drugs, increasing the potential for adverse effects and drug interactions.

Hepatic impairment

Hepatic metabolism and elimination of drugs such as metronidazole may be impaired in patients with severe liver disease. In addition, drugs associated with dose-related or idiosyncratic hepatotoxicity may produce their adverse effects more frequently in patients with pre-existing hepatic impairment. For example, flucloxacillin and nitrofurantoin should be used with caution because of the risk of cholestatic jaundice. Monitoring of liver function tests is advised when some antibacterials (e.g. co-amoxiclav) are prescribed for patients with liver disease.

Renal impairment

Dose adjustment is required if reduced renal excretion may lead to drug or metabolite accumulation and toxicity (see Table 1.2.2). Aminoglycosides and glycopeptides should be avoided, or used with caution and careful therapeutic drug monitoring. Some antimicrobial agents, such as nitrofurantoin, will be ineffective for the treatment of UTIs if renal function is impaired because the drug will not achieve therapeutic concentrations in the urine. Expert advice should be sought about the appropriate dosing of antimicrobial agents in patients receiving renal replacement therapy.

The immunocompromized patient

Immunocompromized patients are at greater risk of severe and opportunistic infections. The type and severity of the immunodeficiency or immunosuppression determines the spectrum of likely infections; for example, neutropenic patients are particularly vulnerable to severe bacterial infections, including Gram-negative sepsis. Clinical signs and symptoms of infection may appear atypical as a result of the impaired host immune response. It is therefore important to remain vigilant for evidence of infection, obtain appropriate diagnostic samples, and institute empirical treatment as soon as a clinical diagnosis of severe bacterial infection is made (Fig. 1.2.3). Bactericidal agents are generally preferred for the treatment of severe infections in immunocompromized patients.

Antibiotic allergy

Before prescribing, it is important to ensure that there is no history of drug hypersensitivity. Attempts should be made to establish the nature of the allergic reaction and this should be clearly documented in the medical records. Penicillin allergy is relatively common, occurring in up to 10% of exposed individuals, however anaphylaxis is reported in less than 0.05%.[11] All penicillins should be avoided by patients allergic to one type of penicillin because of the risk of cross-hypersensitivity. Cephalosporins and other beta-lactams should also be avoided if there is a history suggesting an immediate hypersensitivity reaction to penicillins.[11]

Clostridium difficile infection (CDI)

Antibiotic exposure should be minimized, and avoided if possible, in patients with a past history of CDI. The Department of Health of England has advised that the use of some antibacterial drugs, such as cephalosporins, clindamycin, and ciprofloxacin, should be avoided in order to minimize the risk of CDI.[9] If antibacterial treatment must be given, then it is preferable to choose agents other than these and to keep the course as short as possible.

Colonization or infection with multiresistant bacteria

A history of previous colonization or infection with multiresistant organisms such as MRSA, glycopeptide-resistant enterococci (GRE), or multiresistant Gram-negative bacteria including ESBL-producers and carbapenemase-producing Enterobacteriaceae (CPE) should be considered if empirical therapy or prophylaxis is prescribed. It is useful to establish the patient's recent antimicrobial history because prolonged antibacterial therapy or exposure to multiple antibiotics, particularly in the inpatient setting, may predispose to colonization or infection with multidrug resistant bacteria. A travel history should be obtained to ascertain if the patient has travelled to countries or to areas of the UK known to have problems with the spread of CPE, and if they were treated in healthcare premises in these places. In England, hospital admissions must be risk assessed for MRSA and CPE carriage, and high-risk patients should be screened and isolated until screening results are available.[27,28]

Patients colonized with MRSA may be given topical decolonization therapy.[29] Local guidelines will indicate the circumstances under which this should be attempted, and the recommended topical agents. Preoperative screening ensures that appropriate antibacterial prophylaxis may be chosen for MRSA-positive patients and provides the opportunity to administer perioperative decolonization therapy.

Extremes of body weight

The 2015 health survey for England found that 27% of adults were obese, and the prevalence of morbid obesity was 2% in men and 4% in women.[30] Although treatment of patients at extremes of body weight is an increasing occurrence, there is limited data available to guide dosing. The site of infection is important. While the ideal body weight may help guide dosing in some circumstances, calculated doses may be inadequate for optimal treatment of certain severe infections in morbid obesity, particularly those that involve adipose tissue, such as necrotising fasciitis.[31]

Antibacterial agents

Mechanisms of action

Most antibacterial agents affect one of four targets:

- Cell wall synthesis
- Protein synthesis
- Nucleic acid synthesis
- Cell membrane integrity

Table 1.2.2 Antibacterial agents commonly used in urological practice[7,8,11,34]

Antibacterial agent	Usual dosing regimen	Common indications	Notes
Nitrofurantoin	◆ Treatment: 50–100 mg QDS PO or 100 mg BD for the modified-release formulation ◆ Prophylaxis: 50–100 mg PO nocte	Treatment and prophylaxis of lower urinary tract infection	◆ Avoid if creatinine clearance <45 mL/min/1.73 m^2* ◆ Avoid at term in pregnancy (risk of neonatal haemolysis)
Trimethoprim	◆ Treatment: 200 mg BD PO ◆ Prophylaxis: 100 mg nocte PO ◆ Reduce dose in severe renal impairment	Treatment and prophylaxis of lower urinary tract infection	Avoid during the first trimester of pregnancy
Co-trimoxazole	◆ Treatment: 960 mg BD PO ◆ Reduce dose in severe renal impairment	Consider as second-line directed therapy for lower urinary tract infection if pathogen sensitive and there is justification for use in place of trimethoprim	◆ Avoid in first and third trimesters of pregnancy ◆ Coadministration of warfarin and co-trimoxazole may result in a rise in INR
Amoxicillin	◆ 250–500 mg TDS PO or 500 mg–1 g tds IV ◆ Reduce dose in severe renal impairment	Treatment of uncomplicated urinary tract infection where uropathogen is known to be sensitive	
Ampicillin	◆ 250–500 mg QDS PO or 500 mg QDS IV ◆ Reduce dose in severe renal impairment	Treatment of uncomplicated urinary tract infection where uropathogen is known to be sensitive	
Flucloxacillin	◆ 500 mg QDS PO or 500 mg–2 g QDS IV ◆ Reduce dose in severe renal impairment (eGFR <10 mL/min/1.73 m^2)	Treatment of skin and soft tissue infections such as surgical wound infections	
Co-amoxiclav	◆ 375 mg or 625 mg PO 6–8 hourly or 1.2 g 8-hourly IV ◆ In renal impairment (eGFR <30 mL/min/1.73 m^2), give initial dose, then reduce dose	◆ Second-line agent for treatment of simple cystitis caused by bacteria resistant to first-line agents ◆ Consider as treatment for complicated UTIs including pyelonephritis, depending on local antimicrobial sensitivity patterns ◆ Perioperative prophylaxis	
(Piv)mecillinam	◆ 400 mg po initial loading dose then 200–400 mg TDS PO ◆ Reduce dose in renal impairment if prolonged treatment planned	Second-line agent for treatment of lower urinary tract infection caused by uropathogens resistant to first-line agents	Useful option for oral treatment of infections caused by beta-lactamase-producing organisms
Piperacillin-tazobactam	◆ 4.5 g TDS IV ◆ Increase interval between doses to 12-hourly in severe renal impairment (eGFR <20 mL/min/1.73 m^2)	Treatment of complicated UTIs such as pyelonephritis and urosepsis	
Cefalexin	◆ 250 mg qds or 500 mg TDS PO ◆ Reduce dose in renal impairment	Treatment of uncomplicated lower UTIs	Useful option in pregnancy
Cefuroxime	◆ 750 mg–1.5 g TDS IV ◆ Reduce dose in renal impairment (eGFR of less than 20 mL/min/1.73 m^2)	◆ Treatment of complicated UTIs, and urosepsis including pyelonephritis ◆ May be used as prophylaxis for urological procedures	◆ Useful option in pregnancy ◆ May be associated with *Clostridium difficile* infection
Ceftazidime	◆ Treatment: 1–2 g BD or TDS IV ◆ Reduce dose in renal impairment (eGFR less than 50 mL/min/1.73 m^2) ◆ Prophylaxis: 1 g IV	Treatment of serious, complicated urinary infections caused by pathogens resistant to first-line agents	May be associated with *Clostridium difficile* infection

(continued)

Table 1.2.2 Continued

Antibacterial agent	Usual dosing regimen	Common indications	Notes
Ertapenem	◆ 1 g OD IV ◆ Reduce dose in renal impairment	Licensed for abdominal infection, acute gynaecological infections, community-acquired pneumonia, and diabetic foot infections of skin and soft tissue	◆ Not active against *Pseudomonas aeruginosa* ◆ Off-license uses include treatment of severe sepsis, including complicated UTIs, polymicrobial infections, and infections caused by multi-resistant organisms, including ESBL producers
Meropenem	◆ 500 mg–1 g TDS IV ◆ Reduce dose in renal impairment	Treatment of severe sepsis, including complicated UTIs, polymicrobial infections, and infections caused by multiresistant organisms, including ESBL producers	Has antipseudomonal activity
Aztreonam	◆ 1 g TDS IV ◆ Reduce dose in renal impairment (eGFR less than 30 mL/min/1.73 m^2)	Treatment of serious Gram-negative infections, including urosepsis, caused by sensitive pathogens	
Gentamicin	◆ Treatment: 4–7 mg/kg IV OD ◆ Monitor serum levels and adjust dose ◆ To avoid excess dosing in obese patients, use ideal weight for height to calculate dose ◆ For once-daily dosing, a trough level (24-hours post-dose) of <1 mg/L gentamicin is satisfactory ◆ Alternatively, measure serum levels collected between 6 and 14 hours post-dose and use a nomogram to guide subsequent doses ◆ Prophylaxis: 1.5 mg/kg IV	◆ Treatment of complicated UTIs including pyelonephritis and urosepsis ◆ Prophylaxis for urological surgery	◆ Has antipseudomonal activity ◆ Use with caution in patients with renal impairment (reduce dose) ◆ Avoid in pregnancy ◆ Avoid once-daily regimens in patients with burns of >20%, endocarditis, or creatinine clearance of <20 mL/min
Vancomycin	◆ 1–1.5 g bd by slow IV infusion ◆ Monitor serum levels and adjust dose ◆ Maintain pre-dose (trough) levels between 10 and 15 mg/L—higher trough levels of 15–20 mg/L may be required for some specific indications ◆ Reduce dose in renal impairment	◆ Treatment of serious infections caused by resistant Gram-positive bacteria such as MRSA and *Enterococcus faecium* ◆ Second-line Gram-positive treatment for patients with penicillin allergy	
Oral vancomycin	◆ 125 mg PO QDS ◆ Dose may be increased up to 500 mg QDS PO for severe infections	Treatment of severe or recurrent *Clostridium difficile* infection	
Teicoplanin	◆ Weight ≤70 kg: loading dose of 400 mg IV BD for three doses, followed by 400 mg OD IV ◆ Weight >70 kg: loading dose of 6 mg/kg IV BD for three doses, followed by 6 mg/kg OD IV ◆ Reduce dose in renal impairment	◆ Treatment of serious infections caused by resistant Gram-positive bacteria such as MRSA and *Enterococcus faecium*. ◆ Second-line Gram-positive treatment for patients with penicillin allergy	Common indications: Treatment of Clostridium difficile infection
Fidaxomicin	200 mg PO BD for 10 days	Treatment of *Clostridium difficile* infection	Limited clinical data available for use in severe or life-threatening infection therefore caution advised
Ciprofloxacin	◆ 250–750 mg BD PO or 400 mg BD IV ◆ Reduce dose in renal impairment	◆ Second-line treatment of UTIs caused by uropathogens resistant to first-line agents ◆ Treatment of pyelonephritis, prostatitis, and epididymo-orchitis	◆ Has antipseudomonal activity although resistance may develop ◆ Avoid in children and pregnancy ◆ May be associated with *Clostridium difficile* infection

(continued)

Table 1.2.2 Continued

Antibacterial agent	Usual dosing regimen	Common indications	Notes
Colistin	◆ 1–2 million units IV TDS for patients over 60 kg ◆ Reduce dose and monitor levels in renal impairment	Reserve for the treatment of serious Gram-negative infections resistant to other antimicrobial agents	Avoid in pregnancy, especially during second and third trimesters
Linezolid	600 mg BD PO or IV	In UK, licensed for complicated skin and soft tissue infections and pneumonia—usually reserved for treatment of serious infections caused by resistant Gram-positive pathogens such as MRSA or for treatment of patients allergic to first-line agents	◆ A reversible non-selective monoamine oxidase inhibitor (MAOI) ◆ Use not advised while taking, or within two weeks of stopping, another MAOI ◆ Treatment usually limited to 10 days or less to minimize risk of adverse effects
Metronidazole	◆ Treatment: 400–500 mg TDS PO or 500 mg TDS IV ◆ Prophylaxis: 500 mg IV perioperatively ◆ Alternatively, prophylaxis may be given two hours prior to the procedure via the oral route (400 mg PO) or by the rectal administration of a 1 g suppository	◆ Treatment or prophylaxis of anaerobic infections ◆ Treatment of *Clostridium difficile* infection of mild or moderate severity (oral treatment is preferable to IV)	Disulfiram-like reaction if taken with alcohol

BD = 12 hourly; IV = intravenous; eGFR = estimated glomerular filtration rate; TDS = 8 hourly; PO = orally; INR = international normalized ratio; QDS = 6 hourly; nocte = at night; UTI = urinary tract infection.
*Nitrofurantoin may be used with caution in adults with eGFR 30–44 mL/min/1.73 m^2 for a short course only (3–7 days) to treat uncomplicated UTI caused by suspected/proven multiresistant bacteria and only if potential benefit outweighs risk.

Cell wall active agents

These include the beta-lactam agents (penicillins, cephalosporins, carbapenems, and monobactams) and glycopeptides. They competitively inhibit the carboxypeptidase and transpeptidase enzymes (also known as penicillin binding proteins, PBPs) that cross-link the bacterial cell wall polymer, peptidoglycan. This results in cell wall disruption, bacterial lysis, and death.

Inhibitors of protein synthesis

Mammalian and bacterial ribosomes differ in structure and the use of antibacterial agents affecting bacterial protein synthesis exploits

Fig. 1.2.3 Automated blood culture system (BioMerieux BacT/ALERT 3D). Appropriate diagnostic samples, including blood cultures, should be collected from patients presenting with serious urinary infections and urosepsis. Whenever possible, these should be taken before antimicrobial therapy is commenced.
With kind permission of Jesmond IT.

these differences. Aminoglycosides work by blocking the formation of the bacterial initiation complex. Other protein synthesis inhibitors include erythromycin, chloramphenicol, and tetracycline.

Inhibitors of nucleic acid synthesis

Sulphonamides and trimethoprim inhibit DNA synthesis by preventing the formation of purine and thymidine, acting at two different stages in the synthesis of folic acid. Sulphonamides are competitive agonists of para-aminobenzoic acid and trimethoprim inhibits the enzyme dihydrofolate reductase. Fluoroquinolones such as ciprofloxacin inhibit bacterial topoisomerases (DNA gyrases) that are involved in the supercoiling of DNA during nucleic acid synthesis. Metronidazole causes DNA breakage in anaerobic microorganisms.

Cell membrane disruption

Colistin is a polymyxin, which has detergent-like properties. It disrupts bacterial cell membranes, causing cell lysis and death.

Mechanisms of resistance

Bacteria may be intrinsically resistant to certain antimicrobial agents; for example, enterococcal resistance to cephalosporins, or resistance may develop via new mutations or by acquisition of genes from other bacteria. This allows rapid spread of resistance, which is promoted by antimicrobial selection pressure. Individual drugs may be susceptible to inactivation by several resistance mechanisms and some bacteria possess more than one mechanism of resistance.

There are five main mechanisms of antimicrobial resistance:

1. Inactivation or destruction;
2. Inhibition of transport into the cell;
3. Alteration of target site;
4. Bypass of affected metabolic pathway;
5. Active efflux.

Inactivation or destruction of the antimicrobial agent

Beta-lactamases are bacterial enzymes that can inactivate beta-lactam antibiotics by hydrolysis of the beta-lactam ring. There is a wide range of beta-lactamases; their classification is complex, based on spectrum of activity and inhibition or molecular structure. Extended spectrum beta-lactamase (ESBL) enzymes may be produced by some strains of *E. coli* and other coliform organisms, making them resistant to penicillins, aztreonam, and cephalosporins.

Inhibition of transport into the cell

Altered bacterial outer membrane proteins in some strains of *Pseudomonas aeruginosa* affect transport of imipenem into the cell, leading to resistance.

Alteration of antimicrobial target site

MRSA contains a penicillin binding protein (PBP) with a lower affinity for flucloxacillin than the PBP of methicillin-sensitive strains of *S. aureus*. Target site alteration is also a common cause of ciprofloxacin resistance and resistance to antimicrobial agents that act on the bacterial ribosome, such as erythromycin.

Bypass of affected metabolic pathway

Auxotrophs are strains of bacteria with different nutritional requirements from the original or 'wild strain'. These sometimes allow the organism to bypass the adverse effect of an antimicrobial agent. Thymidine-dependent bacteria have lost the enzyme thymidilate synthetase, and therefore require exogenous sources of thymidine for DNA synthesis. Use of pre-formed thymidine bypasses the earlier stages of folic acid production inhibited by trimethoprim and sulphonamides, causing resistance.

Active efflux of antimicrobial agent

Certain bacteria can actively pump antimicrobials, such as beta-lactams and quinolones, out of the cell causing resistance.

Antimicrobial susceptibility testing

Directed therapy requires culture, identification of potential pathogens, and antibacterial susceptibility testing to help to assess the likelihood of the infection responding to treatment with different antimicrobial agents. Disc diffusion testing by internationally standardized methods (e.g. EUCAST[32]) is widely used in diagnostic laboratories, categorizing isolates as sensitive, intermediately sensitive, or resistant to the agents tested (Fig. 1.2.4). The Minimum Inhibitory Concentration (MIC) of an isolate may be determined by the commercial Epsilometer test (Etest), by using automated methods that determine the MICs to a panel of agents (e.g. Vitek®) or occasionally by conventional broth dilution testing. Isolates may also be tested for resistance determinants such as ESBL production.[33]

Common antimicrobial agents used in urological practice

A summary of usual indications and adult doses of antimicrobial agents used in urology and their common or serious adverse effects are shown in Tables 1.2.2 and 1.2.3, respectively.[7,8,11,34]

Nitrofurantoin

Nitrofurantoin affects several different bacterial enzymes, inhibiting ribosomal protein synthesis. It is bactericidal and usually active against a range of Enterobacteriaceae (coliform organisms) such as *E. coli, Klebsiella,* and *Enterobacter* and Gram-positive cocci such as enterococci, including GRE, and staphylococci including MRSA. Some species, such as *Proteus spp.* and *P. aeruginosa*, are intrinsically resistant.

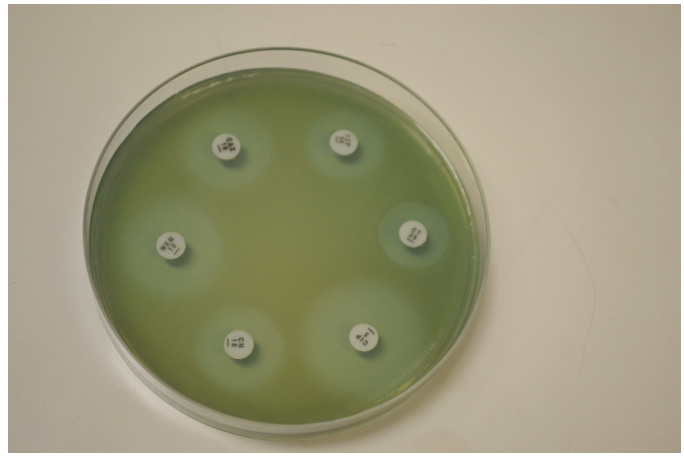

Fig. 1.2.4 Disc diffusion sensitivity tests carried out on an isolate of *Pseudomonas aeruginosa.*
With kind permission of Jesmond IT.

Table 1.2.3 Common and serious adverse events associated with antibacterial agents

Antibacterial agent	Common/serious side effects
Nitrofurantoin	◆ Dose-related GI disturbances (anorexia, nausea, vomiting) ◆ Parotitis ◆ Hypersensitivity reactions (rashes, eosinophilia, fever, anaphylaxis) ◆ Neurological toxicity: headache, confusion, peripheral neuropathy ◆ Pulmonary reactions include pneumonitis, BOOP, and interstitial fibrosis ◆ Hepatotixicity (rare) ◆ Risk of neonatal haemolysis if given to pregnant women at term
Trimethoprim/Co-trimoxazole	◆ GI disturbances: nausea, vomiting, diarrhoea ◆ Hypersensitivity: rash particularly associated with sulphonamide component, including rarely SJS, TEN ◆ Bone marrow depression (inhibition of folic acid pathway), rarely neutropenia/agranulocytosis (sulphonamide-related) ◆ Aseptic meningitis/encephalitis ◆ Hepatotoxicity (rare) ◆ Warfarin interaction; increase in INR ◆ Teratogenic risk in first trimester of pregnancy (trimethoprim) ◆ Neonatal haemolysis and methaemoglobinaemia in third trimester of pregnancy (sulphonamide)
Amoxicillin,* Ampicillin,* Flucloxacillin*, Pivmecillinam*	◆ GI disturbances: nausea, vomiting, diarrhoea ◆ Hypersensitivity reactions (1–10% of exposed patients), ranging from rash to anaphylaxis (less than 0.05%) ◆ Rarely—interstitial nephritis, haemolytic anaemia, neutropenia and, in high doses, encephalopathy with seizures or hepatitis ◆ Cholestatic jaundice or hepatitis may occur up to two months after completion of flucloxacillin treatment ◆ Antibiotic-associated diarrhoea may occur ◆ Pivmecillinam associated with oesophageal stricture formation; advise patients to swallow tablets with plenty of fluid during a meal while sitting or standing
Co-amoxiclav* (amoxicillin/clavulanate)	◆ GI disturbances (nausea, vomiting, diarrhoea) commoner than with amoxicillin alone ◆ Hypersensitivity reactions, ranging from rash to anaphylaxis ◆ Hepatotoxicity (six times more common than with amoxicillin), especially cholestatic jaundice (usually reversible) ◆ CDI ◆ Blood dyscrasias ◆ CNS toxicity (rare, high doses may cause encephalopathy and seizures)
Piperacillin/tazobactam*	◆ GI disturbances, especially diarrhoea ◆ Hypersensitivity: rashes, eosinophilia, fever, pruritis ◆ Abnormal LFTs, jaundice ◆ Blood dyscrasias (neutropenia, haemolytic anaemia, pancytopenia) ◆ CDI (it may be less associated with CDI than many other broad-spectrum antibiotics) ◆ CNS toxicity (rarely, high doses may cause encephalopathy and seizures) ◆ Hepatitis
Cephalosporins*	◆ GI disturbances: nausea, vomiting, diarrhoea ◆ Headache ◆ Hypersensitivity, including rash, anaphylaxis ◆ CDI ◆ Nephrotoxicity rare; may potentiate nephrotoxicity of gentamicin
Carbapenems*	◆ GI upsets: nausea, vomiting, diarrhoea ◆ Hypersensitivity, rashes, eosinophilia, anaphylaxis; there is a low incidence of cross-allergic reactions with penicillins* ◆ Headache ◆ Abnormal LFTs, hepatitis, jaundice ◆ CDI may occur ◆ Ertapenem and imipenem are associated with seizure, rare with meropenem

Table 1.2.3 Continued

Antibacterial agent	Common/serious side effects
Aztreonam*	◆ GI disturbances ◆ Rarely—GI bleeding, thrombocytopenia, neutropenia ◆ Jaundice, hepatitis ◆ Seizures ◆ Flushing, bronchospasm, rash including TEN and erythema multiforme; there is a low incidence of cross-allergic reactions with penicillins*
Aminoglycosides	◆ Ototoxicity, usually only with prolonged high levels; vestibular > cochlear toxicity ◆ Nephrotoxicity (ATN), dose related; less likely with once-daily dosing than multiple daily doses ◆ Neuromuscular blockade ◆ Skin rashes and hypersensitivity reactions are rare
Vancomycin and Teicoplanin	◆ Phlebitis ◆ Hypersensitivity, rashes ◆ Nephrotoxicity at high doses with vancomycin ◆ Ototoxicity is rare; high-frequency hearing loss may occur ◆ Rapid infusion of vancomycin may cause 'red man syndrome' related to histamine release: hypotension, dypnoea, wheeze, pruritis, urticaria, and flushing of the upper body ◆ Both vancomycin and teicoplanin may be associated with leucopenia and thrombocytopenia
Ciprofloxacin	◆ GI disturbances (abdominal pain, nausea, vomiting, diarrhoea) ◆ CNS effects, including headaches, dizziness, seizures (avoid in known epilepsy) ◆ Hypersensitivity reactions; rashes, pruritis, anaphylaxis, photosensitivity ◆ Arthropathy and tendonitis ◆ Renal Impairment, interstitial nephritis ◆ CDI ◆ Haematological side effects (reversible) ◆ Prolonged QT interval
Colistin	◆ Nephrotoxicity ◆ Rash ◆ Parenteral therapy may cause neurotoxicity including apnoea, paraesthesiae (perioral and peripheral), headache, vertigo, muscle weakness ◆ Rarer neurotoxic manifestations include confusion, psychosis, visual disturbances, slurred speech, and vasomotor instability
Linezolid	◆ GI side effects, taste disturbance ◆ Headache ◆ Pancreatitis, hypertension, dizziness ◆ Leucopenia, thrombocytopenia, eosinophilia, pancytopenia ◆ Electrolyte disturbances ◆ Blurred vision, rash, paraesthesia ◆ Rarely—lactic acidosis, pancytopenia, anaemia ◆ Severe optic neuropathy reported rarely on prolonged therapy
Metronidazole	◆ GI disturbances, taste disturbance, anorexia ◆ Very rarely hepatitis, jaundice, pancreatitis, pancytopenia, thrombocytopenia, erythema multiforme ◆ Peripheral neuropathy, seizures, leucopenia reported during prolonged therapy ◆ Patients advised not to drink alcohol because of risk of disulfiram-like reaction

ATN = acute tubular necrosis; BOOP = bronchiolitis obliterans organizing pneumonia; CDI = *Clostridium difficile* infection; CNS = central nervous system; GI = gastrointestinal; INR = international normalized ratio; LFTs = liver function tests; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis.

*In patients who have a hypersensitivity or anaphylactoid reaction to penicillin, there is cross-reactivity with all classes of penicillins (aminopenicillins, piperacillin-tazobactam, pivmecillinam) and a low incidence of cross-allergenicity with other beta-lactam antibiotics (cephalosporins, carbapenems, monobactams).

Source: data from the Joint Formulary Committee. *British National Formulary*. 72 ed. London: BMJ Group and Pharmaceutical Press; 2016: 459–546.

Nitrofurantoin is well absorbed after oral administration, but serum levels remain low and therapeutic levels are achieved only in the urine. Consequently, nitrofurantoin is suitable for treatment of simple, uncomplicated lower UTIs. It will not reach therapeutic urinary concentrations and should therefore usually be avoided when the eGFR is less than 45 mL/min/1.73 m^2 (see Table 1.2.2).[11] As development of resistance is relatively rare, and nitrofurantoin is unlikely to affect bowel or vaginal flora, it may be considered as long-term prophylaxis for selected patients suffering from frequent recurrence of UTI caused by susceptible isolates.[7,11] Nitrofurantoin can be given in pregnancy, but should be avoided at term because it may cause neonatal haemolysis.[11]

Trimethoprim and co-trimoxazole

Trimethoprim prevents bacterial DNA replication by inhibiting the enzyme dihydrofolate reductase, which is involved in bacterial folic acid synthesis. Trimethoprim demonstrates synergistic antibacterial activity with sulphonamides, which act earlier in the same metabolic pathway. Co-trimoxazole is a combination drug comprising trimethoprim and the sulphonamide, sulfamethoxazole.

These drugs are active against coliform organisms such as *E. coli* and staphylococci including *Staphylococcus saprophyticus*. Enterococcal UTIs are felt unlikely to be responsive to either agent as they can bypass the inhibition of folate synthesis by utilizing preformed folic acid found in urine.[35] Trimethoprim is only available as an oral formulation, while co-trimoxazole is available as oral and intravenous preparations. Both drugs have high oral bioavailability and reach therapeutic concentrations in the urine.

Trimethoprim is used mainly for the treatment of acute uncomplicated bacterial cystitis but it should not be used empirically in areas with high resistance rates in *E coli*.[36] Trimethoprim penetrates prostatic tissue and a 28-day course may therefore be used for the treatment of acute prostatitis. Long-term, low-dose prophylactic trimethoprim may be considered in selected patients with frequent, recurrent UTIs.[7,11] In the United Kingdom, co-trimoxazole is generally restricted for the treatment of *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) pneumonia, toxoplasmosis, and nocardia infections because of the risk of serious adverse events including Stevens–Johnson syndrome and blood dyscrasias.[11] As a folate antagonist, trimethoprim poses a risk of teratogenicity and should be avoided during the first trimester of pregnancy.[11]

Amoxicillin and ampicillin

Penicillins are bactericidal drugs that inhibit the formation of cross-links in the peptidoglycan layer of bacterial cell walls, resulting in bacterial lysis. Ampicillin and amoxicillin are semi-synthetic penicillins known as aminopenicillins. They have good activity against streptococci, many enterococci, and some Gram-negative bacilli, including some strains of *E. coli* and *Proteus mirabilis*. However, aminopenicillins are destroyed by bacterial beta-lactamases and are therefore inactive against most staphylococci and many coliform organisms. Amoxicillin and ampicillin are both available as oral, intravenous, and intramuscular preparations. Both drugs are excreted in urine.

Amoxicillin and ampicillin may be used to treat UTIs caused by sensitive uropathogens; however, resistance to these agents is widespread. In one international study, more than half the strains of *E. coli* isolated from patients with uncomplicated UTI were reported to be amoxicillin resistant.[37] For this reason, these agents should not be used empirically.

Penicillin hypersensitivity reactions occur in 1–10% of exposed patients, ranging from rash to anaphylaxis, which occurs in less than 0.05% of treated patients. There is cross-hypersensitivity between aminopenicillins and other penicillins, and a lower cross-hypersensitivity rate with cephalosporins and carbapenems. As a general rule, these agents should all be avoided in patients with a history of anaphylaxis, urticaria, or rash that develops immediately following penicillin treatment.[11]

Flucloxacillin

Flucloxacillin is a semi-synthetic penicillin, which is stable to staphylococcal beta-lactamase. It is active against streptococci and methicillin-sensitive staphylococci including *S. aureus*, but its spectrum of activity does not extend to MRSA, enterococci, or Gram-negative bacteria. Oral and intravenous formulations are available.

Flucloxacillin is used for the treatment of staphylococcal infections including skin and soft tissue infections such as surgical site infections.

Co-amoxiclav

Co-amoxiclav is a combination of amoxicillin and clavulanic acid (a beta-lactamase inhibitor) that protects amoxicillin from enzymatic degradation by many bacterial beta-lactamases, broadening its spectrum of activity. Co-amoxiclav is active against *S. aureus* and many amoxicillin-resistant coliform organisms, although MRSA and *P. aeruginosa* remain resistant. Oral and intravenous formulations are available.

Therapeutic concentrations of both drugs can be achieved in urine. Co-amoxiclav may be used as second-line treatment for simple cystitis caused by uropathogens resistant to narrow spectrum antimicrobial agents. It is also suitable for the treatment of complicated UTIs and some centres use it as perioperative prophylaxis for invasive urological procedures such as cystourethroscopy or ureteroscopy.[7,8]

(Piv)mecillinam

Pivmecillinam is the oral pro-drug of mecillinam, a penicillin that is relatively stable to bacterial beta-lactamases, including ESBLs. Mecillinam is active against a range of coliform organisms, including some multiresistant strains of *E. coli, Klebsiella, Enterobacter,* and *Proteus. Pseudomonas* species are not susceptible; *Morganella* and *Serratia* species are often resistant, and mecillinam has little activity against Gram-positive organisms such as enterococci.

Pivmecillinam is used to treat lower UTIs and may be particularly useful in the outpatient setting for infections caused by beta-lactamase-producing organisms.

Piperacillin-tazobactam

This is a combination of piperacillin, an antipseudomonal penicillin, and tazobactam, a beta-lactamase inhibitor. Piperacillin-tazobactam is an intravenous antibiotic with a broad spectrum of activity against most Gram-negative uropathogens, including *Pseudomonas* species, and many Gram-positive and anaerobic bacteria. MRSA is resistant to piperacillin-tazobactam and some bacteria produce beta-lactamases that are stable to tazobactam, resulting in piperacillin-tazobactam resistance. Piperacillin-tazobactam is used for the treatment of complicated UTIs and urosepsis.

Oral cephalosporins

Cephalosporins are beta-lactam antibiotics, classified into different generations according to their spectrum of activity. The oral cephalosporins include cefalexin and cefradine, which are relatively narrow spectrum first generation cephalosporins, and cefaclor, which is a second generation product. First and second generation cephalosporins are active against *S. aureus* and susceptible strains of coliform organisms such as *E. coli* and *Klebsiella pneumoniae*, but MRSA and *Pseudomonas* species are resistant, as are many *Proteus* and *Enterobacter* species. Enterococci are intrinsically resistant.

Oral cephalosporins are used for the treatment of uncomplicated lower UTIs. Cephalosporins are safe to use in pregnancy and in children. There is a low incidence of cross-hypersensitivity with penicillins (0.5–6.5%);[11] however, cephalosporin use should still be avoided in patients with a history of anaphylaxis, urticaria, or immediate development of rash associated with penicillin treatment.

Cefuroxime

Cefuroxime is a second generation cephalosporin. It has the same basic structure and mechanism of action as the first generation cephalosporins but a broader spectrum of Gram-negative activity. Although it is stable to some beta-lactamases, cefuroxime is inactivated by ESBLs. It has no activity against enterococci, *P. aeruginosa*, or many opportunistic pathogens such as *Acinetobacter* species. Cefuroxime is available in parenteral and oral formulations, although the latter is not well absorbed.

Its uses include treatment of urosepsis and complicated UTIs including pyelonephritis, and is safe to use in children and pregnancy.[11] It may be used as prophylaxis for invasive urological procedures such as transurethral resection of the prostate (TURP).[7,8] The adverse drug reactions of cefuroxime are similar to those of other beta-lactams, however, cefuroxime is associated with a relatively high risk of *C. difficile* infection. Some centres minimize its use for this reason.[9]

Ceftazidime

Ceftazidime is an intravenous third generation cephalosporin. It has a broader spectrum of Gram-negative activity than cefuroxime, including good activity against *P. aeruginosa*, but it is not stable to ESBL-producing bacteria which are becoming increasingly prevalent. Unlike first and second generation cephalosporins, it does not provide good antistaphylococcal cover.

In urology, ceftazidime should be restricted for the treatment of serious UTIs caused by pathogens resistant to first-line agents. It may be considered as prophylaxis for procedures such as TURP in areas with a high prevalence of coliform organisms resistant to first-line prophylactic agents.[7] Side effects of ceftazidime are similar to those of other cephalosporins, and include the risk of promoting *C. difficile* infection. Some hospitals therefore limit its use.[9]

Carbapenems

Carbapenems are broad-spectrum, bactericidal beta-lactams with good activity against the majority of Gram-positive and Gram-negative pathogens, including ESBL-producing bacteria and anaerobes. They are inactive against MRSA and destroyed by carbapenemase-producing bacteria. Carbapenems include ertapenem, imipenem, meropenem, and doripenem. All except ertapenem are active against *P. aeruginosa*. Ertapenem has a long half-life and is therefore suitable for once-daily dosing. Carbapenems are only available in parenteral formulations.

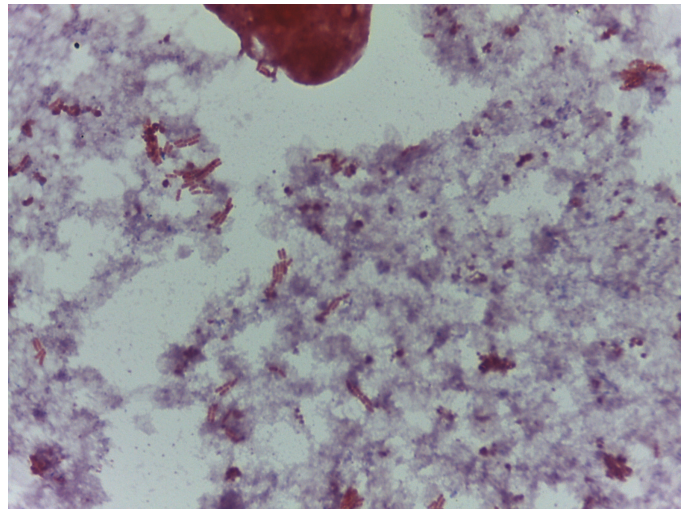

Fig. 1.2.5 Gram-stained preparation of a blood culture showing Gram-negative rods (×1,000 magnification). This blood culture, which subsequently grew *Escherichia coli (E. coli)*, was collected from a patient with urosepsis.

As a result of their broad spectrum of activity and stability against bacterial enzymes, carbapenems are indicated for the treatment of severe sepsis, including complicated UTIs, for polymicrobial infections and for the treatment of infection caused by multiresistant bacteria, including ESBL producers (Fig. 1.2.5).

There is a low incidence of cross-hypersensitivity with penicillins, so carbapenems should be avoided if the patient has a history of an immediate hypersensitivity-type reaction to penicillins.[11]

Aztreonam

Aztreonam is a monocyclic beta-lactam agent or monobactam. It inhibits bacterial cell wall synthesis and is bactericidal. Aztreonam is active against a range of Gram-negative bacteria but inhibited by some beta-lactamases including ESBLs and considered to have reduced activity against *Pseudomonas*. Gram-positive and anaerobic bacteria are resistant. It is available only for parenteral administration. Effective serum levels of aztreonam are achieved and the drug is widely distributed in body tissues and urine.

Aztreonam can be used for the treatment of serious Gram-negative infections caused by sensitive pathogens. It is less likely than other beta-lactam agents to cause hypersensitivity reactions in patients with penicillin allergy and may therefore be used with caution.[11]

Aminoglycosides

Gentamicin, tobramycin, and amikacin are bactericidal antibiotics that inhibit bacterial protein synthesis by binding to the 30S ribosomal subunit. They have good activity against coliform organisms, *Pseudomonas* species, and staphylococci, but no activity against streptococci or anaerobes. Amikacin provides a broader spectrum of Gram-negative activity than gentamicin or tobramycin. Aminoglycosides are not absorbed after oral administration and are usually given intravenously.

They are useful for treating complicated UTIs and urosepsis, including infections caused by *P. aeruginosa* and coliform organisms that may be resistant to beta-lactam antibiotics. Single-dose aminoglycoside prophylaxis may be administered for urological procedures.[8] The main adverse drug reactions are dose related. These agents are excreted in the urine; they may accumulate in renal tissue where, in high doses, they can cause acute tubular necrosis.

Once-daily dosing of aminoglycosides reduces the risk of toxicity without reducing the therapeutic response for most infections.[38] Renal function should be assessed prior to the administration of aminoglycosides and regularly during treatment. Therapeutic drug monitoring should be carried out because of the narrow therapeutic index.[11] Aminoglycosides should be avoided in pregnancy and avoided or used with caution in patients with renal impairment.[11] If possible, the concomitant use of other potentially nephrotoxic or ototoxic agents such as furosemide should be avoided and treatment courses should not exceed seven days.

Glycopeptides

The glycopeptides, vancomycin and teicoplanin, are bactericidal drugs that inhibit bacterial cell wall synthesis by binding to cell wall peptidoglycan precursors. They have a broad spectrum of Gram-positive activity covering staphylococci including MRSA, *Clostridium difficile*, and enterococci, although glycopeptide-resistant enterococci are now well recognized. Glycopeptides have no activity against Gram-negative uropathogens. These drugs are not absorbed by mouth and, for systemic use, intravenous administration is required.

The main use of glycopeptides in urology is for the treatment of serious infections caused by resistant Gram-positive bacteria such as MRSA and *Enterococcus faecium*, or as second-line Gram-positive treatment for patients with penicillin allergy. Oral vancomycin is used for the treatment of recurrent or severe *Clostridium difficile* infection including pseudomembranous colitis. Intravenous vancomycin has a narrow therapeutic index and therapeutic drug monitoring is used to monitor levels and guide dosing.[11] Teicoplanin levels are not routinely measured but may be required in order to optimize treatment of certain severe infections.

Ciprofloxacin

Quinolones inhibit the bacterial enzyme DNA gyrase, which is involved in the folding of DNA during nucleic acid synthesis. Ciprofloxacin is the most commonly used fluoroquinolone; oral and intravenous preparations are available. In general, ciprofloxacin has reasonable activity against coliform organisms, *P. aeruginosa,* and many staphylococci, other than MRSA, although ciprofloxacin resistance in both community and hospital settings is an increasing problem. It has limited activity against streptococci and enterococci and most anaerobes are resistant. Oral ciprofloxacin is very well absorbed. Ciprofloxacin penetrates well into tissues including kidney and prostate, and achieves good urine levels in patients with normal renal function.

In urology, ciprofloxacin is used to treat pyelonephritis, prostatitis, epididymo-orchitis, and UTI caused by isolates resistant to first-line agents.[7,11] It should be avoided in children and in pregnancy. Many centres now restrict the use of quinolones in order to minimize the risk of *C. difficile* infection.

Colistimethate sodium (colistin)

Colistin is active against a very wide range of Gram-negative bacteria including *P. aeruginosa* and multiresistant isolates such as ESBL producers, *Acinetobacter baumanii*, and carbapenemase-producing *Klebsiella* species. It has no activity against Gram-positive pathogens. Oral colistin is not absorbed and remains in the bowel. Formulations are available for administration orally, intravenously, or by inhalation of a nebulized solution.

The use of intravenous colistin is usually overseen by a medical microbiologist or other infection specialist and is generally reserved for the treatment of serious Gram-negative infections resistant to other antimicrobial agents. Nebulized colistin may be used as adjunctive topical treatment for patients with cystic fibrosis[39] and oral colistin may be given as part of a bowel decontamination regimen in certain groups of patients in intensive care units.[40]

Linezolid

Linezolid acts by blocking the initiation of bacterial protein synthesis. It is active against a wide range of Gram-positive bacteria including MRSA and GRE, but has no useful Gram-negative activity. Intravenous and oral preparations are available. It is very well absorbed orally, achieving good concentrations in tissue.

In the United Kingdom, linezolid is licensed for the treatment of complicated skin and soft tissue infections and pneumonia.[11] It achieves adequate levels in urine and may sometimes be considered for the off-licence treatment of serious Gram-positive infections, where the use of other agents has been precluded by allergy or multidrug resistance.

Metronidazole

Metronidazole is active against anaerobic bacteria and protozoa. It is metabolized by nitroreductase enzymes to form active compounds that cause DNA breakage. Oral, intravenous, rectal, and topical preparations are available.

Metronidazole is used for the treatment and prophylaxis of anaerobic infections. In urological practice, it is used to provide anaerobic cover for invasive procedures where the colon may be breached, such as transrectal biopsy of the prostate, or cystectomy and bladder reconstruction.[7,8] Oral metronidazole is the treatment of choice for CDI of mild or moderate severity.[9,11]

Antifungal agents

Fungal infections in urology

Candiduria is usually seen in hospital settings where it may reflect contamination of the urine at collection or colonization of a urinary catheter or stent (Fig. 1.2.6).[41] Removal of predisposing factors, such as broad-spectrum antibiotics, urinary catheters, or stents will clear candiduria in almost 50% of asymptomatic patients[42] and few patients require antifungal therapy. Candida species can, however, cause lower UTIs or even invasive upper tract infections, including pyelonephritis, perinephric abscess, and fungal balls.[43,44] Infection is more common in people with diabetes, the immunosuppressed, and patients with indwelling catheters or stents. *Candida albicans* is the most frequently isolated species, but previous antifungal treatment and hospitalization may alter the spectrum of pathogenic yeasts and antifungal susceptibility.[45]

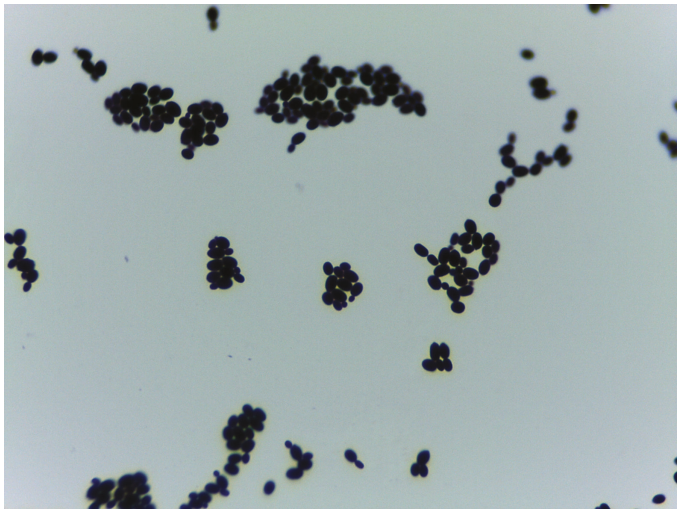

Fig. 1.2.6 Gram stain of *Candida albicans* isolated from a catheter sample of urine (×1,000 magnification).

Antifungal agents

There are four groups of systemic antifungal agent:

1. Azoles
2. Polyenes
3. Echinocandins
4. Flucytosine

Azoles

Azoles are fungicidal, blocking the synthesis of ergosterol, the main sterol in the fungal cell membrane. Fluconazole, itraconazole, voriconazole, and posaconazole are triazoles. While most candida species are susceptible to fluconazole, some are intrinsically resistant and acquired resistance may arise following long-term exposure. Fluconazole is available as oral or intravenous preparations. It has high oral bioavailability and, unlike the other azoles, achieves good urinary concentrations.[46] Fluconazole may be used for the treatment of candidal cystitis, pyelonephritis, and candidaemia. Adverse effects of fluconazole include gastrointestinal upset, rash, and headache. Hepatotoxicity is more common in patients with pre-existing liver abnormalities. Fluconazole inhibits CYP450 isoenzymes in the liver leading to important interactions with some drugs, including warfarin, antiarrhythmics, and calcineurin inhibitors. The dose of fluconazole depends on the clinical indication, and requires adjustment in renal impairment.[11]

Polyenes

Polyenes bind to ergosterol, the main sterol in the fungal cell membrane, causing increased permeability and cell death. Amphotericin B (AMB) has a narrow therapeutic index; liposomal preparations (L-AMB) including amphotericin B-lipid complex (ABLC) and liposomal amphotericin (Ambisome) are less nephrotoxic. Intravenous amphotericin is used to treat systemic fungal infections, usually under the direction of an infection specialist. It should be noted that liposomal preparations do not achieve therapeutic levels in urine. It has a broad spectrum of antifungal activity including *Aspergillus fumigatus* and most yeasts. Acquired resistance is rare.

Adverse effects include infusion reactions (headaches, fever, chills, myalgia), nephrotoxicity, and anaemia. Doses of liposomal amphotericin depend on the formulation chosen. If conventional amphotericin is used, a test dose of 1 mg is followed by a regimen of escalating doses up to a maximum of 1–1.5 mg/kg od by intravenous infusion.[11] Amphotericin should be used with caution in patients with renal impairment.

Echinocandins

These include caspofungin, anidulafungin, and micafungin. Echinocandins cause fungal lysis by inhibiting the synthesis of glucan, a major component of the fungal cell wall. They are active against the majority of candida species, and acquired resistance is rare. Echinocandins may be used for the treatment of systemic candidal infections, but therapeutic levels are not achieved in urine. Adverse effects include gastrointestinal disturbances, rash, flushing, hypokalaemia, and abnormal liver function tests. Echinocandins are given as intravenous infusions. Individual doses should be checked before prescription.[11]

Flucytosine

Flucytosine is a pyrimidine analogue that inhibits fungal DNA synthesis. It is largely excreted unchanged in urine and is active against most yeasts. Flucytosine has a narrow therapeutic index, causing dose-related myelosuppression. It is usually prescribed under the direction of an infection expert and restricted for the treatment of severe life-threatening fungal infections, where it is given in combination with other agents.[11] Short course flucytosine monotherapy may occasionally be considered as treatment for intractable cystitis caused by yeasts resistant to other therapy.[46]

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CHAPTER 1.3

Hospital-acquired urinary tract infection

Roger Bayston

Introduction to hospital-acquired urinary tract infection

In the United States (USA), over 100,000 hospitalized patients suffer a catheter-associated urinary tract infection (CAUTI) each year, and many sources state that CAUTI is the commonest hospital-acquired infection, accounting for 40% of the total.[1] The corresponding figure for the United Kingdom (UK) is 20% of hospital-acquired infections.[2] However, the distinction between catheter-associated asymptomatic bacteriuria (CAASB) and CAUTI is not consistently made, and the majority of these cases are asymptomatic. Guidelines on diagnosis and treatment of nosocomial urinary tract infections are available, and the principles of prevention of infection, including the role of antimicrobial catheters, have been evaluated. Progress is being driven by governments and health insurers which are reluctant to pay the extra costs associated with hospital-acquired infections that they consider preventable.

Microbiology of urinary tract infection

Uncomplicated urinary tract infection

The spectrum of causative organisms differs in community-acquired or uncomplicated urinary tract infection (UTI), and complicated or catheter-related UTI. Most community-acquired UTI is caused by *Escherichia coli*, with approximately 10% of cases due to *Staphylococcus saprophyticus*.[3–5] Most community-acquired UTI occurs in women. In those infections acquired in hospital, both genders are affected and the bacterial spectrum is more varied. The normal habitat of *E. coli* is the large intestine, but the majority are not intestinal pathogens. Many strains of *E. coli* have an array of fine fibres, or fimbriae, on their surfaces, and these are important in attachment of the bacterial cells to various sites. Uropathogenic *E. coli* strains have specialized fimbriae, which are able to attach to uroepithelium and aid in colonization of the urethra and bladder. *E coli* strains that do not possess uroepithelium-specific fimbriae are mainly associated with asymptomatic bacteriuria. Attachment of fimbriated *E. coli* provokes cytokine release and induces an inflammatory response. Recently, uropathogenic fimbriated *E. coli* strains have been shown to impair ureteric peristalsis, leading to reflux.[6] *S. saprophyticus* also possesses specific adhesins for uroepithelium, but it is also a strong urease producer, increasing urinary pH, and further hampering innate defences.

Catheter-associated urinary tract infection

Urinary catheter use changes the microbial spectrum considerably. In one study of short-term catheterization,[7] many infections were due to mixed organisms, with *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *E. coli* predominating, alone or together. In another study of short-term catheterization[8] 94% were due to single organisms, with *E. coli* and other enteric bacteria contributing 42% and candida 31%. Candiduria has been associated clearly with antibiotic use.[9] For patients with long-term catheters, *Proteus mirabilis* is more prominent, causing between 30% and 40% of infections.[10,11] A variety of Gram-positive bacteria, notably *Enterococcus spp.*, make up 34% of the remainder. In recent years, enterococci have become a major nosocomial pathogen showing increasing resistance to antibiotics. Catheterization of the urinary tract has been shown to be the strongest risk factor for hospital-acquired UTI, with an estimated 80% reduction in numbers of UTI cases if catheterization were not performed.[12] However, this is not always a realistic option. From the point of view of infection, the process of urethral catheterization can be considered in two groups: short-term and long-term use. The definition of short-term use varies in the literature, but is usually less than 28 days.[13] Intermittent catheterization should also be considered, but this is often not feasible in hospital. Short-term catheters are widely used in hospitals as part of patient care around interventions, particularly those which are surgical. In arthroplasty, they are used mainly for postoperative urinary retention following epidural anaesthesia, and either indwelling or clean intermittent catheterization can be used.[14] Long-term catheters are used when there is no alternative for the management of lower urinary tract dysfunction particularly in the elderly, in those with spinal injuries, especially where loss of upper limb function means that intermittent self-catheterization cannot be used, and after stroke. Though the introduction of closed systems has reduced the infection rate, over 50% of patients with long-term catheters will eventually develop an infection,[15] and all catheters will be colonized within one month[16] with 50% colonized after five days.[17] However, in most cases this is asymptomatic bacteriuria, although 20–30% of bacteriuric patients will go on to develop symptomatic CAUTI.[18]

Pathogenesis of catheter-associated urinary tract infection

The catheter provides a conduit from the environment directly to the bladder, and the normal voiding pattern is converted to continual