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Reducing bacterial resistance with

IMPACT

Interhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy

Fifth Edition

Edited by P.L. Ho & T.C. Wu

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Reducing bacterial resistance with IMPACT –

Interhospital **M**ulti-disciplinary **P**rogramme on
Antimicrobial **C**hemo**T**herapy

Editors: Pak Leung, HO & Tak Chiu, WU

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We seek to improve the quality of this document. If you have comments or suggestion on this publication, please email to plho@hkucc.hku.hk

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Foreword

I am most delighted to write the foreword for the fifth edition of the IMPACT guideline.

I wish to express my appreciation to the Chairman of the IMPACT Editorial Board, Professor HO Pak-Leung (PL) for his decades-long commitment and contribution to science in antimicrobial resistance, and for his invaluable advice to improving our public health policy on infectious diseases. PL is a clinician scientist with a strong passion on containment of antimicrobial resistance. I still remember vividly our many discussions on policy issues related to multidrug-resistant bacteria – notification, public disclosure, and investment in public health intervention and vaccinations. The IMPACT guideline is an initiative he pioneered in 1999. It was initially launched in one hospital but has since then extended to become territory-wide. I also thank the many people and organizations that have contributed to the continuous improvement of this project including its dissemination in App and eBook platforms.

Antimicrobial resistance is a worldwide problem with serious health and economic consequences. At the Sixty-eighth World Health Assembly in May 2015, the Global Action Plan on Antimicrobial Resistance was adopted. In 2016, the Chief Executive in his policy address has announced the setting up of High Level Steering Committee and Expert Committee on antimicrobial resistance and the Hong Kong Strategy and Action Plan on Antimicrobial Resistance was subsequently launched in 2017. As set out in the Hong Kong Action Plan, one of the six key areas is to optimise the use of antimicrobial agents. The launch of the fifth edition of IMPACT is most timely. With the focus on local epidemiology and insights from experts in the editorial broad, I am confident that the fifth edition of IMPACT will continue to be an important reference for empowering our medical practitioners in meeting this objective.

Dr. Ko Wing-man, BBS, JP
Secretary for Food and Health
The Government of the Hong Kong Special Administrative Region
June 2017

Foreword

It gives me great pleasure to congratulate the Interhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy (IMPACT) Editorial Board for its publication of the fifth edition of IMPACT. Antimicrobial resistance (AMR) is a global threat that has received greater international attention in recent years. Locally, formidable challenge of AMR is obvious given the increasing infections caused by multi-drug resistant organisms, which often result in major morbidity and even mortality. The IMPACT first released in 1999 is a pioneer on this front, and it is most timely to have a new edition.

In this fifth edition, with updated local and overseas information, the IMPACT continues to focus on promoting the use of the right antimicrobials in the right way for hospital infections. There are coverage on antibiotic-resistant organisms, various antimicrobials, as well as specific clinical conditions and settings. A part on tuberculosis has been added to address the rising concern on drug resistance. I am sure local readers and beyond will find the IMPACT a comprehensive and useful reference.

I would like to take the opportunity to thank all people who have contributed to this new IMPACT, in particular the Editors and Members of the Editorial Board. A few colleagues of the Centre for Health Protection (CHP) are honoured to serve the Board. Furthermore, the CHP's Infection Control Branch provides secretariat and technical support to the production of IMPACT, including a new website this time. Optimising the use of antimicrobials is crucial not just for individual health but also public health. The CHP is committed to protect health of the community through continual work in partnership.

Dr. WONG Ka Hing
Controller
Centre for Health Protection
Department of Health
June 2017

Foreword

It is a great honor for me to write a brief foreword to the fifth edition of Interhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy (IMPACT). Antimicrobial resistance (AMR) is a major global public health crisis. Inappropriate use of antimicrobials as well as frequent use of broad-spectrum ones accelerates the emergence of newer resistant strains of microorganisms. Antibiotic stewardship programme (ASP) across the healthcare systems could decrease the prevalence of AMR. Evidence-based clinical guidelines is an essential component of ASP to ensure that patients receive the right antibiotic, at right dose, at the right time, and for the right duration that leads to the best clinical outcome for the treatment or prevention of infection while producing the fewest possible side effects and the low risk for subsequent resistance. IMPACT definitely served this purpose as an invaluable reference tool for medical and health professionals to achieve rational use of antimicrobials.

AMR leads to prolonged illness and hospital stays, the use of more aggressive treatment, increased deaths, loss of productivity, and increased healthcare and social costs. Smart and rational use of antimicrobials is very important to contain AMR. Concerted effort from all stakeholders in the community is the key to success. The Hospital Authority (HA) works in partnership with the government to contain AMR under the “one health” framework. HA had established ASP since 2005 to optimize antimicrobials usage in public hospitals. With the launching of Hong Kong Strategy and Action Plan on Antimicrobial Resistance early this year, efforts from inter-departmental and various sectors of the society could join hands together to fight against this AMR battle.

The IMPACT Editorial Board, comprising members of academics and professionals of high standing from all major medical disciplines especially in the field of antimicrobial use, offered invaluable expert advice to the new revision. I would like to express my heartfelt thanks and congratulations to the successful launching of the fifth edition of IMPACT. Their great contribution has safeguarded the health of Hong Kong citizens.

Dr. P Y Leung
Chief Executive
Hospital Authority
June 2017

Preface

Antimicrobial agents are unique in that their activities vary inversely with time. Today, the efficacy of antimicrobial agents is seriously threatened by an alarming increase in microbial resistance. In 2016, the United Nations General Assembly adopted a political declaration giving full attention to antimicrobial resistance, following a call for global action by the World Health Organization. In Hong Kong, owing to the high population density and lack of hospital space for implementation of infection control measures, it has long been recognized that rates of antibiotic resistance among bacteria are higher than in many other regions. It is for this reason that our medical profession has taken many actions and strategies ahead of time. A web-based platform has been established by the Hospital Authority for surveillance of multidrug-resistant bacteria and audit of big gun antibiotic usage. MRSA infection has been made a key performance indicator for the organization. There is a pledge that the first dose of life-saving antibiotic should be administered within one hour of the patient's arrival. Protocols for hospital admission screening of carbapenemase-producing *Enterobacteriaceae* (CPE), vancomycin-resistant enterococcus (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) are now widely implemented in both public and private hospitals. Among the frontline doctors, there is now a broad consensus that proper use of antibiotics should be given high priority and that unfounded patient requests for antibiotics should be resisted.

IMPACT is a coordinated and multifaceted effort that aims to support prudent use of antimicrobial agents. The content has been extensively reviewed and recommendations carefully considered after a review of the evidence base. The focus is on clinical situations in which the local epidemiology is unique; highlighting the antimicrobial agents with a strong link to development of multidrug-resistant organisms or situations where dosing is complicated. Where appropriate, comments are provided to indicate the situations where the advice of a specialist should be sought. This edition of IMPACT involved and is supported by the Hospital Authority, Centre for Health Protection, University of Hong Kong, Chinese University of Hong Kong, Hong Kong Medical Association, and Hong Kong Private Hospital Association. The publication is freely available at the homepages of the partner organizations and made accessible as an app (Android and iOS) and website for mobile PC and phones. Features that are only available in the app version include medical calculators and up-to-date antibiograms from the Hospital Authority, private hospitals and Department of Health.

I am grateful to the members of the Editorial Board for their contributions. We thank the Centre for Health Protection for providing secretarial support and resources for printing and production of the app and website; as well as the Hospital Authority for granting access to the data and figures.

PL Ho, JP
Chairman, IMPACT Editorial Board
August 2017

Part I: Antibiotic resistance - Local scenario

1.1 Background: the problem of antimicrobial resistance (AMR) in Hong Kong (HK)

1. The emergence of AMR has threatened the successful treatment of patient with infections (1–5).
2. AMR increases drug costs and length of hospital stay, and adversely affects patient's outcome (6).
3. Resistance to all classes of antibiotics has developed to various extents among common and important nosocomial pathogens (Tables 1.1–1.3).
4. In HK, methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum β-lactamase (ESBL)-producing *E. coli* are the two most important multidrug-resistant organisms (Table 1.4). Increase in the annual number of vancomycin-resistant *Enterococcus faecium* (VREfm) in 2013 and 2014 was attributed to a major interhospital outbreak which was eventually controlled. Carbapenem-resistant *Acinetobacter* and carbapenemase-producing *Enterobacteriaceae* (CPE) are on the rise (Figure 1.3).
5. Factors contributing to the rapid rising and high prevalence of AMR in HK (7):
   - Hospital: overcrowding, manpower shortage, lapse in infection control measures, inappropriate use of antibiotics, environmental contamination, lack of transparency of surveillance data and lack of incentive in healthcare setting at administrative level.
   - Community: antimicrobial misuse including in animal husbandry, lack of awareness, and inadequate food and personal hygiene.

Table 1.1 Top eight organisms isolated from different clinical specimens in 2016. Data from a regional hospital in HK

Blood			**Respiratory specimens**			**Urine**		
Organism	Non-ICU/ HDU rank	ICU/HDU rank	Organism	Non-ICU/ HDU rank	ICU/HDU rank	Organism	Non-ICU/ HDU rank	ICU/HDU rank
E. coli	1 (31%)	2 (9%)	*P. aeruginosa*	1 (12%)	2 (7%)	*E. coli*	1 (33%)	2 (20%)
Klebsiella spp.	2 (12%)	6 (6%)	*H. influenzae*	2 (9%)	-	*Candida* spp.	2 (13%)	1 (35%)
CoNS[1]	3 (9%)	1 (28%)	*S. aureus*	3 (8%)	3 (6%)	*Enterococcus* spp.	3 (12%)	3 (17%)
S. aureus	4 (7%)	4 (8%)	*Klebsiella* spp.	4 (6%)	1 (8%)	*Klebsiella* spp.	4 (10%)	4 (8%)
Enterococcus spp.	5 (4%)	3 (8%)	*A. baumannii*	5 (4%)	7 (3%)	*Proteus* spp.	5 (5%)	8 (1%)
P. aeruginosa	6 (2%)	7 (4%)	*S. maltophilia*	6 (3%)	4 (6%)	*P. aeruginosa*	6 (4%)	5 (5%)
Bacillus spp.[1]	7 (2%)	-	*Enterobacter* spp.	7 (3%)	5 (4%)	CoNS[1]	7 (3%)	6 (4%)
P. mirabilis	8 (2%)	-	*E. coli*	8 (3%)	6 (3%)	*S. agalactiae*	8 (3%)	-

Note:

[1] Some of these could be contaminants

CoNS, coagulase-negative staphylococci; ICU, intensive care unit; HDU, high dependency unit

Table 1.2 Intrinsic and associated resistance to antimicrobial agents among five nosocomial pathogens

Bacteria	Intrinsic resistance	Associated resistance
MRSA	All ß-lactams[1], ß-lactam/ß-lactamase inhibitor combinations	Common: erythromycin, clindamycin, aminoglycosides, cotrimoxazole, fluoroquinolones
VREfm	Glycopeptides, cotrimoxazole, clindamycin, aminoglycosides	Common: ampicillin, carbapenems, fluoroquinolones, high level aminoglycoside resistance
ESBL-producing *Enterobacteriaceae* (CTX-M, SHV-, TEM-derived)	All cephalosporins including third generation cephalosporins, (variable activity against fourth-generation cephalosporins), all penicillins and monobactams	Common: fluoroquinolones, aminoglycosides, cotrimoxazole
Carbapenem-resistant *Enterobacteriaceae* (CRE)	All ß-lactams including carbapenem (except monobactam)	Common: fluoroquinolones, aminoglycosides, cotrimoxazole
Carbapenem-resistant *A. baumannii* (CRAB)	Cross-resistance to other ß-lactams are common	Common: fluoroquinolones, aminoglycosides, cotrimoxazole

Note:

[1] Except anti-MRSA cephalosporins such as ceftaroline

Table 1.3 Resistance of common bacterial isolates from all specimens in four regional hospitals (Kowloon, Hong Kong Island and the New Territories) in 2015

Organisms (No. of isolates)	% Non-susceptible																	
	Ampicillin	Ampicillin + sulbactam	Amoxicillin + clavulanate	Piperacillin	Ticarcillin + clavulanate	Piperacillin + tazobactam	Cefoperazone + sulbactam	Cefuroxime (parenteral)	Ceftriaxone	Ceftazidime	Cefepime	Gentamicin	Amikacin	Ciprofloxacin	Cotrimoxazole	Imipenem	Nitrofurantoin
Escherichia coli (26,943)	76		26			5	4.9	33	36	20	19	30	2	40	50	<1	3
Klebsiella spp. (8,958)	100		27		29	8	6	27	20	18	10	8	1	15	29	<1	45
Enterobacter spp. (2,094)	95		96		34	22	13	40		24	5	3	<1	5	11	2	27
Acinetobacter spp. (2,461)		50			56	56	48			34	53	31	26	56	30	55	
Pseudomonas aeruginosa (8,151)				9	43	4	11			5	4	1	<1	10		8	
Stenotrophomonas maltophilia (1,088)					40					44				22	5	100	

Note:

The results were interpreted according to the Clinical Laboratory Standards Institute (CLSI), M100–S20. Most ceftriaxone-non-susceptible isolates were ESBL-producers.

Table 1.4 Estimates of microorganisms significantly associated with AMR, HK, 2013–2016

Antibiotic-resistant microorganism	Included in estimates	Number of cases by year[4]			
		2013	2014	2015	2016
MRSA	Blood only	672	671	686	816
ESBL-producing *E. coli*	Blood only	1,319	1,371	1,470	1,470
Carbapenem-resistant *Acinetobacter*	Blood only	93	108	113	84
MRSA	All clinical specimens	12,462	12,305	12,864	13,001
ESBL-producing *E. coli*	All clinical specimens	10,778	10,954	11,436	11,033
ESBL-producing *Klebsiella* spp.	All clinical specimens	2,502	2,592	2,777	2,917
Carbapenem-resistant *Acinetobacter* spp.	All clinical specimens	2,684	3,314	3,359	3,191
Multidrug-resistant *Acinetobacter* spp.[1]	All clinical specimens	1,161	1,598	969	665
Ceftazidime-resistant *Pseudomonas aeruginosa*	All clinical specimens	850	847	900	1,030
Vancomycin-resistant *Enterococcus* spp.[2]	All clinical specimens	1,810	1,321	410	232
Erythromycin-resistant *Streptococcus pyogenes*[3]	All clinical specimens	556	614	528	620
Multidrug-resistant *Pseudomonas aeruginosa*[1]	All clinical specimens	18	16	6	9
Clostridium difficile	Stool only	2,077	2,171	2,130	2,167

Note:

[1] Per surveillance definitions used by the Hospital Authority (HA).

[2] Mostly vancomycin-resistant *Enterococcus faecium*.

[3] Erythromycin-resistant strains are also resistant to other macrolides such as clarithromycin and azithromycin.

[4] Annual number of cases was estimated by using microbiological results collected from all HA laboratories. Each patient was only counted once in the estimation.

1.2 Methicillin-resistant *Staphylococcus aureus* (MRSA)

Due to the alteration of penicillin binding protein, MRSA are resistant to penicillins (including oxacillin, cloxacillin and flucloxacillin), ß-lactam/ß-lactamase inhibitor combinations, cephalosporins, and carbapenems. Only the new anti-MRSA ß-lactams (e.g. ceftaroline) retain activity against MRSA. However, in vitro and in vivo reduced susceptibility to ceftaroline has recently been reported (8–9).

MRSA has been categorised into healthcare-associated (HA-MRSA) and community-associated (CA-MRSA). The Centers for Disease Control and Prevention (CDC) classification, which is the most widely accepted, classified HA-MRSA and CA-MRSA epidemiologically (10). However the border between the two is becoming blurred and surveillance using epidemiological criteria alone has become insufficient.

1.2.1 Healthcare-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA)

1. For *S. aureus* that are susceptible to methicillin, vancomycin is inferior to anti-staphylococcal ß-lactam (11). However, vancomycin remains the treatment of choice for infection caused by MRSA. The efficacy of vancomycin may be limited by inadequate potency of generic drug, suboptimal dosing, poor tissue penetration, slow bactericidal activity and strains with reduced susceptibility to the drug (11–12).
2. In the recent years, a silent and gradual increase in the vancomycin minimal inhibitory concentration (MIC) has been observed. This phenomenon is known as 'vancomycin creep' (13–14). Since the increment is small and the MIC still falls within the 'sensitive' range, it usually goes unnoticed. This phenomenon has also been observed in HK (15). In HK, there has been a gradual increase in the number of strains with vancomycin MIC = 1 μg/mL from 1997 to 2008. The elevated MIC paralleled an increase in consumption of vancomycin (15).
3. The vancomycin creep has been observed in some, but not all hospitals. This is probably due to difference in the susceptibility testing methods, clonal dissemination of more resistant strains and the intensity of vancomycin usage (15).
4. Unfortunately, there is no international consensus on the appropriate breakpoint for interpretation of vancomycin MIC results for staphylococci (Table 1.5). Vancomycin MIC ≥ 2 μg/mL has been associated with vancomycin treatment failure (16–18). Therefore, guidelines have recommended isolates with vancomycin MIC ≥ 2 μg/mL be treated with an alternative antibiotic instead of vancomycin (11).

Table 1.5 Interpretation of vancomycin susceptibility for staphylococci

	Vancomycin MIC (µg/mL)		
	Susceptible	**Intermediate**	**Resistant**
Staphylococcus aureus			
EUCAST 2017	≤2	none	>2
CLSI 2017	≤2	4–8	≥16
Coagulase-negative staphylococci			
EUCAST 2017	≤4	none	>4
CLSI 2017	≤4	8–16	≥32

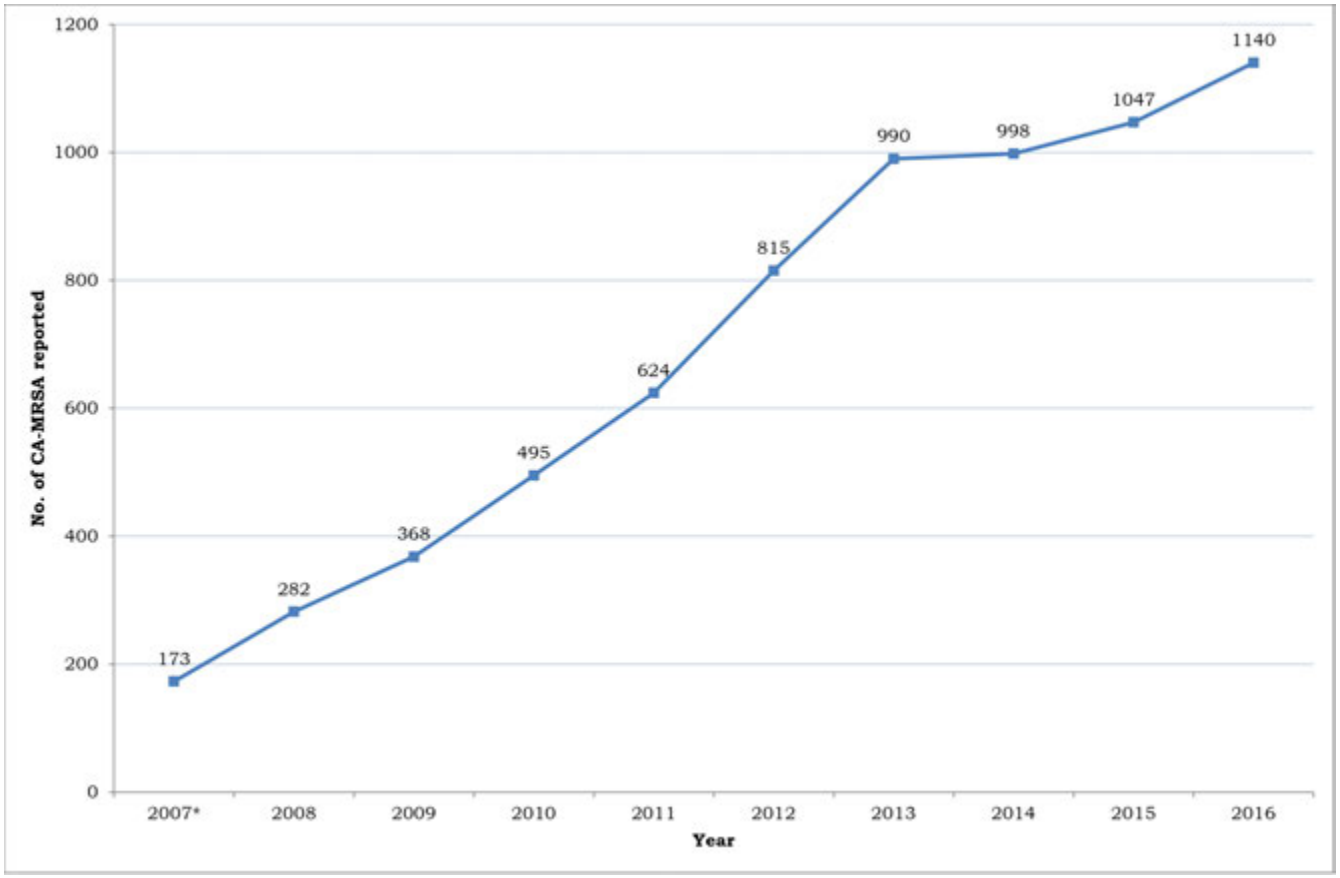
CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing

5. The susceptibility profile cannot be used as a differentiating feature of HA-MRSA and CA-MRSA. In a recent local report, it demonstrated an increase in prevalence of multi-susceptible MRSA (MS-MRSA) over the past few years in the hospital setting. The increase in multi-susceptible strains actually represents a rise in HA-MRSA, which was associated with the spread of the clone ST45/t1081 possessing SCCmec type IV or V. About 75% of these isolates were recovered from elderly living in residential care homes. This suggests that these strains may be more transmissible among the elderly in residential care home and convalescent care settings, serving as a reservoir (19).
6. In 2011, a local study on MRSA carriage at admission to 15 acute medical units showed that the overall carriage rate was 14.3%. Risk factors include MRSA history within the past 12 months, old age home residence, bed-bound state. Molecular typing revealed that ST45/t1081 is a major clone circulating among the patients (20).

1.2.2 Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA)

1. CA-MRSA was first reported in HK in 2001, and is rapidly emerging over the past 10 years (21–22). Reporting to the Department of Health (DH) has been made mandatory since January 2007. It is responsible for 10.4% of purulent cellulitis and 5% of cutaneous abscess in the Accident & Emergency setting (23).
2. In 2007, a total of 173 cases of CA-MRSA infection were notified to the Centre for Health Protection (CHP). The number increased by more than 6 times to 1,148 in 2016. Among the reported cases, about two-thirds of the cases required hospitalisation, while the remaining cases were managed in outpatient settings. The absolute increase in the total number of cases reflects the increasing burden of CA-MRSA in HK (24–25).
3. A total of 3,650 cases of CA-MRSA were recorded between January 2012 and October 2015. Majority of the CA-MRSA presented with uncomplicated skin and soft tissue infections (98%) and 74% of these cases required surgical management. Fifty-three (2%) of the cases presented with invasive CA-MRSA infections, where 14 cases were admitted to the ICU for treatment. Four (0.1%) cases died from sepsis (n=2), pneumonia (n=1) and necrotising fasciitis (n=1) (24).
4. Patients infected with CA-MRSA do not have the usual risk factors associated with HA-MRSA. Locally, case control studies revealed that ethnic minority and sharing of personal items with other persons were risk factors for CA-MRSA while frequent hand washing was protective against CA-MRSA infection (21,26).
5. Panton-Valentine leukocidin (PVL) toxin is a pore forming cytotoxin that is capable of destroying human monocytes and neutrophils. PVL toxin has been associated with virulence and transmissibility of CA-MRSA. While presence of PVL toxin in MRSA is used as a criterion for reporting of CA-MRSA in HK, it has been showed that some of the CA-MRSA causing skin and soft tissue infection were PVL negative (21).
6. Other than skin and soft tissue infections, PVL toxin is also associated with necrotising pneumonia, necrotising fasciitis and meningitis. CA-MRSA has also been reported to co-infect with influenza resulting in fulminant pneumonia (27–29).

Figure 1.1 Number of CA-MRSA reported to the CHP from 2007–2016



* Notifiable since 5 January 2007

1.3 Vancomycin-resistant enterococci (VRE)

1. VRE were first reported in Europe in 1986. Since then, this resistant organism has spread throughout the world and has become a major nosocomial pathogen. Currently, *Enterococcus faecium* is the most important vancomycin-resistant species. In the United States and some European countries, VREfm has disseminated widely in the hospitals and old age homes (30).
2. In HK, the first case of VREfm was identified in 1997 in a patient returning from the United States. During 1997–2008, the occurrence of VRE was sporadic which on several occasions have led to small clusters (<5 to 10 cases) of nosocomial transmission. There had been no continued transmission in our healthcare system. In the mid-2000s, two ad hoc studies demonstrated that VRE was carried by <0.1% of patients in high risk areas (31–32).
3. In our public hospitals, a protracted outbreak of VREfm occurred since 2011. With the implementation of directly observed patient hand hygiene and other infection control measures, the outbreak was finally contained in 2015. In this outbreak, a total of 4,060 VREfm new cases were reported in local public hospitals from 2011–2015 (33).

4. Vancomycin resistance in enterococci is plasmid-mediated. The *vanA* gene is encoded in a transposon Tn*1546* and *vanB* encoded in Tn*1547*. The transposons are mobile and able to disseminate the resistant gene to other more virulent organisms, e.g. *Staphylococcus aureus*. Therefore, despite the low pathogenicity of VRE, they can act as a reservoir of mobile resistance gene (34).
5. Hospital outbreaks caused by VRE have been increasingly reported worldwide. Molecular epidemiology study by multilocus sequence typing revealed that this rise is attributed to the spread of a genetic lineage of *Enterococcus faecium* clonal complex 17 (CC17), Table 1.6 (34–35). CC17 is currently the predominant clone seen in hospital outbreaks worldwide (36–40). The protracted outbreak of VREfm in HK's public hospitals from 2011–2015 also involved strains that belonged to CC17 (33).
6. Most of the *E. faecium* CC17 isolates remained susceptible to linezolid. However in a Germany survey, selection of linezolid-resistance in epidemic-virulent CC17 strains occurred during linezolid therapy (36). It is due to the accumulation of mutations in position 2,576 of the 23S rRNA gene for at least one of the gene copies, necessary for acquisition of phenotypic linezolid resistance in *E. faecium*.
7. Molecular epidemiological study has shown that CC17 has been circulating in hospitals in the United States since early 1980s (34).

Table 1.6 Characteristics of vancomycin-resistant *E. faecium* CC17

1. Multidrug-resistant, including resistance to: a. Ampicillin b. Fluoroquinolones
2. Contains a putative pathogenicity island and the *esp* gene which encodes for a protein involved in colonisation and biofilm formation
3. An association with hospital outbreaks

1.4 ESBL-producing *Enterobacteriaceae*

1. ESBLs are enzymes capable of hydrolysing penicillin, first-, second- and third-generation (extended-spectrum) cephalosporins and aztreonam (except the cephamycins and carbapenems). Most ESBLs can be inhibited by ß-lactamase inhibitors such as clavulanic acid and tazobactam (41) (Table 1.7). TEM, SHV and CTX-M are the three most common families of ESBLs seen worldwide.
2. In HK (Figure 1.2), >90% of strains with an ESBL phenotype produced CTX-M type enzymes (42–43). There is a high rate of resistance towards non-ß-lactam antibiotics, particularly fluoroquinolones, cotrimoxazole and aminoglycosides (42–43). The high rate of resistance to non-ß-lactam antibiotics therefore limits the choice for management of patients in outpatient setting.
3. ESBL-producing *Enterobacteriaceae* has been considered to be a hospital pathogen in the past. However, community-onset infection has been described in different countries including HK in the recent years. Most of the patients presented with lower urinary tract infection, other presentations includes bacteraemia and intra-abdominal infection (44–47).
4. Rectal colonisation with ESBL-producing *Enterobacteriaceae* has been increasingly seen in healthy individuals (48), and this has been postulated to be a risk factor for community-onset ESBL-producing *Enterobacteriaceae* infection. Food animals are a major reservoir of ESBL-producing *E. coli* (49–50).
5. In HK, the burden of ESBL is highest among the elderly population, especially those aged 75 years and above (51).
6. For two decades, ESBL-producing *Enterobacteriaceae* were considered to be clinically resistant to all cephalosporins. Accordingly, all laboratories are advised to edit the results for ceftazidime, ceftriaxone and cefepime to resistant, irrespective of the in vitro inhibition zone diameters or MIC values.
7. Recently, the laboratory testing advisory bodies in the United States and Europe have revised their advice and argued that with the lowered cephalosporin breakpoints that both organisations now adopted, it is unnecessary to edit susceptibility categories if an ESBL is found (52–53). A group of international experts in this field considered such advice is misguided (54). Therefore it is prudent to continue to test for the presence of ESBLs directly and to avoid cephalosporins as treatment.

8. In HK, if we apply the new ceftazidime breakpoint, three-quarters of the ESBL-producing isolates would be re-classified from resistant to susceptible to ceftazidime (55). Caution with this approach is necessary whilst clinical data are limited (54).

Figure 1.2 Burden for ESBL-producing *E. coli* bacteraemia in a regional hospital in HK. Incidence density, number of episodes per 100,000 patient days was used as an indicator (51). R square for fitted line = 0.89 (p<0.001)

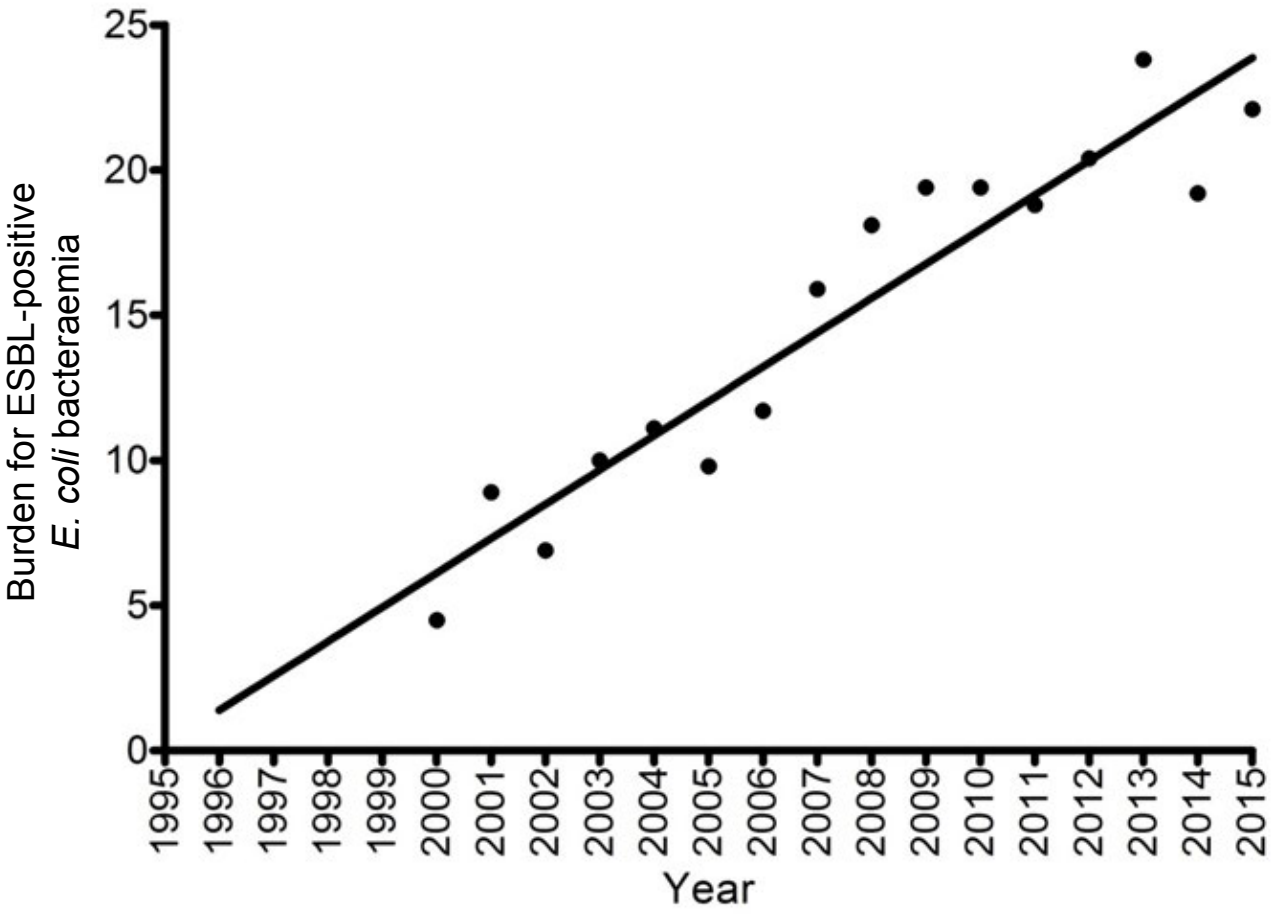


Table 1.7 Characteristics of ESBL and AmpC ß-lactamases

	ESBL	AmpC ß-lactamase
Bush-Jacoby-Medeiro functional class	2be	1
Ambler molecular classification	A	C
Plasmid mediated	Almost always (responsible for the spread)	Most are chromosomal Plasmid increasingly reported
ß-lactamase inhibitor	Inhibited	Not inhibited
Cephamycins - cefoxitin - cefmetazole	Not hydrolysed	Hydrolysed
Oxyimino-ß-lactams - cefotaxime - ceftriaxone - ceftazidime	Hydrolysed	Hydrolysed
Cefepime	Variable	Not hydrolysed
Carbapenem	Not hydrolysed	Not hydrolysed
Examples	TEM, SHV and CTX-M	*Enterobacter*, *Citrobacter* and *Serratia* possess inducible AmpC ß-lactamase encoded in their chromosomes

1.5 Carbapenem-resistant *Enterobacteriaceae* (CRE)

Enterobacteriaceae can acquire resistance to carbapenem through production of carbapenemase (Table 1.8), modification of outer membrane permeability and efflux pump (56).

1. Carbapenemase, KPC-producing *Klebsiella pneumoniae* was first discovered from a clinical isolate through the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) surveillance in North Carolina in 1996 (57–58) and followed by a substantial spread in New York (59), Israel (60) and Greece (61). *Enterobacteriaceae* producing KPC has also been described in South America (Colombia, Brazil and Argentina) (62–64) and China (65–66). Other than *K. pneumoniae*, the KPC-enzyme has also been described in many other *Enterobacteriaceae* species (58). Infection caused by carbapenem-resistant organisms increases the risk of complications and mortality (67).

2. New Delhi metallo-ß-lactamase 1 (NDM-1) was first described in 2009 in a Swedish patient of Indian origin. He was hospitalised in India and acquired urinary tract infection caused by a carbapenem-resistant *K. pneumoniae* (68). Like other metallo-ß-lactamases, the enzyme NDM-1 can hydrolyse all ß-lactams except aztreonam. Resistance to aztreonam is usually due to the coexisting ESBL or AmpC ß–lactamase. Majority of the NDM-1 producing organisms harbour other resistance mechanisms, rendering them resistant to almost all classes of antibiotics with the possible exception of colistin (69–70).
3. NDM-1 producing *Enterobacteriaceae* has spread across Europe. In a recent survey conducted in 29 European countries, cases were reported in 13 countries (69). Majority of the cases had a history of travel to the Indian subcontinent. Many countries have developed their own national guidelines to deal with the problem of NDM-1 (69).
4. The first NDM-1 producing *E. coli* in HK was isolated in October 2009 from a patient with urinary tract infection with travel history to India (71). Several cases of IMP-4 were found in hospitalised patients since mid-2009 in HK (Figure 1.3) (72). The first KPC-2 producing *K. pneumoniae* was described in February 2011 (73).
5. The spread of NDM-1 is probably due to the huge selection pressure created by widespread non-prescription use of antibiotics in India (74) and involvement of promiscuous mobile elements in the gene's dissemination (75).
6. A local review of the NDM detected from 2009–2014 was performed by the CHP. From 2009–2013, there was a gradual rise of NDM cases detected, ranging from 1 to 19 patients, but there were no local cases of NDM detected during this period. Twelve local cases of NDM was first detected in 2014, where four patients had signs of infection. Majority of the imported NDM cases were from China, followed by India and other South East Asian countries (76).
7. A local study in 2016 investigated the clonality and mechanism of resistance of 92 strains of CRE isolated between 2010 and 2012. Only 10% were genotypic carbapenemase-producing *Enterobacteriaceae* (CPE) confirmed by polymerase chain reaction (PCR). Porin loss combined with AmpC and/or CTX-M type ESBL was the major mechanism of resistance of the CRE isolated (77).
8. Plasmid-mediated colistin resistance by *mcr*-1, a gene that can be transferred horizontally among bacteria has been first described in China in both food animals and human (78). HK has also detected CPE with *mcr*-1 recently (79). The coexistence of *mcr*-1 with carbapenemase (e.g. NDM, KPC) has been described in China (80–82), South America (83), Singapore (84), Germany (85).

Figure 1.3 Number of carbapenemase-producing *Enterobacteriaceae* confirmed at the Public Health Laboratory Services Branch, CHP, 2009 to 2016. A HK wide surveillance was implemented since the last quarter of 2010.

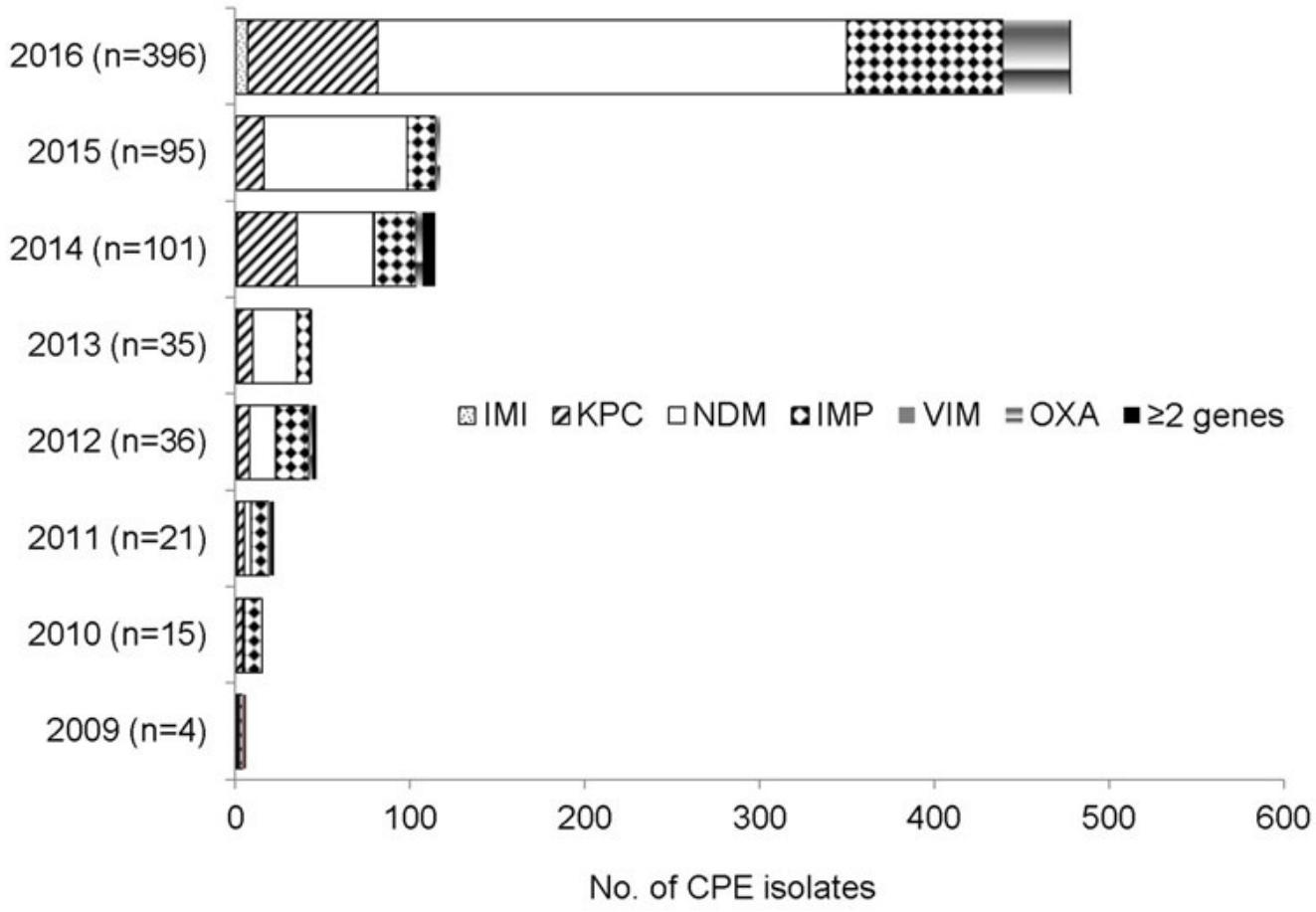


Table 1.8 Different classes of carbapenemase

	Class A	Metallo-ß-lactamase	OXA carbapenemase
Molecular class	Class A	Class B	Class D
Functional class	2f	3	2d
Gene location	Usually transposon	Usually plasmid	Usually plasmid
Examples	KPC[1] GES SME IMI/NMC[1]	IMP[1] VIM[1] NDM[1]	OXA-23, 24, 51, 58 (types in *Acinetobacter* spp.)[2] OXA-48, 181, 232 (types in *Enterobacteriaceae*)[1]
Found in	*Enterobacteriaceae*	Non-fermenters and *Enterobacteriaceae*	Non-fermenters and *Enterobacteriaceae*
Inhibited by	Clavulanate and tazobactam	EDTA	No effective inhibitor
Active site	Serine	Zinc ion	Serine
Carbapenem	Hydrolysed	Hydrolysed	Hydrolysed
Aztreonam	Hydrolysed	Not hydrolysed	Not hydrolysed
Early ß-lactam	Hydrolysed	Hydrolysed	Hydrolysed
Extended spectrum cephalosporin	Hydrolysed (except SME)	Hydrolysed	Hydrolysed poorly

Note:

[1] Seen in HK

[2] Common in HK

1.6 Carbapenem-resistant *Acinetobacter baumannii* (CRAB)

Multidrug-resistant *Acinetobacter baumannii* (MRAB) is a widely used, and yet ill-defined and non-specific term (Figure 1.4). There is no internationally agreed definition for MRAB. Carbapenem is a critically important class of antimicrobial in the treatment of infection caused by *Acinetobacter baumannii* (86–87). Therefore, resistance to the carbapenems have been defined as a sentinel event (88–90). Using the term CRAB allows better communication and surveillance data could be comparable between different centres (Figure 1.4). Moreover, the recent rise in resistant strains of *A. baumannii* seen worldwide is mainly due to the dissemination of strains possessing the Class D OXA type ß-lactamase (91–94). Therefore, for surveillance purpose, the term CRAB reflects the current situation more accurately than MRAB. In February 2017, the World Health Organization published a list of antibiotic-resistant priority pathogen for which new antibiotics are urgently needed; the term CRAB is used.

1. Resistance to carbapenem can be due to enzymatic degradation and efflux pump. However the recent spread in resistant strains of *A. baumannii* is mainly due to strains producing the class D OXA type ß-lactamase (95–96). OXA-23, OXA-24 and OXA-58 are the most common type of carbapenemase produced by *A. baumannii*. They contribute to carbapenem resistance in *A. baumannii* globally (96).
2. The metallo-ß-lactamases are class B ß-lactamases which contain at least one zinc ion at their active sites (Table 1.8). They are more potent carbapenemases and can hydrolyse all ß-lactamase except the monobactam, aztreonam (96). However, metallo-ß-lactams is less commonly seen in *A. baumannii*. Due to the simultaneous presence of resistance determinants often carried on integrons, CRAB has concomitant resistance to other classes of antibiotics (19).
3. In a local survey of CRAB in 2010, majority of the strains belonged to HKU1 and HKU2 clones (89). OXA-23 was found in all HKU1 isolates and correlated with high level of resistance to carbapenems. OXA-51 was found in both HKU1 and HKU2 clones. Chronic wounds were found to be associated with MRAB colonisation or infection, which acts as a potential reservoir for MRAB. This study demonstrated the spread of CRAB is due to the dissemination of two novel clones (91).

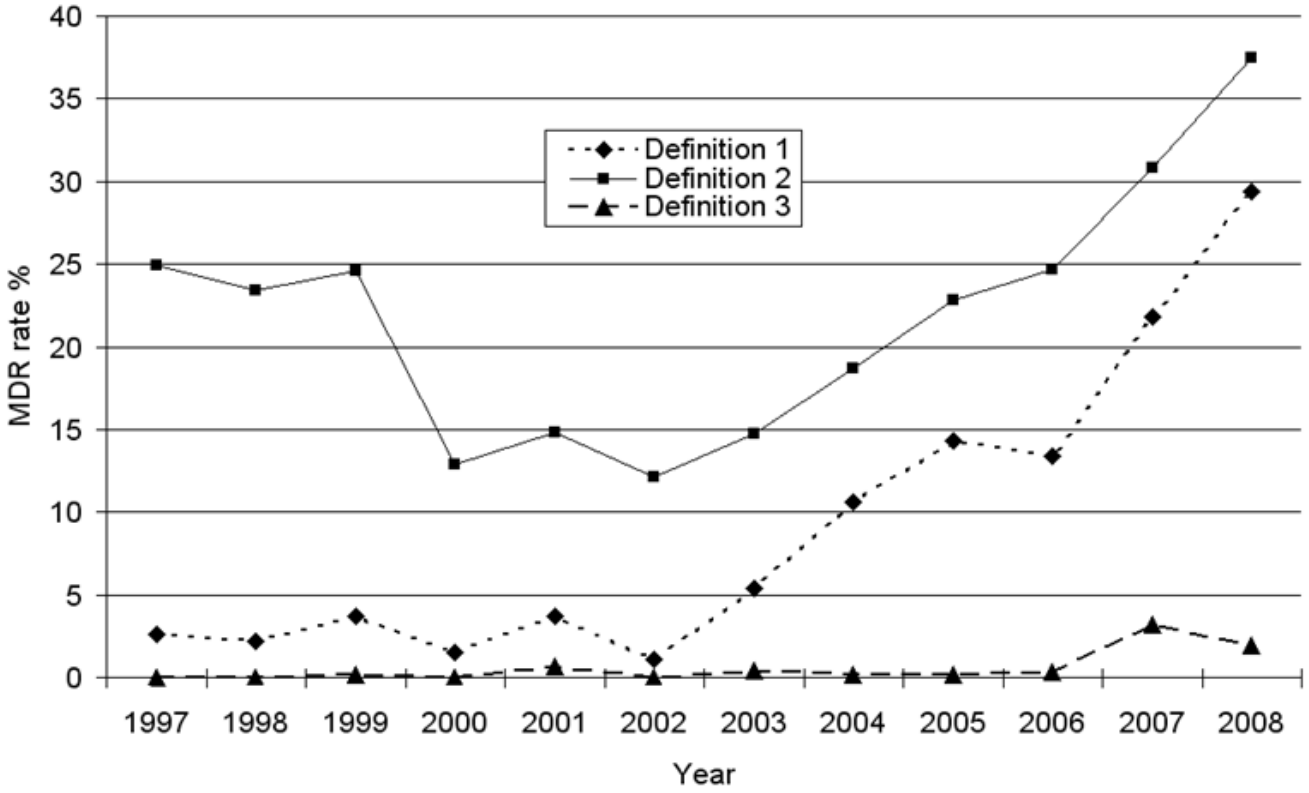
4. Imipenem resistance was found to have a significant impact on the mortality of *Acinetobacter* bacteraemia (97), which is mainly accounted by the higher rate of discordant antimicrobial therapy. *Acinetobacter* resistant to imipenem was also found to have a higher rate of resistance to other classes of antimicrobial agents.
5. There is an increasing endemicity of CRAB ST457 in HK, the incidence of CRAB bacteraemia was 0.27/100,000 patient-days in 2009. A rapid increase of incidence to 1.86/100,000 patient-days occurred in 2013. The increase in the absolute number of CRAB bacteraemia better reflects the true burden to the healthcare system caused by CRAB. Risk factors include resident of elderly home, use of carbapenem and ß-lactam/ß-lactamase inhibitor combinations 90 days before admission (98).
6. A recent local study screened 17,760 faecal specimens for CRAB and MRAB from 9,469 patients over a 7-month study period in a 3,200-bed healthcare network. Screening result showed that 2.6% (244/9,469) patients were CRAB carriers, where 0.57% (54/9,469) were MRAB carriers. Quantitative bacterial counts in various body sites were performed in 33 of the 54 MRAB carriers. Use of fluoroquinolones 6 months before admission was the only significant factor associated with high bacterial load in nasal and rectal swabs (99).

1.7 Macrolide Resistant *Mycoplasma pneumoniae* (MRMP)

1. Respiratory tract infections caused by *Mycoplasma pneumoniae* is primarily a disease of school-age children and adolescents (Figure 1.5). Infections are often self-limiting even without specific antibiotic treatment.
2. MRMP was first reported in Japan in 2001 (100). Since then, there has been reports in China (101–104), Taiwan (105–106), Korea (107), the United States of America (108–109) and various European countries, including Scotland (110), Spain (111) and Germany (112).
3. In China, the prevalence of MRMP is exceptionally high constituting over 90% of all *Mycoplasma pneumoniae* isolates (102). The first imported case of MRMP in HK was reported in an adult returning from Xi'an in 2009 (113). The first locally acquired case of MRMP in HK has been reported in 2010 (114).

4. Two local studies have described the rate of MRMP among patients requiring hospital admission. The first study evaluated different molecular methods to detect genotypic resistance in *M. pneumoniae* in both adult and paediatric subjects (115). Pyrosequencing identified mutation at the position A2063G in 79% of the *M. pneumoniae* PCR positive cases, where Sanger sequencing and melting curve analysis only identified the genotypic mutation in less than 40% of the PCR positive cases. The difference is mainly due to the ability of pyrosequencing to identify low-frequency MRMP quasispecies. Another local study evaluated the antibiotics treatment efficacy against MRMP in the paediatric age group only (116). Among the paediatric community-acquired pneumonia (CAP) cases with a positive *Mycoplasma* PCR, 70% were MRMP. A recent study has demonstrated a high rate of *M. pneumoniae*-associated pneumonia in younger children, where 18% were infants of age group 0–1 years and 30% were between 2–11 years.
5. According to the CHP laboratory surveillance statistics from January to September 2016, 35% of the *M. pneumoniae* detected in respiratory specimens harboured a macrolide-resistant mutation (117).

Figure 1.4 Changes in the multidrug-resistant rate of *Acinetobacter baumannii* according to three different definitions, 1997–2008

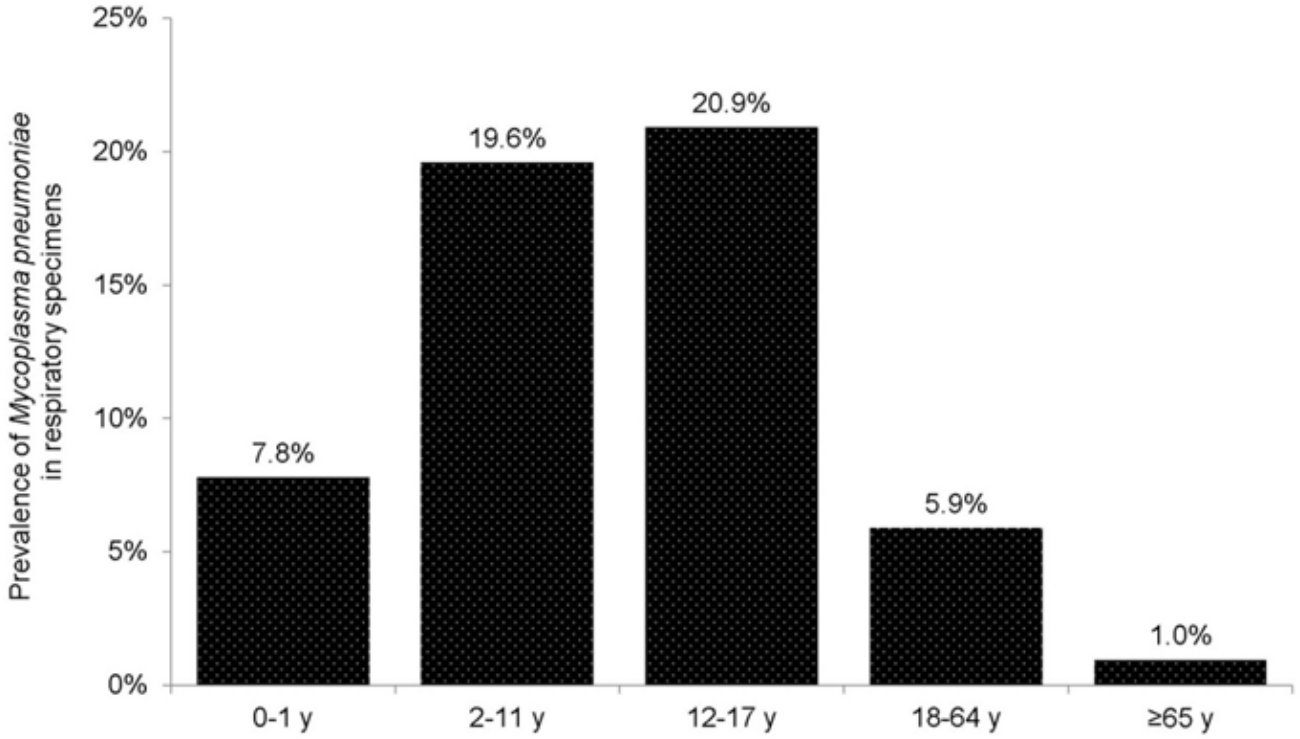


Definition 1: resistance to carbapenem class (imipenem, meropenem)

Definition 2: resistance to representative agents from at least three antibiotic classes, including aminoglycosides (gentamicin, amikacin), antipseudomonal penicillins (ticarcillin/clavulanic acid, piperacillin/ tazobactam), carbapenems (imipenem, meropenem), cephalosporins (ceftazidime) and fluoroquinolones (ciprofloxacin)

Definition 3: resistance to all agents or with the exception of amikacin

Figure 1.5 Prevalence of *Mycoplasma pneumoniae* in respiratory specimens according to patient age groups, all HA hospitals, 2015–2016. During the period, over 20,000 respiratory specimens were tested by PCR assays. In HK, annual *M. pneumoniae*-positive rate in respiratory specimens have been reported to vary widely, ranging from 9.8% to 27.2% (118).



Part II: Antimicrobial stewardship programme

2.1 Antimicrobial stewardship programme (ASP)

1. ASP is defined as the optimal selection, dosage, route of administration and duration of antibiotic treatment (119–120).
2. Benefits of ASP include improved patient outcomes (121–122), reduced adverse reactions, reduced *Clostridium difficile* infection rate (121,123), minimal impact on subsequent antibiotic resistance (124–125) and optimisation of resource utilisation (125–126).
3. ASP is one of the core components of infection control which is one of the mandatory criteria in the Australian Council on Healthcare Standards Evaluation and Quality Improvement Program Hong Kong Guide (127).
4. It involves a multidisciplinary, programmatic, prospective, interventional approach to optimising the use of antimicrobial agents.
5. ASP team comprises clinical microbiologists, infectious disease physicians, infection control nurses, and infectious disease pharmacists.

Table 2.1 Methods to implement ASP in hospital setting

Preauthorisation	• Restricted use of certain antibiotics • Prior approval by an ASP team • Reduces initiation of unnecessary/inappropriate antibiotics
Prospective audit and feedback	• Use of antibiotic order form • Provides educational benefit to clinicians • Can increase visibility of ASP and build collegial relationships
Administrative control	• Restriction of hospital drug formulary through the Drug and Therapeutics Committee • Use of antibiotic order form • Selective or cascade reporting of antibiotic susceptibility test results
Guidelines, education & consultation	• Written hospital guidelines for common infectious diseases syndromes • Educational efforts aimed at changing prescribing practices of clinicians • Providing consultation from clinical microbiologist or infectious disease physician
Review and surveillance	• On-going monitoring and analysis of antibiotics usage • On-going surveillance of antibiotic susceptibility • On-going monitoring of *Clostridium difficile* infection rate

2.2 Tips on safe use of antibiotics in outpatient setting

1. Understand the local prevalence of pathogens and associated antibiotic susceptibility profiles. Information on surveillance of AMR at community outpatient setting is available at the CHP webpage (128).
2. Management of patients with respiratory tract infections should be personalised. A careful clinical evaluation (e.g. patient's age, underlying comorbidity, duration and severity of symptoms, physical findings) is essential in making decision to use or to avoid antibiotics. Upper respiratory tract infections are often viral in origin. In a study, antibiotics were prescribed in 68% of visits for symptoms of acute respiratory tract infections; among those, 80% were unnecessary according to CDC guidelines (129). Clinical discrimination is required in using clinic-based, point-of-care testing (e.g. flu A and B, C-reactive protein, white blood cell (WBC), urinalysis).
3. It is a good clinical practice to explain to the patient the reasons for giving or not giving antibiotics (130) and to provide information on the average total length of the illness (131) as below:

    a). Acute otitis media: 4 days

    b). Acute sore throat/acute pharyngitis/acute tonsillitis: 1 week

    c). Common cold: up to 10 days

    d). Acute rhinosinusitis: 2 to 3 weeks

    e). Acute bronchitis: 3 weeks

4. Whenever appropriate, prescribe the simplest regimen and shortest duration of treatment (132).
5. Take an 'antibiotic timeout' if possible, e.g. reassessing need of antibiotics after 48–72 hours.
6. Advise patients to observe the following precautions while on antibiotics (Figure 2.1):

    a). Practice frequent hand hygiene;

    b). Eat or drink only thoroughly cooked or boiled items;

    c). Disinfect and cover all wounds;

    d). Wear mask if he/she has respiratory symptoms;

    e). Young children with symptoms of infection should minimise contact with other children.

7. Take the opportunity to educate patients on proper use of antibiotics:

   a). Only take antibiotics prescribed for him/her;

   b). Do not share or use leftover antibiotics;

   c). Do not save antibiotics for the next illness;

   d). Do not ask for antibiotics when your doctor thinks you do not need them. In a study of paediatric care, doctors prescribe antibiotics 62% of the time if they perceive pressure from parents and 7% of the time if they feel parents do not expect them (133).

Figure 2.1 Cue card for patient education

Table 2.2 Core elements of outpatient ASP (134)

Commitment	• Identify a single leader to direct antibiotic stewardship activities • Include antibiotic stewardship-related duties in position description or job evaluation criteria • Communicate with all clinic staff members to set patient expectations
Action for policy and practice	• Use evidence-based diagnostic criteria and treatment recommendations • Use delayed prescribing practices or watchful waiting when appropriate • Require explicit written justification in the medical record for nonrecommended antibiotic prescribing • Provide support for clinical decisions
Tracking and reporting	• Provide audit and feedback at the individual clinician level or at the facility level • Comparison of clinicians' performance with that of their peers • Identify high-priority conditions as opportunities to improve clinician adherence to guidelines for antibiotic prescribing
Education and expertise	• Use effective communications strategies to educate patients about when antibiotics are and are not needed • Provide patient education materials • Provide continuing education activities for clinicians

Part III: Guidelines for selected antimicrobial use

3.1 Vancomycin

3.1.1 Situations in which the use of vancomycin is appropriate

1. Treatment of serious infections caused by ß-lactam resistant Gram-positive bacteria (e.g. MRSA, coagulase-negative staphylococci) (135–136).
2. Treatment of CA-MRSA in severe and extensive skin and soft tissue infection (multiple sites), rapid progression of cellulitis, immunosuppression, extremes of age, site of infection difficult to drain (11).
3. Treatment of infections caused by Gram-positive bacteria in patients who have serious allergies to ß-lactam antibiotics (e.g. anaphylactic reaction, Stevens-Johnson syndrome).
4. When *Clostridium difficile* colitis fails to respond to metronidazole therapy or is severe and life-threatening (137–138).
5. As prophylaxis for endocarditis before dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth, or perforation of the oral mucosa in inpatients at high risk for endocarditis; according to recommendation from the American Heart Association (139–140).
6. As prophylaxis for major surgical procedures involving the implantation of prosthetic material or devices in known carriers of MRSA in addition to the routine regimen. For elective procedures, daily washing of skin and hair with a suitable antiseptic soap (e.g. 4% chlorhexidine liquid soap) and topical treatment of the anterior nares with nasal mupirocin ointment (for 3 to 5 days) are recommended before the procedures. Vancomycin may be less effective in preventing surgical wound infection due to methicillin-sensitive staphylococci (141).

3.1.2 Situations in which the use of vancomycin is not advised

1. Treatment of MRSA nasal carriage or colonisation at other sites such as the isolation of MRSA from:
   a). Surface swab of superficial wounds
   b). Surface swab of chronic ulcers
   c). Surface swab of pressure ulcers
2. Routine surgical prophylaxis other than in a patient who has serious allergy to ß-lactam antibiotics.

3. Vancomycin is not a standard part of empirical antibiotic therapy for neutropenic fever, except in known MRSA carriers, haemodynamically unstable neutropenic patients or in presence of severe oral mucositis (142).
4. Treatment in response to a single blood culture positive for coagulase-negative staphylococci, if other blood cultures taken during the same time frame are negative.
5. Continued empirical use for presumed infections in patients whose cultures (blood, joint fluid, peritoneal fluid, pus, etc.) are negative for ß-lactam-resistant Gram-positive bacteria (e.g. MRSA).
6. Systemic or local (e.g. antibiotic lock) prophylaxis against infection (or colonisation) of indwelling (central or peripheral) intravascular catheters.
7. As routine prophylaxis, before insertion of Hickman/Broviac catheter or Tenckhoff catheter.
8. Primary treatment of *Clostridium difficile* colitis, except when it is severe and life-threatening.
9. Routine prophylaxis for patients on continuous ambulatory peritoneal dialysis or haemodialysis.
10. Treatment (e.g. chosen for dosing convenience) of infection caused by ß-lactam-sensitive Gram-positive bacteria in patients who have renal failure.
11. Use of vancomycin solution for topical application (e.g. to burn wound, ulcers) or irrigation (e.g. of T-tube, drains).

3.1.3 Vancomycin dosing

1. In adults, the standard recommended dose of vancomycin is 30 mg/kg/day (I.V. 1 g q12h or I.V. 0.5 g q6h in a normal 70 kg person).
2. In seriously ill patients with suspected MRSA infection, a loading dose of 25–30 mg/kg of actual body weight may be considered.
3. For individual doses over 1g, infuse over 1.5–2 hours (143).

3.1.4 Dosing in patients with impaired renal function

1. For daily dosing based on creatinine clearance when it can be accurately measured or estimated, see Table 3.1 (this table is not suitable for functionally anephric patients).
2. An initial single dose of 15mg/kg should be given.
3. For anuric patient, 1g every 7–10 days.

Table 3.1 Dosage table for vancomycin using creatinine clearance (144)

Creatinine clearance	Dosing
>50 mL/min	500 mg I.V. every 6–12 hours
10–50 mL/min	500 mg I.V. every 24–48 hours
<10 mL/min	500 mg I.V. every 48–96 hours

3.1.5 Therapeutic drug monitoring

- Usage of vancomycin therapeutic drug monitoring as a guide to treat MRSA infections is controversial (145–147).
- Vancomycin therapeutic drug monitoring can be considered in patients with impaired renal function (147), in order to avoid vancomycin-related nephrotoxicity.

3.2 Linezolid

1. Indications
   a). Suspected or confirmed infection caused by antibiotic-resistant Gram-positive bacteria such as MRSA with vancomycin MIC ≥2 μg/mL, VRE and some mycobacteria.
   b). Infections by MRSA in the case of vancomycin failure (e.g. unexplained breakthrough bacteraemia) or serious vancomycin allergy. In these complicated circumstances, the opinion of a clinical microbiologist or infectious disease physician should be sought.
2. Not active against Gram-negative bacteria (e.g. *Haemophilus influenzae, Moraxella catarrhalis*).
3. Most VRE identified in HK so far are susceptible to linezolid (both *E. faecalis* and *E. faecium*) at ≤4 μg/mL and quinupristin/dalfopristin (*E. faecium* only, at ≤1 μg/mL) (148). However, multidrug resistant strains including linezolid-resistant clinical isolates of *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, coagulase-negative staphylococci, *Mycobacterium tuberculosis*, which develop during therapy with linezolid have been reported.
4. Dosage: P.O. or I.V. 600 mg q12h.
5. Side effects include myelosuppression; thrombocytopenia, anaemia and neutropenia reported especially for treatment >2 weeks (149); lactic acidosis, peripheral neuropathy, optic neuropathy due to inhibition of intramitochondrial protein synthesis (150); serotonin syndrome (fever, tremor, agitation and mental state changes), risk with concomitant selective serotonin reuptake inhibitor (151).
6. Please consult clinical microbiologist or infectious disease physician for the use of linezolid.

3.3 Daptomycin

1. Daptomycin belongs to the antibiotic group lipopeptide. It possesses in vitro activities against a range of Gram-positive bacteria such as methicillin-sensitive *Staphylococcus aureus* (MSSA), MRSA, VRE, *Staphylococcus epidermidis* (including methicillin resistant), *Streptococcus pyogenes* and other streptococci.
2. Indications
   a). Bacteraemia associated with intravascular catheter
   b). *S. aureus* bacteraemia, including right-sided infective endocarditis
   c). Complicated skin and soft tissue infection
3. Not indicated for pneumonia because of drug inactivation by pulmonary surfactant.
4. Dosage: 4–6 mg/kg I.V. once daily.
5. Side effects
   a). Myopathy and rhabdomyolysis especially in patients taking statins.
   b). Eosinophilic pneumonia related to the use of daptomycin has been reported (152).
6. Please consult clinical microbiologist or infectious disease physician for the use of daptomycin.

3.4 Tigecycline

1. Prototype drug of antibiotic class glycylcyclines derived from minocycline (153).
2. Indications: MRSA, VRE and other multidrug-resistant organism with in vitro activity, when standard treatment has failed or is contraindicated (e.g. allergy).
3. As for tetracyclines, this drug is not licensed for use in children.
4. Poorly active or inactive against the non-fermenters, such as *Stenotrophomonas maltophilia*, *Pseudomonas* spp. and CRAB.
5. Limitation of use
   a). Food and Drug Administration (FDA) warnings: Reports showed an increased mortality in patients treated for nosocomial pneumonia, especially ventilator-associated pneumonia, and also complicated skin and skin structure infections, complicated intra-abdominal infections and diabetic foot infections (154).
   b). An updated FDA warning has showed a higher mortality risk among patients who received tigecycline compared to other antibacterial drugs. The deaths resulted from worsening infections, complications of infection, or other underlying medical conditions (155).
6. Dosage:
   a). I.V. loading dose of 100 mg, then 50 mg q12h.
   b). Given as slow I.V. infusion (30–60 minutes).
   c). Reduce maintenance dose (25 mg q12h) for patients with severe liver disease (Child Pugh C).
7. Side effects similar to tetracycline.
8. Please consult clinical microbiologist or infectious disease physician for the use of tigecycline.

3.5 Colistin/colomycin

1. Colistin belongs to the polypeptide antibiotic class polymyxin.
2. Mainly used in infections caused by multidrug-resistant Gram-negative bacteria like CRE, pandrug-resistant *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.
3. All Gram-positive bacteria, *Moraxella catarrhalis*, *Morganella morganii*, *Proteus* spp., *Providencia* spp. and *Serratia marcescens* are intrinsically resistant to colistin.
4. Poor lung penetration after intravenous administration. For pneumonia cases, use high I.V. dose with possible addition of nebulised colistin (156).
5. Dosing and administration
    a). Despite being available for more than 50 years, colistin use is still not optimised. This is due to confusion in dosing due to different conventions, outdated and diverse product information and uncertainties about susceptibility testing and breakpoints (157).
    b). Colistin strength is expressed in colistin base activity (mg CBA), milligrams (mg) or international units (IU) in different parts of the world.
    c). Consider 30 mg CBA approximately equal to 1 million IU colistin (158).
6. Please consult clinical microbiologist or infectious disease physician for the use of colistin.

3.6 Fosfomycin trometamol

1. Indications
   a). Indicated for treatment of complicated or uncomplicated urinary tract infections caused by ESBL-producing *Enterobacteriaceae*.
   b). Systematic review showed 96.8% of ESBL-producing *E. coli* isolates and 81.3% of ESBL-producing *Klebsiella pneumoniae* isolates were susceptible to fosfomycin (159).
2. Also active against enterococci and MRSA. (160–161)
3. Dosage:
   a). Uncomplicated urinary tract infection: 3 g sachet P.O. for 1 dose with/ without food.
   b). Complicated urinary tract infection: 3 g sachet P.O. every 2–3 days (up to 21 days) on an empty stomach.
4. Please consult clinical microbiologist or infectious disease physician for the use of fosfomycin disodium in treatment of infections other than uncomplicated cystitis.

3.7 Carbapenems

3.7.1 Indications for using imipenem/meropenem/ertapenem

1. Therapy of infections attributed to ESBL-producing bacteria (such as *E. coli* or *Klebsiella* spp.) such as:
   a). Bacteraemia with isolation of ESBL-producing bacteria from blood culture.
   b). Deep-seated infection with isolation of ESBL-producing bacteria from normally sterile body site or fluid (cerebrospinal fluid, peritoneal fluid, pleural fluid, joint fluid, tissue, pus, etc.).
   c). Nosocomial pneumonia, as defined by CDC guidelines, with isolation of ESBL-producing bacteria in a significant quantity, from a suitably obtained, good quality respiratory tract specimens[1].
2. Empirical therapy of neutropenic fever in high-risk patients. (As ertapenem has no anti-pseudomonal activity, it should not be used as empirical therapy of neutropenic fever patients or patients with non-fermenters infection such as *Pseudomonas aeruginosa* and *Acinetobacter* spp.)

[1]Footnotes

Colonisation of the respiratory tract by ESBL-producing bacteria, especially in mechanically ventilated patients is common. Antimicrobial therapy of colonisation is not indicated. Isolation of ESBL-producing bacteria at the indicated quantity and specimen type is suggestive of infection rather than colonisation (in descending order of clinical significance):

1. 10^2–10^3 CFU/mL or moderate/heavy growth for protected specimen brush.
2. 10^3–10^4 CFU/mL or moderate/heavy growth for bronchoalveolar lavage.
3. Moderate/heavy growth for tracheal/endotracheal aspirate specimens with ++ to +++ white cells and absent/scanty epithelial cells.
4. Expectorated sputum (as defined by the American Society for Microbiology) with >25 WBC/low power field and <10 epithelial cells/low power field.

3.7.2 Situations/conditions in which imipenem/meropenem/ ertapenem is not advised

1. Treatment of colonisation by ESBL-producing bacteria such as the isolation of these organisms from:
   a). Surface swab of superficial wounds
   b). Surface swab of chronic ulcers
   c). Surface swab of pressure ulcers
2. Empirical therapy of most community-acquired infections including pneumonia, appendicitis, cholecystitis, cholangitis, primary peritonitis, peritonitis secondary to perforation of stomach, duodenum or colon, skin and soft tissue infections, etc.
3. As known-pathogen therapy for infections caused by organisms susceptible to other ß-lactams.

3.8 Once daily aminoglycosides

1. Once daily aminoglycoside is an effective, well-established method to achieve therapeutic efficacy while limiting the risk of toxicity and simplifying the processes of dosing and monitoring (162–163).
2. The addition of an aminoglycoside to β-lactams for sepsis should be discouraged. Combination treatment carries a significant risk of nephrotoxicity without survival benefits (164–165).
3. With the exception of *Enterococcus* endocarditis (166), aminoglycosides should not be given for more than one or two doses.
4. As concentration-dependent antibiotics, dosing of gentamicin and amikacin should keep the maximum serum concentration (C_{max}) to minimum inhibitory concentration (MIC) ratio to 8–10 for optimal treatment outcome (167).

3.9 Ceftaroline

1. Ceftaroline is a newer cephalosporin with in vitro activity against MRSA.
2. Ceftaroline is inactive against ESBL-producing or AmpC-overexpressing *Enterobacteriaceae* and has limited activity against non-fermenting Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (168).
3. Dosing
   a). Community acquired pneumonia: 600 mg I.V. q12h
   b). Skin and soft tissue infection: 600 mg I.V. q12h
4. Consult clinical microbiologist or infectious disease physician for the use of ceftaroline.

3.10 Antifungal agents

1. The mechanism of action for the major antifungal classes is summarised in Table 3.2.
2. It is important to note that there are significant within and between class variations in the antifungal spectrum of the agents (Table 3.3). They also differ in their pharmacokinetic properties and dosage adjustment in renal and hepatic dysfunction (Table 3.4).
3. Echinocandins are not active or show very limited activity against *Cryptococcus neoformans*, *Trichosporon beigelii*, dematiaceous moulds, *Zygomycetes*, *Fusarium* spp. and dimorphic fungi (*Blastomyces*, *Histoplasma*, *Coccidioides*) because these fungi do not have the target for the echinocandins to act.
4. Fluconazole shows activity against *Candida albicans*. It is also active against non-albicans *Candida* but MICs are higher, especially for *C. glabrata*.
5. Analysis of fungaemia data in local hospitals showed that about 10% of the isolates were potentially resistant to fluconazole and the echinocandins (Figure 3.1).
6. Table 3.5 showed a suggested scheme for choosing antifungals.
7. Table 3.6 summarised the antifungal agents that have been evaluated in randomised controlled trials for their five major indications. In general, the different agents were non-inferior to each other for the major outcomes. In several studies, superior results were demonstrated for certain outcomes.

Table 3.2 Mechanisms of antifungal action

	Primary mode of action	Target
Azoles (fluconazole, itraconazole, voriconazole)	Inhibit ergosterol biosynthesis	Fungal cytochrome P-450 dependent 14 α-sterol demethylase
Echinocandins (caspofungin, anidulafungin, micafungin)	Inhibit fungal cell wall glucan synthesis	Fungal β-1, 3-glucan synthase
Amphotericin B	Bind to and make fungal cell membrane 'leaky'	Fungal cell membrane

Table 3.3 General patterns of antifungal susceptibility

	FLU	ITR	5FC	AMB	VOR	POS	CAS	MFG	AFG
Yeasts									
C. albicans	S	S	S	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S	S	S	S
C. glabrata	S-DD to R	S-DD to R	S	S-I	S	S	S	S[1]	S
C. krusei	R	S-DD to R	I-R	S-I	S	S	S	S	S
C. lusitaniae	S	S	S	S-R	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S	I	S[1]	S
C. guillermondii	S	S	S	S	S	S	I	S	S
Cryptococcus neoformans	S	S	S	S	S	S	R	R	R
Trichosporon	R	I	R	I	S	S	R	R	R
Moulds									
Fusarium	R	R	R	++	++	++	R	R	R
Aspergillus	R	+	+	+	++	+++	++	++	++
Pseudallescheria	R	S	R	R	++	++	R	R	R
Zygomycetes	R	+	R	+	R	+	R	R	R
Dimorphic fungus									
H. capsulatum	+	++	R	++	++	++	R	R	R
P. marneffei	+	++	+	++	++	++	R	R	R

S, susceptible; S-DD, susceptibility is dose-dependent; I, intermediate; R, resistant

Amphotericin B (AMB); 5-flucytosine (5FC); fluconazole (FLU); itraconazole (ITR); posaconazole (POS); voriconazole (VOR); caspofungin (CAS); anidulafungin (AFG); micafungin (MFG)

Note:
[1]Sporadic cases of breakthrough *C. glabrata* and *C. parapsilosis* infection have been reported in the literature

Reference: (169–179)

Table 3.4 Comparison of selected pharmacokinetic parameters for the azoles and caspofungin

Generic name (Trade name)	Fluconazole (Diflucan)	Itraconazole (Sporanox)	Voriconazole (Vfend)	Posaconazole (Noxafil)	Caspofungin (Cancidas)	Anidulafungin (Eraxis)	Micafungin (Mycamine)
Oral bioavailability	>80%	Capsule: 30–55% Solution: 60–80%	90%	> 90%	Only I.V.	Only I.V.	Only I.V.
C_{max}	10.2	0.2–0.4 µg/mL after 2–4 h of 200 mg P.O.	2 µg/mL after 200 mg P.O.	0.28 µg/mL after 5h	10 µg/mL end infusion	3.55 to 10.9 µg/mL	10 µg/mL end infusion
Time to C_{max} (hour)	2–4	4–5	1–2	3–5	-	-	-
Cerebrospinal fluid (CSF) penetration	50–94%	<1%	20–50%	<1%	Unknown (very low)	Unknown	Undetectable
Plasma half-life (hour)	22–35	24–42	6–24	35	9–11 (terminal half-life 40–50)	26	11–21
Tissue distribution	Widely distributed in most tissues including CSF.	Levels in body fluids/CSF low; concentrations in lung, liver & bone 2–3 times > serum. High concentration in stratum corneum due to drug secretion in sebum.	Widely distributed into body tissues & fluid including brain & CSF.	Widely distributed into body tissues except CSF.	Widely distributed; highest concentration in liver.	Widely distributed.	Widely distributed.
Principal route of elimination	Renal	Hepatic	Hepatic	Hepatic	Hepatic	-	Hepatic

Generic name (Trade name)	Fluconazole (Diflucan)	Itraconazole (Sporanox)	Voriconazole (Vfend)	Posaconazole (Noxafil)	Caspofungin (Cancidas)	Anidulafungin (Eraxis)	Micafungin (Mycamine)
Active drug in urine (%)	80%	<1%	2%	14%	1%	<1%	<15%
Dosage	P.O. or I.V. 50–400 mg/day depending on indications	P.O. 200–400 mg/day	Adult, P.O. 200–400 mg q12h for 24 h, then 100–200 mg q12h; I.V. 6 mg/kg q12h for 24 h, then 4 mg/kg q12h	*Aspergillosis*/ *Candida*: Adult, P.O. 200 mg q8h *Mucormycosis*/ *Cryptococcus*: Adult, P.O. 400 mg q12h	I.V. infusion of 70 mg loading, then 50 mg daily	I.V. infusion of 200 mg on day 1, then 100 mg daily	I.V. 100–150 mg daily
Renal insufficiency	Reduce dose; removed by haemodialysis.	Usual dose. At glomerular filtration rate <10 mL/min, some recommend decrease dose 50%.	No dose adjustment need with P.O. voriconazole. Avoid I.V. voriconazole in renal failure.	No dose adjustment necessary	No dose adjustment needed. Not removed by haemodialysis.	No dose adjustment	No dose adjustment. Poorly dialysed.
Hepatic insufficiency	-	Avoid	Mild to moderate (Child A/B) same loading, reduce maintenance 50%. Avoid in severe impairment.	-	Reduce dose to 35 mg daily (after the 70 mg loading dose) in moderate (Child's score 7–9). No data on usage in patient with severe hepatic failure.	No dose adjustment	No dose adjustment

Table 3.5 A suggested scheme for systemic antifungal agents

	First-line	Alternative
Invasive candidiasis/candidaemia (180)		
Neutropenic or critically ill	Echinocandin	• Lipid formulation amphotericin B
Stable and nonneutropenic	Echinocandin	• Fluconazole, lipid formulation amphotericin B
Invasive aspergillosis (181)		
	Voriconazole	• Amphotericin B and its lipid derivatives for initial and salvage therapy when voriconazole cannot be administered • Echinocandins

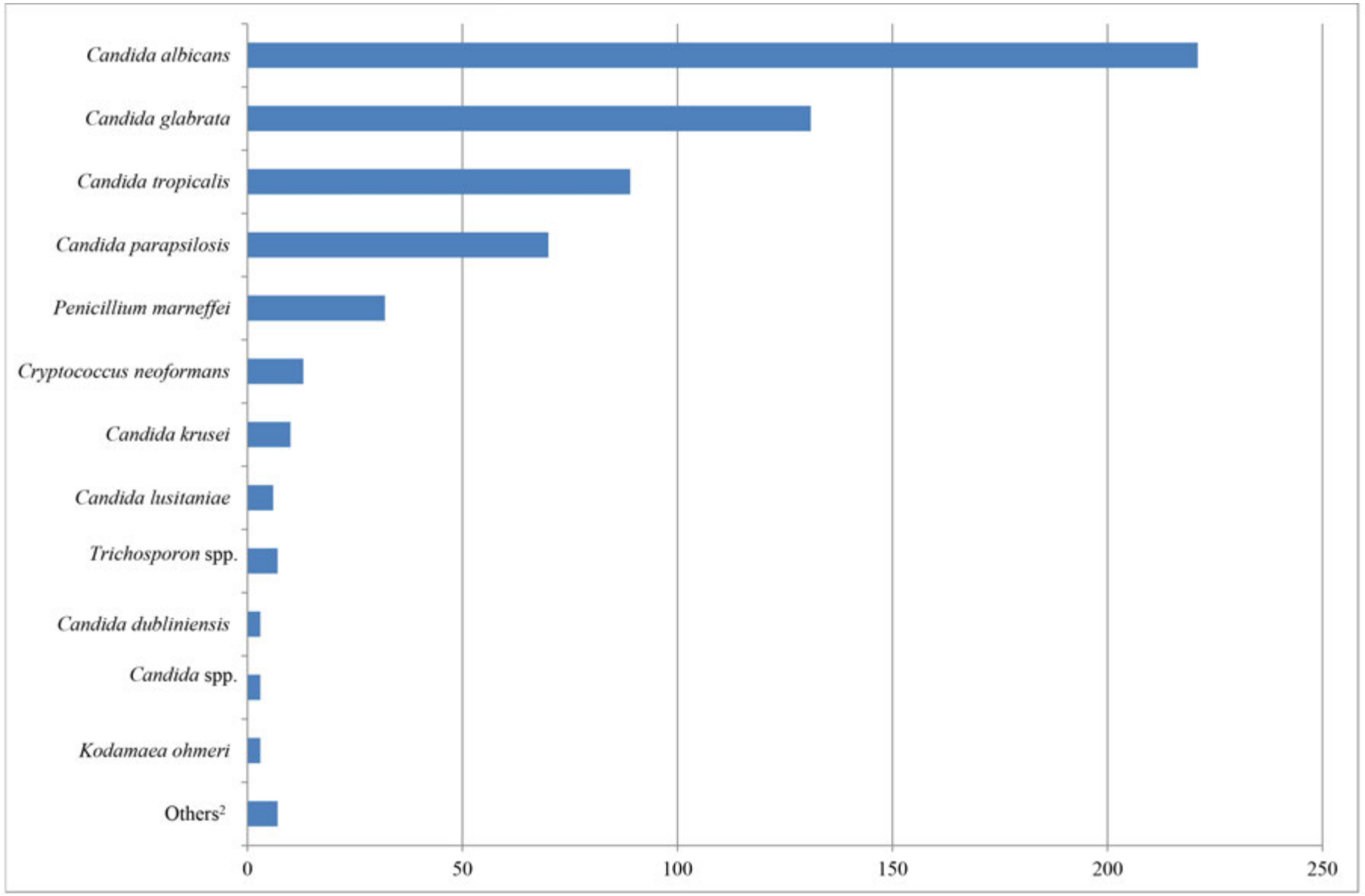
Table 3.6 Selected clinical trials conducted on licensed antifungals

Antifungal prophylaxis	Neutropenic fever	Invasive aspergillosis	Candidaemia or invasive candidiasis	Oesophageal candidiasis
Voriconazole vs placebo (182)	Micafungin vs caspofungin (183)	Posaconazole vs liposomal amphotericin B ± caspofungin (184)	Caspofungin vs amphotericin B (172); Caspofungin vs amphotericin B in newborn infants (185)	Caspofungin vs amphotericin B (186–187)
Micafungin vs fluconazole (188); Micafungin vs fluconazole (189); Micafungin vs fluconazole, liposomal amphotericin B or caspofungin post-liver-transplant (190)	Caspofungin vs liposomal amphotericin B (191); Caspofungin vs liposomal amphotericin B (192)	Voriconazole vs amphotericin B (173,193)	Caspofungin (standard vs high dose) (194)	Caspofungin vs fluconazole (195)
Itraconazole vs fluconazole (196–197)	Voriconazole vs liposomal amphotericin B (198)	Liposomal amphotericin B (standard dose vs high loading dose) (199)	Anidulafungin vs fluconazole (200); Anidulafungin vs fluconazole in critically ill (201)	Anidulafungin vs fluconazole (202)
Posaconazole vs fluconazole or itraconazole (203–205)	Itraconazole vs amphotericin B (206–207)	Isavuconazole vs voriconazole (for invasive mould disease) (208)	Micafungin vs caspofungin (177)	Micafungin vs fluconazole (209–210)
Voriconazole/ posaconazole vs fluconazole/ itraconazole in AML/MDS undergoing chemotherapy (211); Voriconazole vs itraconazole in post allogeneic HSCT (212); Voriconazole vs fluconazole in post allogeneic HSCT (213)	Different amphotericin B formulations (214–215)	Voriconazole and anidulafungin vs voriconazole monotherapy (216)	Micafungin vs liposomal amphotericin B (217–219)	Voriconazole vs fluconazole (220)

Antifungal prophylaxis	Neutropenic fever	Invasive aspergillosis	Candidaemia or invasive candidiasis	Oesophageal candidiasis
Aerosolized liposomal amphotericin B vs placebo inhalation (221)	Micafungin vs itraconazole (222)		Voriconazole vs amphotericin B followed by fluconazole (223)	Isavuconazole vs fluconazole (224)
Voriconazole vs low dose amphotericin B in paediatric acute leukaemia induction (225)	Immediate voriconazole vs deferred placebo (226)		Micafungin vs voriconazole in kidney transplant recipients (227)	
Anidulafungin vs fluconazole in high-risk liver transplant patients (228)			Preemptive micafungin following gastrointestinal surgery (229)	
Caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis (230)			Caspofungin vs micafungin (231)	

Note:
AML, acute myelogenous leukaemia
HSCT, haematopoietic stem cell transplantation
MDS, myelodysplastic syndromes
Agent with superior results for some outcomes is underlined.

Figure 3.1 Distribution by species for 595 episodes of fungaemia in HA, 2015-2016[1]



Note:

[1] Each species from each patient is only counted once.

[2] Including one each of *Candida doobushaemulonii*, *Candida guilliermondii*, *Candida haemulonii*, *Candida novegensis*, *Cryptococcus* spp., *Fusarium solani* and *Malassezia furfur*.

Part IV: Recommendation for the empirical therapy of common infections

4.1 Guidelines for empirical therapy

Table 4.1 Guidelines for empirical therapy

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Musculoskeletal infections				
Septic arthritis, adult (232–234)	*S. aureus*; streptococci, *N. gonorrhoeae*	I.V. cloxacillin + ampicillin	I.V. ceftriaxone or cefazolin (if *N. gonorrhoeae* is suspected, ceftriaxone is the preferred regimen)	• Urgent diagnostic tapping for Gram stain to guide therapy. • If smear reveal Gram-negative cocci or bacilli: ceftriaxone or cefotaxime to replace cloxacillin. • Factors suggest *N. gonorrhoeae* aetiology: sexually active teenager/adult ± rash. • Consider dilute cloxacillin into larger volume of solution (e.g. 250 mL D5 solution) to avoid infusion related phlebitis. • CA-MRSA concern: local prevalence of invasive infection is still rare (24). Consider empirical vancomycin if known recurrent CA-MRSA infection or patient coming from highly endemic areas e.g. United States of America.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Osteomyelitis, haematogenous, adult (235)	*S. aureus*	I.V. cloxacillin	I.V. cefazolin or ceftriaxone	• Occasionally *Salmonella* spp. • Often vertebral. • Intravenous drug user (IVDU): *S. aureus* (vertebral); *P. aeruginosa* (ribs, sternoclavicular joint). Consider broaden empirical Gram-negative coverage if risk factors: concomitant urinary/ intra-abdominal infections, immunocompromised, or elderly. • Associated with MRSA bacteraemia: vancomycin (236). Local prevalence of CA-MRSA invasive infection is still rare (24). Consider empirical vancomycin if known recurrent CA-MRSA infection or patient coming from highly endemic areas e.g. United States of America.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Diabetic foot infection (237–238)				
(a) Previously untreated, no osteomyelitis	*S. aureus,* ß-haemolytic streptococci	I.V./P.O. amoxicillin-clavulanate or ampicillin-sulbactam (239)	I.V./P.O. clindamycin or P.O. cephalexin	
(b) Chronic, recurrent, limb threatening	Polymicrobial: aerobes + anaerobes	I.V./P.O. levofloxacin/ ciprofloxacin + I.V./P.O. clindamycin or I.V./P.O. amoxicillin-clavulanate or ampicillin-sulbactam (239)	I.V./P.O. moxifloxacin or I.V. ertapenem (237,240–241) For severe infections: piperacillin-tazobactam or imipenem-cilastatin	Cultures from ulcers unreliable. Early radical debridement to obtain tissue for culture; to exclude necrotising fasciitis and for cure. Ability to insert probe to bone suggest concomitant osteomyelitis.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Skin and soft tissue infections				
Erysipelas or cellulitis (242)	Groups A, B, C, G streptococci (± *S. aureus*)	(I.V. penicillin or I.V. ampicillin or P.O. amoxicillin) + I.V./P.O. cloxacillin	P.O. cephalexin or I.V./P.O.amoxicillin-clavulanate or ampicillin-sulbactam If CA-MRSA concern: P.O. cotrimoxazole or I.V. vancomycin (if severe infection)	• In HK, 50–80% group A streptococci are resistant to clindamycin (243–244). • Consider CA-MRSA coverage in cases of purulent cellulitis if risk factors present (26), non-responsive to first line treatment and/or severe infection (systemic signs of infection, hypotension)(24).

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Necrotising fasciitis (242,245–246)				• Immediate radical surgical intervention essential. Urgent consult clinical microbiologist or infectious disease physician. • If CA-MRSA is a concern (e.g. risk factors) (24), consider empirical coverage with linezolid (26).
1. Following exposure to freshwater; seawater or seafood	*Aeromonas hydrophilia, A. caviae; Vibrio vulnificus*	I.V. fluoroquinolone + I.V. amoxicillin-clavulanate		
2. Following cuts and abrasion; recent chickenpox; IVDU; healthy adults	Group A streptococci	I.V. penicillin G + I.V. linezolid (247)		Add high dose intravenous immunoglobulin (IVIG) (1g/kg day 1, followed by 0.5g/kg on days 2 and 3) for streptococcal toxic shock syndrome (248–251)[1]. In HK, Group A streptococci: more often resistant to clindamycin (50–80%) (243–244). No clinical data exists on the benefit of clindamycin in clindamycin-resistant strains. In vitro and mice data are limited and contradictory (251–254).
3. Following intra-abdominal; gynaecological or perineal surgery (255)	Polymicrobial: *Enterobacteriaceae*, streptococci, anaerobes	I.V. imipenem or I.V. meropenem	I.V. amoxicillin-clavulanate + I.V. levofloxacin	

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Infected bite wound (animal or human) (242,256–257)	Streptococci, *S. aureus*, anaerobes, *Pasteurella multocida* (dog), *Capnocytophaga* spp. (dog), *Eikenella* spp. (human)	I.V./P.O. amoxicillin-clavulanate	(P.O. penicillin V or P.O. ampicillin) + P.O. cloxacillin	• Up to 18% of dog bites become infected; 28–80% of cat bites become infected (258). • Monotherapy with penicillin, cloxacillin or first generation cephalosporin inadequate. • Penicillin allergy: clindamycin plus (levofloxacin/moxifloxacin). • Increasing prevalence of resistance in anaerobes (259); consider adding metronidazole empirically if poor response to cover anaerobes resistant to ß-lactams or ß-lactam/ß-lactamase inhibitor combinations. • Preemptive antimicrobial therapy for 3–5 days is recommended for patients who (a) are immunocompromised, (b) are asplenic, (c) have advanced liver disease, (d) have pre-existing or resultant oedema of the affected area, (e) have moderate to severe injuries, especially to the hand or face, or (f) have injuries that may have penetrated the periosteum or joint capsule (242).

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Central nervous system infections				
Brain abscess (260–261)	Usually polymicrobial with aerobes and anaerobes	I.V. [ceftriaxone or cefotaxime] plus I.V. metronidazole	I.V. meropenem	• Urgent consult neurosurgical. • Exclude primary focus in middle ear, mastoid, paranasal sinuses, dental and lung. • Carbapenem use is associated with a small increased risk of seizures compared with non-carbapenem group of antibiotics (262).
Meningitis (263–265)	*S. suis, S. pneumoniae, N. meningitidis,* Group B *Streptococcus*	I.V. [ceftriaxone or cefotaxime] plus I.V. vancomycin (266)	I.V. meropenem plus I.V. vancomycin (266)	• If impaired cellular immunity e.g. high dose steroid, add ampicillin to cover *Listeria* spp. • If rapid test (e.g. Gram smear, antigen detection) or other clues suggest *S. pneumoniae*, add vancomycin until sensitivity data available. • An adjuvant 4-day regimen dexamethasone 0.15 mg/kg I.V. q6h 10–20 min before the first dose of antibiotic or simultaneously with first antibiotic dose (267). In adults, adjunctive steroids have been shown to reduce mortality and/or hearing loss only in meningitis caused by *Streptococcus pneumoniae* or *Streptococcus suis*. The benefit of steroids in meningitis caused by other bacteria is unclear (267–268).

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Intra-abdominal and gastrointestinal system infections (community-acquired)				
Secondary peritonitis (269–272) (perforated peptic ulcer, other bowel perforation, ruptured appendicitis, diverticulitis)	*Enterobacteriaceae, B. fragilis*, other anaerobes, enterococci	I.V. amoxicillin-clavulanate	I.V. cefuroxime + I.V. metronidazole Severe infections (e.g. due to ruptured colon): I.V. piperacillin-tazobactam	• Surgical intervention essential. • ß-lactam/ß-lactamase inhibitors usually can provide coverage against anaerobes. However, due to increasing prevalence of resistance in anaerobes to ß-lactams and ß-lactam/ß-lactamase inhibitors (259), consider adding metronidazole empirically if poor response or treatment failure.
Cholangitis, cholecystitis or other biliary sepsis (271,273)	*Enterobacteriaceae,* enterococci, *Bacteroides*	I.V. amoxicillin-clavulanate	I.V. piperacillin-tazobactam or (I.V. cefuroxime + I.V. metronidazole)	• Adequate biliary drainage essential. • Send bile for culture. • ß-lactam/ß-lactamase inhibitors cover most *Enterobacteriaceae*, enterococci and anaerobes.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Liver abscess (community-acquired)	*Klebsiella pneumoniae* and other *Enterobacteriaceae, Bacteroides,* enterococci, *Entamoeba histolytica, Streptococcus milleri* group	I.V. ceftriaxone + I.V./P.O. metronidazole (for *E. histolytica*)	I.V. amoxicillin-clavulanate + I.V./P.O. metronidazole (for *E. histolytica*)	• For all cases: serology for *E. histolytica.* • Computerised tomography guided or open drainage for large abscess. • For amoebic infection: metronidazole for 10 days then followed by diloxanide. • Ophthalmological assessment to rule out endophthalmitis if pus aspirate grew *Klebsiella pneumoniae*. Endogenous endophthalmitis in patient with *Klebsiella* liver abscess occurred in 3% to 10.4%, especially if diabetes mellitus (273–280). • Ceftriaxone (meningitic dose) is the drug of choice for better central nervous system penetration if concomitant central nervous system involvement is likely to occur. Use of amoxicillin-clavulanate should be reserved for patients with drained abscess, clinical responding and without evidence of endophthalmitis.
Mild to moderate gastroenteritis	Food poisoning (*B. cereus, S. aureus, C. perfringens*), *Salmonella* spp., *E. coli, Campylobacter* spp., *Aeromonas* spp.	Routine antibiotic therapy not recommended		Fluid and electrolytes replacement.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Moderate to severe gastroenteritis (presume bacterial) in persons with immunosuppressive disease (e.g. for human immunodeficiency virus (HIV) +ve; high dose steroid when laboratory results not available)	*Salmonella* spp., *Campylobacter* spp.	P.O. fluoroquinolone		Fluoroquinolone resistance among *Campylobacter* increasing. If symptoms not improving or worsening when diagnosis of *Campylobacter* gastroenteritis is made; stop fluoroquinolone and prescribe a course of P.O. macrolide for 5–7 days.
Severe gastroenteritis (281–285) (laboratory results not available)	≥6 unformed stool /day, fever ≥38.5°C; tenesmus; blood or faecal WBC +ve	P.O. fluoroquinolone		Add metronidazole if suspect *Clostridium difficile* infection; replace fluid and electrolytes; avoid antimotility agents. Please refer to known-pathogen therapy if suspected *Clostridium difficile* infection.
Traveller's diarrhoea (285–287) Incidence 10–40%, usually self-limiting	Enterotoxigenic *E. coli* and Enteroaggregative *E. coli*, *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., rarely *Aeromonas*, *Plesiomonas*	P.O. ciprofloxacin 500–750 mg daily, P.O. levofloxacin 500 mg daily or P.O. moxifloxacin 400 mg daily for 1–3 days	P.O. azithromycin 500 mg daily for 3 days or 1g once (first choice in Southeast Asia, India and Nepal, high quinolone resistant *Campylobacter* spp.)	• Chemoprophylaxis is not advised except in immunocompromised patients or HIV patients with CD4 < 200. • Avoid loperamide (Imodium) if fever or blood in stool (enteroinvasive). • Rifaximin 200 mg t.d.s. for 3 days as alternative in non-invasive disease.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Cardiovascular infections				
Subacute infective endocarditis (chronic rheumatic heart disease, degenerative or congenital valvular diseases) (166,288–293)	*S. viridans*, *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp. (HACEK), enterococci	I.V. ampicillin 2 g q4h + gentamicin 3 mg/kg q24h or 1 mg/kg q8h		The choice of empirical therapy should take into account of the most likely pathogens. Obtain at least 3 sets of blood cultures by 3 different venepuncture over 24 h (put down 'suspected infective endocarditis' in test request); then start I.V. antibiotics (294). HACEK organisms: ceftriaxone
Acute infective endocarditis (IVDU) (166,288–293)	*S. aureus*	I.V. cloxacillin 2 g q4h	I.V. cefazolin 2 g q8h	• Usually tricuspid valve infection ± metastatic lung abscesses. • Blood culture for 3 sets (label '? IE' in laboratory form); then start I.V. antibiotics immediately (294). • MRSA concern: Local prevalence of CA-MRSA is low and invasive infection is still rare (24). Consider adding empirical vancomycin if known recurrent CA-MRSA infection, or in critically ill IVDU patients. • Consider adding empirical coverage for Gram-negative and fungal organism such as *Pseudomonas aeruginosa* and *Candida* spp. in critically ill IVDU patients.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Gynaecological infections				
Pelvic inflammatory disease (PID) (or upper genital tract infection) (295–298)	*N. gonorrhoeae, C. trachomatis, Enterobacteriaceae,* anaerobes	Inpatient: I.V. ceftriaxone + P.O. doxycycline ± P.O. metronidazole or (I.V. amoxicillin-clavulanate + P.O. doxycycline) or (I.V. cefoxitin 1–2 g q6h + P.O. doxycycline)	Inpatient: I.V. clindamycin 600–900 mg q8h + I.V. gentamicin (299)	Coverage of anaerobes important in tubo-ovarian abscess, co-existing bacterial vaginosis, HIV +ve (300). The following regimen can be considered for outpatient therapy of mild-to-moderately severe acute PID: I.M. ceftriaxone 250–500 mg single dose + P.O. doxycycline ± P.O. metronidazole (298). Due to high prevalence of gonococcal resistance, P.O. ceftibuten, fluoroquinolones not suitable for empirical treatment of acute PID (301–302).
Breast abscess (303–305)	Usually *S. aureus* (± anaerobes in non-puerperal abscess)	I.V./P.O. cloxacillin (+ P.O. metronidazole if anaerobes likely)	I.V. cefazolin or I.V./P.O. amoxicillin-clavulanate	Incision and drainage essential; send pus for Gram smear and culture.
Head and neck infections				
Odontogenic or neck infection (306–307)	Oral anaerobes	(I.V. penicillin + P.O. metronidazole) or I.V./P.O. clindamycin	I.V./P.O. amoxicillin-clavulanate	

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Urinary tract infections				
Cystitis (308–311)	*E. coli; S. saprophyticus,* Group B *Streptococcus*	P.O. nitrofurantoin or P.O. amoxicillin-clavulanate		• Encourage fluid intake. • Nitrofurantoin should be used with caution in elderly patients; avoid in patients with creatinine clearance <30 mL/min (312). • U.S. FDA has recently warned against the use of fluoroquinolones in uncomplicated cystitis due to concern for serious side effects, unless there are no alternative options (313–315).
Acute pyelonephritis (308–311,316)	*Enterobacteriaceae, Enterococcus*, (*Pseudomonas* in catheter-related, obstruction, transplant)	I.V. amoxicillin-clavulanate	(I.V. piperacillin-tazobactam if suspect *P. aeruginosa*) or I.V. imipenem or I.V. meropenem	• Blood culture and midstream urine (MSU) cultures, need to rule out obstructive uropathy. • I.V. until afebrile 24–48 h, then complete 14 days course with oral drugs. • Carbapenem is recommended for severe or rapid deteriorating clinical cases.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Respiratory tract infections				
Acute bacterial exacerbation of chronic bronchitis (ABECB) (317–321) Appropriate use of antibiotics in ABECB is imperative to help control the emergence of multidrug resistant organisms	Respiratory viruses, *S. pneumoniae, H. influenzae, M. catarrhalis*	I.V./P.O. amoxicillin-clavulanate	I.V. cefotaxime [I.V./P.O. fluoroquinolone may be considered for penicillin allergy, or suspected *Pseudomonas aeruginosa* infection]	• Latest Global Initiative for Chronic Obstructive Lung Disease 2017 Recommendation: Antibiotics should be given to patients with: a. Following three cardinal symptoms: increased dyspnoea, increased sputum volume, increased sputum purulence; b. Increased sputum purulence and one other cardinal symptom; c. Requiring mechanical ventilation (invasive or non-invasive). • *S. pneumoniae* (MIC 1–2 μg/mL) can be treated by high dose P.O. amoxicillin e.g. at least 1.5 g/day or I.V. penicillin G (high dose amoxicillin-clavulanate e.g. 1 g b.d. if co-infection by ampicillin-resistant *H. influenzae*) (318). • U.S. FDA has recently warned against the use of fluoroquinolones in ABECB due to concern for serious side effects, unless there are no alternative options (313–315).

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Acute bacterial exacerbation or pneumonia in patient with bronchiectasis (322–324)	*P. aeruginosa* *H. influenzae, M. catarrhalis, S. pneumoniae*	I.V. piperacillin-tazobactam	I.V. ceftazidime [Anti-pseudomonal fluoroquinolones may be used for treatment of susceptible *P. aeruginosa*]	For *P. aeruginosa*, levofloxacin should be given at high dose (e.g. P.O. 500–750 mg once daily).
Aspiration pneumonia (325)	Oral anaerobes: *Bacteroides*, *Peptostreptococci*, *Fusobacterium, S. milleri* group	I.V./P.O. amoxicillin-clavulanate or (I.V. ceftriaxone + P.O. metronidazole)	I.V. ticarcillin-clavulanate or I.V. piperacillin-tazobactam	Penicillin allergy: levofloxacin plus (clindamycin or metronidazole).
Community-acquired pneumonia (CAP)				
1. CAP, not hospitalised (326–327)	*S. pneumoniae, H. influenzae, M. pneumoniae, C. pneumoniae, C. psittaci* (influenza A, *M. tuberculosis*)	P.O. amoxicillin-clavulanate (e.g. 1 g b.d.) ± doxycycline *or* P.O. high dose amoxicillin (at least 1.5 g/day) ± doxycycline	P.O. levofloxacin	Penicillin allergy: levofloxacin meta-analysis of 127 studies (n=33,148): *S. pneumoniae* (73%); *H. influenzae* (14%); *S. aureus* (3%); Gram-negative rods (2%). In HK, macrolide/azalide, tetracycline or cotrimoxazole should not be used alone for empiric treatment of CAP. Locally, 50–70% penicillin-sensitive and penicillin-resistant *S. pneumoniae* isolates (both community and hospital isolates) are multi-resistant to these agents (1,328–329).

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
2. CAP, hospitalised in general ward (326–327,330–333)	As above	I.V./P.O. amoxicillin-clavulanate ± P.O. doxycycline	I.V. ceftriaxone ± P.O. doxycycline	• Modifying factors: bronchiectasis: either (ticarcillin-clavulanate or piperacillin-tazobactam or cefepime) + a macrolide; or fluoroquinolone + an aminoglycoside. • Rapid test for diagnosis of *Legionella* infection: - Urine antigen for *Legionella pneumophila* serogroup 1 (sensitivity 70%, specificity100%). Or - Detection of nucleic acid of *Legionella* spp. from respiratory specimens by a validated assay (e.g. PCR) in selected cases. • Local prevalence of MRMP is estimated to be >40%, hence doxycycline is the preferred atypical coverage for hospitalised patients in general wards (118). • With concern for influenza: add oseltamivir 75 mg b.d.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
3. CAP, hospitalised in ICU or serious pneumonia (326–327,330–333)	As above + *Enterobacteriaceae*	I.V. piperacillin-tazobactam or ceftriaxone + a macrolide (doxycycline is preferred over macrolides for young patients at low risk of *Legionella* pneumonia, to cover MRMP) [+P.O. oseltamivir 75 mg b.d. during influenza season]	I.V. cefepime + a macrolide (or P.O. doxycycline)	• Ticarcillin-clavulanate and ceftazidime are not useful against penicillin-non-susceptible *S. pneumoniae.* • Rapid test for diagnosis of *Legionella* infection: - Urine antigen for *Legionella pneumophila* serogroup 1 (sensitivity 70%, specificity 100%). Or - Detection of nucleic acid of *Legionella* spp. from respiratory specimens by a validated assay (e.g. PCR) in <u>all cases</u>. • With concern for CA-MRSA: (e.g. presence of Gram-positive cocci in cluster, history of recurrent boils/ abscesses or skin infections or preceding "flu-like" illness, together with features suggestive the presence of PVL +ve *S. aureus*: shock, haemoptysis, leucopenia, multilobular infiltrates, etc.), then add I.V. linezolid 600 mg q12h (preferred) or I.V. vancomycin 1 g q12h.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Hospital-acquired pneumonia (HAP)				
HAP, onset <4 days after admission + no previous antibiotics (326,334–335)	*S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus*	I.V./P.O. amoxicillin-clavulanate	I.V. ceftriaxone	
HAP, onset ≥4 days after admission + had antibiotics recently, OR onset ≥5 days after admission OR mechanical ventilation (326,334–335)	MRSA, *P. aeruginosa*, *Acinetobacter*, *Klebsiella* spp., *Enterobacter* spp.	I.V. piperacillin-tazobactam	I.V. imipenem-cilastatin OR I.V. meropenem	• With ESBL concern: I.V. imipenem/ meropenem • With MRSA concern: Add vancomycin

Footnote
[1] Classification and definition of group A streptococcal toxic shock syndrome (336)
Definite case = criteria IA + IIA + IIB; *probable case* = criteria IB + IIA + IIB
Criteria IA: Isolation of Group A streptococci (*Streptococcus pyogenes*) from a normally sterile site (e.g. blood, cerebrospinal, pleural, or peritoneal fluid, tissue biopsy, surgical wound).
Criteria IB: Isolation of Group A streptococci (*Streptococcus pyogenes*) from a nonsterile site (e.g. throat, sputum, vagina, superficial skin lesion).

Criteria IIA: Hypotension, systolic blood pressure ≤90 mmHg in adults or <5th percentile for age in children, and;

Criteria IIB: ≥2 of the following signs:

(a) Renal impairment: creatinine ≥177 μmol/L for adults or >2× the upper limit of normal for age. In patients with pre-existing renal disease, a ≥2-fold elevation over the baseline level.

(b) Coagulopathy: platelets ≤100,000/mm^3 or disseminated intravascular coagulopathy defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products.

(c) Liver involvement: alanine aminotransferase (ALT), asparate aminotransferase (AST), or total bilirubin levels >2× the upper limit of normal for age. In patients with pre-existing liver disease, a ≥2-fold elevation over the baseline level.

(d) Adult respiratory distress syndrome defined by acute onset of diffuse pulmonary infiltrates and hypoxaemia in the absence of cardiac failure, or evidence of diffuse capillary leak manifested by acute onset of generalised oedema, or pleural or peritoneal effusions with hypoalbuminaemia.

(e) A generalised erythematous macular rash that may desquamate.

(f) Soft tissue necrosis, including necrotising fasciitis or myositis, or gangrene.

4.2 Guidelines on the use and choice of antibiotics in severe acute pancreatitis (SAP)

1. Criteria for severity assessment of acute pancreatitis (Table 4.2)

Most acute pancreatitis is mild. SAP occurs in about 5–13% of all patients with mortality rates of 30% (337–341). SAP is currently defined as having persistent (>48h) single or multiple organ failure as a result of acute pancreatitis, which is most often associated with local (such as peri-pancreatic collections) and/or systemic complications. Patients diagnosed to have SAP are advised to be transferred for close monitoring and treatment in an ICU. Numerous clinical and laboratory findings have been shown to be associated with severe disease course in acute pancreatitis. A number of well-known scoring systems have been employed to predict disease severity at or shortly after admission, though none of which is clearly superior in performance: (a) Ranson score (≥3); (b) persistent systemic inflammatory response syndrome >48h (Table 4.2); (c) bedside index for severity in acute pancreatitis score (≥3); and acute physiology and chronic health evaluation II (APACHE II) criteria (>8) (340,342–346). A C-reactive protein value of ≥150 μg/mL has also been shown to be useful in predicting the severity of acute pancreatitis (347).

2. Routine antibiotic prophylaxis not beneficial

Despite previous uncertainty over this issue due to conflicting evidence in the literature (348–356), the current consensus is that prophylactic use of antibiotics in acute pancreatitis is not advisable (343–346,357–361). Documented drawbacks of prophylactic antibiotics included selection of multidrug-resistant organisms (MRSA, CRAB, resistant *Enterobacteriaceae*), increased *Candida* infections, and antibiotic-related adverse event which may lead to poorer patient outcomes (337,362–370). Therefore, broad-spectrum antibiotics should only be used when clinical factors point to infected pancreatic necrosis (greatest risk in those with >30% pancreatic necrosis) (371).

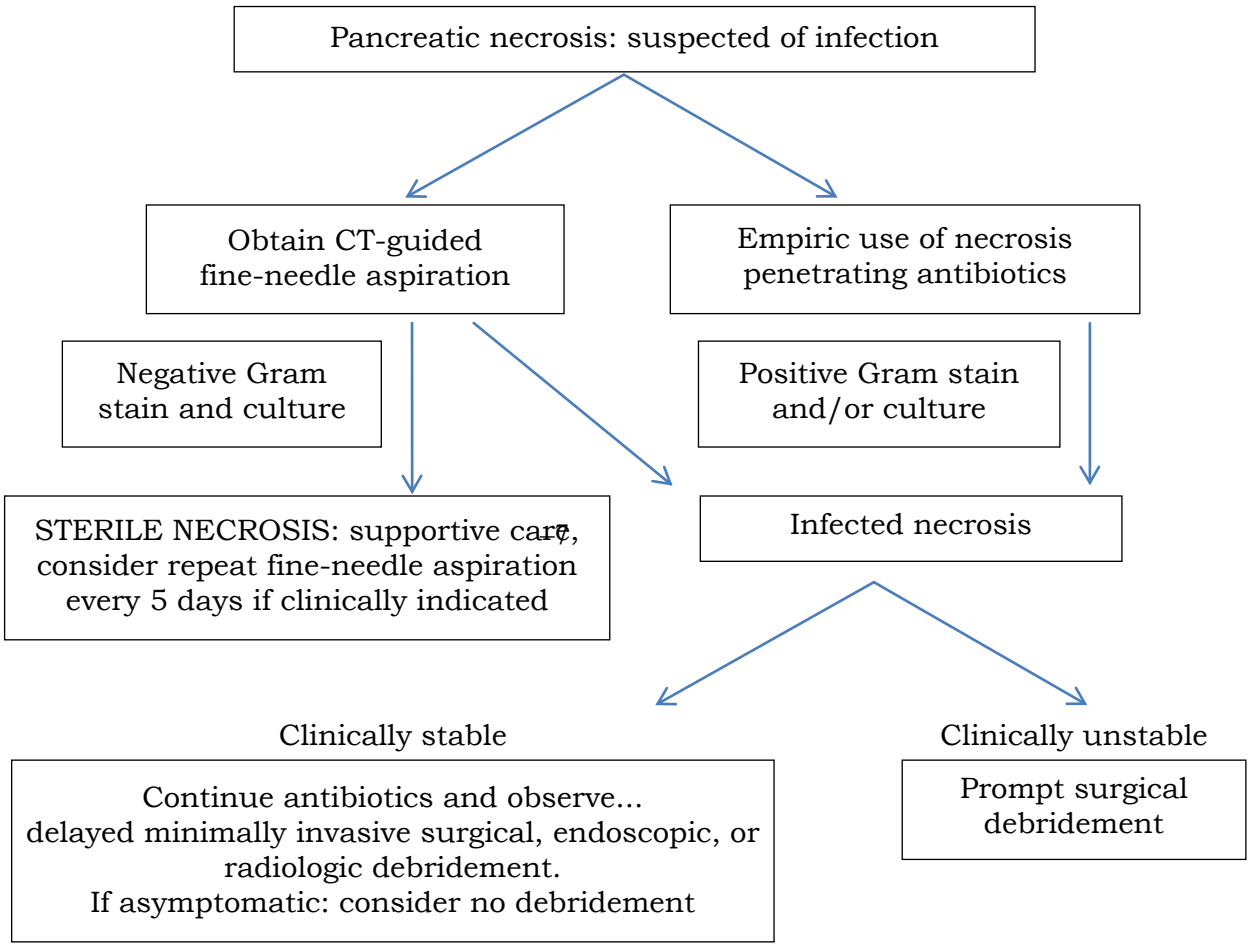
3. Management of pancreatic necrosis when infection is suspected (Figure 4.1) (340–341,343–346,360–361)

Infected necrosis should be considered in patients with pancreatic or extrapancreatic necrosis who deteriorate or fail to improve after 7–10 days of hospitalisation. The finding on computerised tomography of gas within a collection or necrotic area is considered strong evidence of infection. When infected necrosis is suspected, computerised tomography or ultrasound guided-fine-needle aspiration of necrotic area for culture can be performed, or empirical antibiotics with good penetration into pancreatic tissue and providing broad coverage against enteric Gram-negatives bacilli and anaerobes may be given (e.g. an I.V. carbapenem) (338–339,372–373). Although unstable patients with infected necrosis should undergo urgent debridement, current consensus is that the initial management of infected necrosis for patients who are clinically stable should be a course of antibiotics before intervention to allow the inflammatory reaction to become better organised. If the patient remains ill and the infected necrosis has not resolved, minimally invasive necrosectomy by endoscopic, radiologic, video-assisted retroperitoneal, laparoscopic approach, or combination thereof, or open surgery is recommended once the necrosis is walled-off.

Table 4.2 Severity grading of acute pancreatitis according to revised Atlanta criteria (2012) (374)

Mild acute pancreatitis
No organ failure No local or systemic complications
Moderately severe acute pancreatitis
Organ failure that resolves within 48 h (transient organ failure) and/or Local or systemic complications without persistent organ failure
Severe acute pancreatitis
Persistent organ failure (>48 h) • Single organ failure • Multiple organ failure

Figure 4.1 Management of pancreatic necrosis when infection is suspected (343)



4.3 Management of community-acquired pneumonia (CAP)

4.3.1 General considerations and principles

1. A number of guidelines on the management of CAP were released or updated recently. While these guidelines were drawn on the basis of the same set of literature, patient stratification and specific suggestions still vary quite a bit (326,330–332).
2. Newer studies (375–376) continue to support the notion stated in guidelines that *S. pneumoniae* is one of the most common pathogens identified in CAP. Hence, the choice of agents for empirical therapy should consider the regional data on prevalence and risk factors for drug-resistant *S. pneumoniae* (DRSP).
3. Appropriate antimicrobial therapy should be initiated as soon as possible (333,377–378).
4. **Factors to be considered in choosing empirical therapy for CAP:**
   a). **Place of therapy** (outpatient, inpatient ward, or ICU).
   b). **Role of atypical pathogens** (e.g. *Chlamydophila pneumoniae, Mycoplasma pneumoniae* and *Legionella* spp.) is increasingly being recognised. Coverage for atypical pathogens should always be given for hospitalised patients with moderate to severe disease, although it is considered optional for non-hospitalised patients with low-severity CAP (326,330).
   c). **Presence of modifying factors** including risk factors for DRSP (e.g. age >65 years, ß-lactam therapy within past 3 months, alcoholism, multiple medical comorbidities, exposure to a child in a day care centre), enteric Gram-negatives (residence in a nursing home, underlying cardiopulmonary disease, multiple medical comorbidities, recent antibiotic therapy), and *P. aeruginosa* (e.g. bronchiectasis).
   d). **Emerging resistance patterns** among the major pathogens. In Asia, including HK, high prevalence of macrolide resistance has been reported among *Mycoplasma pneumoniae* strains in recent years (113–115,118,379–380).
   e). **Emerging pathogens** including those of regional significance such as CA-MRSA (association with necrotising pneumonia and influenza virus coinfection), *Klebsiella pneumoniae* (association with disseminated infection, liver abscess and diabetes mellitus) and *Burkholderia pseudomallei* (occur in melioidosis endemic area during rainy season) (381–382).

5. Several antibiotics active against *P. aeruginosa*, including cefepime, imipenem, meropenem and piperacillin-tazobactam are generally active against DRSP. They can be used for patients having specific risk factors for *P. aeruginosa*.
6. If a macrolide is relied upon for coverage of *H. influenzae*, the newer macrolides (e.g. clarithromycin or azithromycin) should be used instead of erythromycin.
7. For most patients, appropriately chosen initial antibiotic therapy should not be changed in the first 72 hours, unless there is marked clinical deterioration.
8. Most patients with CAP will have an adequate clinical response within 72 hours. After the patient has met appropriate criteria, switch from I.V. to P.O. therapy can be made.

4.3.2 Management of community-acquired pneumonia (CAP) in the era of pneumococcal resistance: conclusions from the CDC working group

1. Comparative studies of adults and children have reported that pneumonia due to penicillin-nonsusceptible pneumococci (most had MIC >0.1–1 μg/mL) does not influence the outcome of pneumonia treatment (383–384). At higher level of resistance (penicillin MIC 2–4 μg/mL), recent evidence suggests that risk of mortality or suppurative complications were increased (385–386). In one study (387), the observed increase in mortality was confined to patients with pneumococcal isolates with penicillin MIC of ≥4 μg/mL.
2. Since 2012, different breakpoints have been used for interpretation of penicillin susceptibility according to the site of infections and route of drug administration (388–389).

Table 4.3 Interpretation of penicillin susceptibility for *S. pneumoniae*

Syndrome, route of administration and agent	Penicillin or amoxicillin MIC (μg/mL)		
	Susceptible	Intermediate	Resistant
Meningitis, Parenteral penicillin	≤ 0.06	-	≥ 0.12
Non-meningitis, Parenteral penicillin	≤ 2	4	≥ 8
Non-meningitis, Oral (high dose) amoxicillin or amoxicillin-clavulanic acid	≤ 2	4	≥ 8
Oral penicillin V	≤ 0.06	0.12–1	≥ 0.12

By modifying the breakpoints, it is hope that there will be decreased use of broad-spectrum antimicrobial therapy in favour of more narrow-spectrum therapy. Patients with pneumococcal pneumonia caused by strains with penicillin MIC ≤1 μg/mL can be treated appropriately with optimal dosage of I.V. penicillin and several other P.O./I.V. ß-lactams. Comparative anti-pneumococcal activities of commonly used ß-lactams are shown in Table 4.4.

3. Vancomycin is not routinely indicated for treatment of CAP or for pneumonia caused by DRSP.
4. The CDC working group does not advocate the use of newer fluoroquinolones for first line treatment of CAP. The reasons are:
   a). Most penicillin-nonsusceptible *S. pneumoniae* pneumonia can be appropriately treated with a ß-lactam with good anti-pneumococcal activity at optimal dosage.
   b). Concerns that resistance among pneumococci will rapidly emerge after widespread use of this class of antibiotics.
   c). Their activity against pneumococci with high level penicillin resistance (MIC ≥4 μg/mL) makes it important that they should be reserved for selected patients with CAP.
5. Indications for use of fluoroquinolones in CAP
   a). Adults for whom one of the first line regimen has already failed.
   b). Allergic to alternative agents.
   c). Documented infection due to pneumococci with high level penicillin resistance (penicillin MIC ≥4 μg/mL).

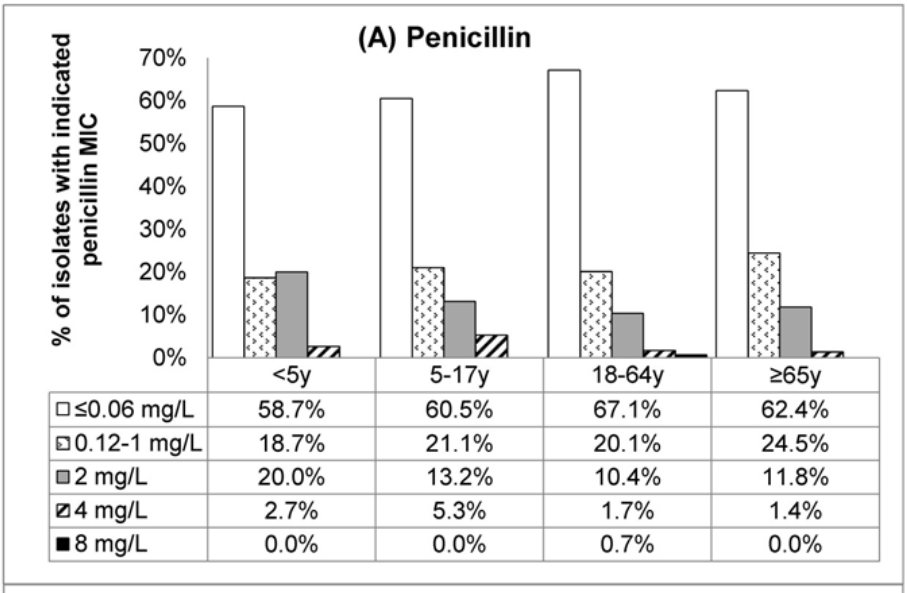
4.3.3 Regional considerations for *S. pneumoniae*

1. In HK, reduced susceptibility to penicillin (Figure 4.2) and resistance to macrolides were high in both hospital (328,390–393) and community settings (394–397). Recent evidence suggests increase in carriage of certain serotypes (such as 15) after introduction of childhood vaccination by pneumococcal conjugate vaccine-13 (392–393,397), although the significance of this phenomenon remains uncertain at this stage.
2. Erythromycin resistant isolates are also resistant to the newer macrolides/azalides such as clarithromycin and azithromycin (398). In 2012–2016, the age group-specific rates of macrolide resistance among 775 invasive pneumococcal isolates were as follows: 76% in <5 years, 92% in 5–17 years, 74% in 18–64 years and 75% in ≥65 years. Accordingly, macrolides should not be used as sole therapy for empirical treatment of presumed pneumococcal infection.

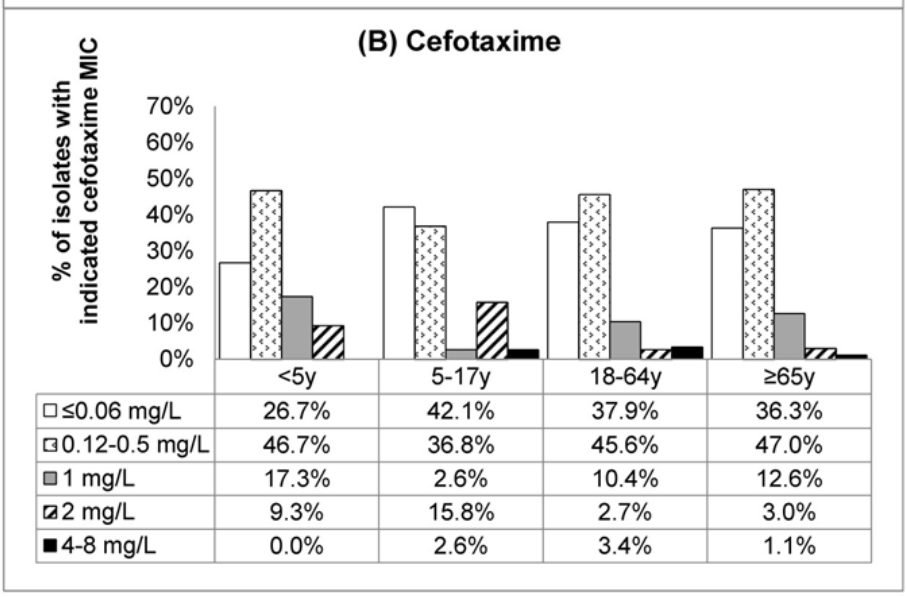
3. Globally, resistance to fluoroquinolones among the pneumococci is low (<1–2%). HK is one of the rare exceptions in which fluoroquinolone resistance (levofloxacin MIC ≥8 μg/mL) is emerging among the *S. pneumoniae*, especially among respiratory isolates from elderly patients with chronic lung diseases (390). One regional study found an association between levofloxacin resistance and mortality in adult patients with invasive pneumococcal disease (399).
4. In view of the above, adherence to the CDC guidelines on the use of the fluoroquinolones seems appropriate. Moreover, tuberculosis (TB) is prevalent in HK and was reported to account for ~10% of CAP in the elderly. Excess use of fluoroquinolones in CAP may lead to: (1) delay in diagnosis of TB; (2) increased fluoroquinolone resistance among *Mycobacterium tuberculosis* (400–401). Hence, this class of agents is not recommended as first line (or routine) therapy in HK for CAP. In this regard, extra care need to be exercised in using fluoroquinolones in patients with risk factors for fluoroquinolone-resistant *S. pneumoniae* (402–403) :
   a). Presence of chronic obstructive pulmonary disease;
   b). Underlying cerebrovascular disease;
   c). Residence in old age home;
   d). Past exposure to fluoroquinolones; and
   e). Healthcare-associated/nosocomial pneumococcal infection.
5. Ciprofloxacin and ofloxacin should not be used to treat pneumococcal infection. Use of a suboptimal dose of fluoroquinolone should be avoided (e.g. the dose/frequency approved by FDA for levofloxacin in CAP is 500 mg/day). Use of <500 mg and in divided doses should be avoided as these have been showed to be associated with the emergence of fluoroquinolone-resistant *S. pneumoniae* (329). If a respiratory fluoroquinolone is indicated, there is evidence to suggest that the more potent ones (e.g. moxifloxacin) are less likely to lead to development of resistance.
6. Penicillin G (I.V.) or ampicillin (P.O./I.V.) or amoxicillin (P.O./I.V.) are generally viewed as the ß-lactam drugs of choice for treating infections with penicillin-susceptible and penicillin-intermediate strains of *S. pneumoniae*. The following ß-lactams are not recommended because of poor intrinsic activities against *S. pneumoniae*: penicillin V, all first generation cephalosporins, cefaclor, cefixime, ceftibuten, and loracarbef.
7. Lung infections involving strains with intermediate susceptibility to penicillin (MIC 0.1–1 μg/mL) may be treated with I.V. penicillin G or P.O. amoxicillin (high dose).

8. Penicillins combined with ß-lactamase inhibitors (ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam) are active against ß-lactamase-producing organisms including *H. influenzae*, *M. catarrhalis*, and methicillin-sensitive *S. aureus*. Except in patients with mixed infection, these drugs offer no advantage over penicillin G or amoxicillin for the treatment of *S. pneumoniae* pneumonia, including those due to penicillin-resistant strains because ß-lactamase is not produced by *S. pneumoniae*. The MIC of ampicillin, amoxicillin, piperacillin for most local strains were similar to that of penicillin. However, the MIC of ticarcillin is increased disproportionately among penicillin non-susceptible strains.

Figure 4.2 Susceptibility of 775 invasive pneumococcal isolates to penicillin and cefotaxime according to patient age groups, 2012–2016, HK



	<5y	5-17y	18-64y	≥65y
≤0.06 mg/L	58.7%	60.5%	67.1%	62.4%
0.12-1 mg/L	18.7%	21.1%	20.1%	24.5%
2 mg/L	20.0%	13.2%	10.4%	11.8%
4 mg/L	2.7%	5.3%	1.7%	1.4%
8 mg/L	0.0%	0.0%	0.7%	0.0%



	<5y	5-17y	18-64y	≥65y
≤0.06 mg/L	26.7%	42.1%	37.9%	36.3%
0.12-0.5 mg/L	46.7%	36.8%	45.6%	47.0%
1 mg/L	17.3%	2.6%	10.4%	12.6%
2 mg/L	9.3%	15.8%	2.7%	3.0%
4-8 mg/L	0.0%	2.6%	3.4%	1.1%

Table 4.4 Comparative activities of commonly used ß-lactams against *S. pneumoniae* with different levels of penicillin susceptibility

Agent	Penicillin MIC			
	≤0.06 µg/mL	0.12–1 µg/mL	2 µg/mL	≥4 µg/mL
Penicillin V	+++	+	-	-
Penicillin G	+++	+++	++	±
Ampicillin P.O.	+++	++	±	-
Ampicillin I.V.	+++	+++	++	±
Amoxicillin P.O.	+++	++	+	-
Piperacillin	+++	++	+	-
Ticarcillin	++	+	-	-
Cefotaxime	+++	+++	++	±
Ceftriaxone	+++	+++	++	±
Cefepime	+++	++	+	±
Cefuroxime I.V.	+++	++	+	-
Cefuroxime P.O.	+++	++	±	-
Cefpodoxime	+++	++	-	-
Ceftazidime	+++	+	-	-
Cefaclor	+++	-	-	-
Cefixime/ceftibuten	+++	-	-	-
Imipenem/meropenem	+++	+++	+	-

Penicillin MIC interpretation criteria (µg/mL) for I.V. penicillin G: meningitis ≤0.06 sensitive, ≥0.12 resistant; nonmeningitis ≤2 sensitive, 4 intermediate and ≥8 resistant.
Approximate in vitro activity was indicated by: - inactive, + weak activity, ++ good activity, +++ excellent activity, ± variable or dose-dependent

Part V: Guidelines for known-pathogen therapy

Table 5.1 Guidelines for known-pathogen therapy

	Drug of choice	Alternatives	Remarks
Acinetobacter baumannii	I.V. ampicillin-sulbactam + an aminoglycoside	• I.V. cefoperazone-sulbactam + an aminoglycoside (mixed infection with *P. aeruginosa*) • Fluoroquinolone + an aminoglycoside (if allergic to penicillin)	• Sulbactam is highly active against *Acinetobacter* • Resistance rates in 2010: ampicillin-sulbactam (24%), cefoperazone-sulbactam (24%), imipenem (37%), gentamicin (32%), amikacin (25%), ciprofloxacin (50%) • For multidrug-resistant isolates: consult microbiologist or infectious disease physician
Clostridium difficile	P.O. metronidazole (404–405)	P.O. vancomycin (if metronidazole fails as documented microbiologically)	• Mild/moderate disease: clinical efficacy of metronidazole = vancomycin • Severe disease, ileus or toxic megacolon: I.V. metronidazole + P.O. vancomycin + consult surgeon • First recurrence: same as primary infection based on severity of disease • Multiple recurrence: consult microbiologist or infectious disease physician, options include vancomycin taper or faecal microbiota transplant (406)

	Drug of choice	Alternatives	Remarks
***Enterobacter cloacae* complex**	• P.O./I.V. levofloxacin/ ciprofloxacin for urinary tract infection • I.V. cefepime (± an aminoglycoside) for severe infection • I.V. piperacillin-tazobactam	• I.V. carbapenem (for severe infection and/or ESBL-producing strain)	• Cefepime is highly active in vitro against almost all *Enterobacter* isolates • Emergence of AmpC derepressed mutants emerge in 20–40% of infections treated with the second or third generation cephalosporins. Use of these agents for serious infections is not recommended • One study in HK found high prevalence of ESBL production among *E. hormaechei* (a member of the *E. cloacae* complex) (407) • Resistance rate in 2010: levofloxacin (8%), gentamicin (4%), amikacin (1%) • For multidrug-resistant isolates: consult microbiologist or infectious disease physician

	Drug of choice	Alternatives	Remarks
***E. coli* (ESBL-neg)**	• I.V./P.O. ampicillin-sulbactam or amoxicillin-clavulanate (add an aminoglycoside if rapid bactericidal action desirable on clinical grounds)	I.V./P.O. cefuroxime (if resistant to amoxicillin-clavulanate), add I.V./P.O. metronidazole (if mixed infection with anaerobes likely) • I.V. piperacillin-tazobactam + an aminoglycoside (if *P. aeruginosa* or *Acinetobacter* are co-pathogens)	
Haemophilus influenzae	• P.O. amoxicillin or P.O./I.V. ampicillin-sulbactam or amoxicillin-clavulanate or cefotaxime or ceftriaxone	• Fluoroquinolones (if allergic to penicillin)	• Amoxicillin-clavulanate also provides good coverage for *M. catarrhalis* and *S. pneumoniae*

	Drug of choice	Alternatives	Remarks
***Klebsiella pneumoniae* (ESBL-neg)**	• I.V./P.O. ampicillin-sulbactam or amoxicillin-clavulanate (add an aminoglycoside if rapid bactericidal action desirable on clinical grounds)	• I.V./P.O. cefuroxime (if resistant to amoxicillin-clavulanate), add I.V./P.O. metronidazole (if mixed infection with anaerobes likely) • I.V. piperacillin-tazobactam + an aminoglycoside (if *P. aeruginosa* or *Acinetobacter* are co-pathogens)	• Ampicillin-sulbactam less satisfactory because of poor inhibitory activity of sulbactam for SHV-1 ß-lactamase
***E. coli / K. pneumoniae* (ESBL-pos)**	• P.O. nitrofurantoin or P.O. amoxicillin-clavulanate (uncomplicated urinary tract infection and other mild infections)	• Carbapenem or I.V. β-lactam/β-lactamase inhibitor for bacteraemia or other serious infection	• Carbapenem has been shown to be effective clinically and is currently the ß-lactam agent of choice for serious infection by ESBL-pos *E. coli*/*Klebsiella* spp.

	Drug of choice	Alternatives	Remarks
Pseudomonas aeruginosa	I.V. piperacillin or ticarcillin-clavulanate or piperacillin-tazobactam + an aminoglycoside	• I.V. cefoperazone-sulbactam + an aminoglycoside (mixed infection with *Acinetobacter*) • I.V./P.O. levofloxacin/ ciprofloxacin + an aminoglycoside (if allergic to penicillin)	• Combination therapy recommended (for synergism) for all serious infection except for uncomplicated catheter-related bacteraemia • Piperacillin-tazobactam used instead of ceftazidime due to rapid rise in AmpC type and ESBL-producers in *Enterobacteriaceae* • For multidrug-resistant isolates: consult microbiologist or infectious disease physician
Methicillin-sensitive *S. aureus*	P.O./I.V. cloxacillin or amoxicillin-clavulanate or ampicillin-sulbactam or first generation cephalosporin	• I.V. cefazolin (if allergic to penicillin, but limited to those with minor allergy such as rash alone) • Clindamycin (if allergic to penicillin)	

	Drug of choice	Alternatives	Remarks
Methicillin-resistant *S. aureus*	I.V. vancomycin (bacteraemia or other invasive infections)	• I.V./P.O. linezolid or I.V. daptomycin if (1) vancomycin allergy - extensive rash, other than red-man syndrome develop after vancomycin, or (2) bacteraemia caused by MRSA with vancomycin ≥ 2 μg/mL	• Cotrimoxazole, fusidic acid or rifampicin are useful adjuncts for deep-seated infections (e.g. osteomyelitis) but these agents should not be administered as monotherapy • Most abscesses or uncomplicated skin and soft tissue infection caused by CA-MRSA could be treated with drainage and oral antibiotics with in vitro activities (e.g. clindamycin or cotrimoxazole) • Vancomycin intermediate *Staphylococcus aureus*/ vancomycin resistant *Staphylococcus aureus*: consult microbiologist or infectious disease physician
Mycoplasma pneumoniae	• P.O. doxycycline (or I.V. minocycline)	• P.O. azithromycin • I.V./P.O. levofloxacin or moxifloxacin	• Doxycycline preferred over azithromycin in view of increasing macrolide resistant *Mycoplasma pneumoniae* (379)

	Drug of choice	Alternatives	Remarks
Stenotrophomonas maltophilia	P.O./I.V. cotrimoxazole + I.V. ticarcillin-clavulanate	• I.V./P.O. cotrimoxazole + fluoroquinolone	• Cotrimoxazole + ticarcillin-clavulanate is synergistic in vitro. Cotrimoxazole is a key component in therapy • Combination therapy recommended for synergy and to prevent resistance • For cotrimoxazole-resistant strain, consult microbiologist or infectious disease physician
Streptococcus pneumoniae (for infection outside the central nervous system)	• Penicillin-sensitive: I.V. penicillin G (4–8 million unit/day, q6h) • Penicillin-intermediate: I.V. penicillin G (high dose, 12–18 million unit/day, q4h)[1] • Penicillin-resistant: I.V. cefotaxime or ceftriaxone	• ß-lactam/ß-lactamase inhibitor combination with the exception of cefoperazone-sulbactam (for mixed infections) • P.O./I.V. levofloxacin or P.O./I.V. moxifloxacin (if allergic to penicillin) for non-meningeal infections and penicillin-sensitive strains	• Most pneumococcal pneumonia can be treated with high dose amoxicillin or high dose amoxicillin-clavulanate • For pure pneumococcal infection, penicillin G instead of amoxicillin-clavulanate is preferred, switch therefore recommended • >70% resistant to erythromycin. Cross-resistance to clindamycin is very common • Resistance to erythromycin = resistance to other newer macrolides (clarithromycin, azithromycin)

	Drug of choice	Alternatives	Remarks
Streptococcus pneumoniae (for central nervous system infection)	• Penicillin-sensitive (MIC ≤ 0.06 µg/mL): I.V. penicillin G (18–24 million unit/day, q4h) or I.V. ampicillin 2 g q4h • Penicillin-resistant (MIC ≥ 0.12 µg/mL) and third-generation cephalosporin (MIC <1 µg/mL): I.V. cefotaxime 2 g q4h or I.V. ceftriaxone 2 g q12h • Penicillin-resistant (MIC ≥ 0.12 µg/mL) and third-generation cephalosporin (MIC ≥ 1 µg/mL): I.V. vancomycin plus I.V. cefotaxime 2 g q4h or ceftriaxone 2 g q12h		• MIC (meningitis) breakpoints for penicillin, ceftriaxone and cefotaxime to be used here • In *S. pneumoniae*, cross resistance between penicillin and ceftriaxone/cefotaxime is common (391,408). Local data indicates that approximately half of the penicillin-resistant (meningitis) isolates are intermediate/resistant (meningitis) to cefotaxime

Note:

[1] CLSI MIC (µg/mL) breakpoints for penicillin G: sensitive ≤ 0.06; intermediate 0.12–1; resistant ≥ 2. These breakpoints were decided mainly for the relevance on meningitis. For pneumococcal pneumonia, pharmacokinetic/dynamic data indicates that isolates with MIC of up to 1–2 µg/mL should be considered 'sensitive' to appropriate dose of penicillin, ampicillin and amoxicillin.

Part VI: Guidelines for surgical prophylaxis

General principles in surgical prophylaxis

1. **Duration of prophylaxis**: The duration of antimicrobial prophylaxis should not routinely exceed 24 hours (1 dose at induction and 2 more doses postoperatively, i.e. 3 doses in total). There is wide consensus that only a single dose of I.V. antimicrobial agent is needed for surgical prophylaxis in the great majority of cases including orthopaedic surgery with prosthesis. Published evidence shows that antimicrobial prophylaxis after wound closure is unnecessary even in the presence of a drain. Most studies comparing single- with multiple-dose prophylaxis have not shown benefit of additional doses.
2. **Timing**: For many prophylactic antimicrobial agents, the administration of an initial dose should be given within 30 minutes before incision (coinciding with the induction of anaesthesia) to achieve a bactericidal serum and tissue concentration at the time of initial incision. This can be facilitated by having the anaesthesiologist administer the drug in the operating room at induction.
3. **Antimicrobial dosing**: The dose should be adequate based on the patient's body weight. An additional dose of antimicrobial agent should be given (intraoperatively) if the operation is still continuing after two half-lives of the initial dose or massive intraoperative blood losses occur.

References: (409–491)

Table 6.1 Suggested initial dose and time to re-dose for selected antimicrobial agents used for surgical prophylaxis

Antimicrobial agent	Standard[1] I.V. dose	Recommended re-dosing interval (hour)
Cefazolin	1–2 g	2–5
Cefuroxime	1.5 g	3–4
Clindamycin	600–900 mg	3–6
Amoxicillin-clavulanate	1.2 g	2–3
Ampicillin-sulbactam	1.5 g	2–3
Metronidazole	500 mg	6–8
Vancomycin	1 g infuse over 60 min	6–12

[1]In patient with normal renal function and not morbidly obese.

Table 6.2 Antimicrobial prophylaxis in clean operations

Type of operation	Indications	Recommended drugs[1]
Cardiac[2]	• Prosthetic valve • Coronary artery bypass • Pacemaker implant • Open heart surgery	• I.V. cefazolin 1 g[3] then every 4 hours **Note:** The duration of antimicrobial prophylaxis should not be longer than 48 hours.
Thoracic[2]	• Pulmonary resection • Closed tube thoracostomy for chest trauma	• I.V. cefazolin 1 g[3] OR • I.V. cefuroxime 1.5 g OR • I.V. amoxicillin-clavulanate 1.2 g[4]
Vascular	• Abdominal aortic operations • Prosthesis • Groin incision • Lower extremity amputation for ischaemia	• I.V. cefazolin 1 g[3] OR • I.V. cefuroxime 1.5 g OR • I.V. amoxicillin-clavulanate 1.2 g[4]
Neurosurgery[2]	• Craniotomy • Ventriculoperitoneal shunt • Implantation of intrathecal pump (492)	• I.V. cefazolin 1 g[3] OR • I.V. cefuroxime 1.5 g
	• Re-exploration or microsurgery	• I.V. cefuroxime 1.5 g OR • I.V. amoxicillin-clavulanate 1.2 g[4]

Type of operation	Indications	Recommended drugs[1]
Orthopaedic & Traumatology[2]	• Total joint replacement with prosthesis • Internal fixation of closed fractures	• I.V. cefazolin 1 g[3] OR • I.V. cefuroxime 1.5 g **Note:** Antimicrobial agents should be completely infused before inflating the tourniquet if applied.
	• Prophylactic antibiotic is indicated for all open fractures and should be given as soon as possible[5] • Wound cultures and sensitivity testing are useful for informing subsequent choice of antimicrobials (493–495) • For Gustilo type III tibial fractures, prophylaxis given within 1 hr was associated with reduced infection risk (496)	• I.V. amoxicillin-clavulanate ± gentamicin[5] OR • I.V. ceftriaxone 2 g ± I.V. penicillin G[5] OR • other third generation cephalosporin ± I.V. penicillin G[5] **Note:** The duration of prophylactic antibiotic for open fractures depends on the classification: 24 hr (for Gustilo type I and II open fractures) and up to 72 hr (for Gustilo type III open fractures). Antibiotics should not be given for more than 24 hr after soft tissue coverage of the wound, whichever occurs first.
Thyroid & parathyroid glands		• Antimicrobial prophylaxis is not indicated

Table 6.3 Antimicrobial prophylaxis in clean-contaminated operations

Type of operation	Indications	Recommended drugs[1]
Oral-pharyngeal/ nasal	• Tonsillectomy • Maxillofacial • Rhinoplasty • Turbinate/septoplasty	• I.V. amoxicillin-clavulanate 1.2 g[4] OR If *Pseudomonas* is suspected: • I.V. amoxicillin-clavulanate 1.2 g[4] + I.V. gentamicin OR • I.V. amoxicillin-clavulanate 1.2 g[4] + I.V. ceftazidime 1–2 g
Ear	• Myringotomy • Tympanostomy tube insertion	• Quinolone or Sofradex eardrop
Upper gastro-intestinal tract	Gastro-duodenal (high risk): • Obstruction • Haemorrhage • Gastric ulcer • Malignancy • H_2 blocker • Proton pump inhibitor • Morbid obesity • Gastric bypass • Percutaneous endoscopic gastrostomy	• I.V. cefuroxime 1.5 g OR • I.V. amoxicillin-clavulanate 1.2 g[4]
	• Oesophageal operation with manipulation of pharynx	• I.V. cefuroxime 1.5 g OR • I.V. cefazolin 1 g[3] ± metronidazole 500 mg

Type of operation	Indications	Recommended drugs[1]
Hepato-biliary system Laparoscopic gall bladder surgery	High risk: • Age more than 70 years • Acute cholecystitis/ pancreatitis • Obstructive jaundice • Common bile duct stones • Morbid obesity • Intraoperative cholangiogram • Bile spillage • Pregnancy • Immunosuppression • Insertion of prosthetic devices • Laparoscopic converts to laparotomy	• I.V. amoxicillin-clavulanate 1.2 g[4] OR • I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg
Endoscopic retrograde cholangio-pancreatography (ERCP)	• Biliary obstruction	• P.O. ciprofloxacin 500–750 mg 2 hours prior to procedure OR • I.V. piperacillin-tazobactam 4.5 g 1 hour prior to procedure
Appendectomy		• I.V. amoxicillin-clavulanate 1.2 g[4] OR • I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg
Colorectal	• Most procedures require parenteral ± oral prophylaxis (497–500)	*Parenteral* • I.V. amoxicillin-clavulanate 1.2 g[4] OR • I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg *Oral* • P.O. neomycin and erythromycin base 1 g each t.d.s. the day before operation

Type of operation	Indications	Recommended drugs[1]
Abdominal/ vaginal hysterectomy		• I.V. cefazolin 1 g[3] OR When vaginal wound is present: • I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg OR • I.V. amoxicillin-clavulanate 1.2 g[4]
Caesarean section (502)	All caesarean sections are indicated for antibiotic prophylaxis (503)	• I.V. cefazolin 1 g[3] OR When vaginal wound is present: • I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg OR • I.V. amoxicillin-clavulanate 1.2 g[4] **Note:** For caesarean section, the initial dose of antimicrobial agents should be given before surgical incision instead of after clamping the umbilical cord (501).
Abortion	Antimicrobial prophylaxis should be based on individual clinical condition and local epidemiology (504–505)	• Refer to footnote 6
Urology[7]	• Significant bacteriuria • Transurethral resection of the prostate (TURP), transurethral resection of bladder tumour (TURBT) • Stone operations • Nephrectomy • Total cystectomy	• Treat according to mid-stream urine culture result prior to elective procedures

Type of operation	Indications	Recommended drugs[1]
Hernia repair[8]	• Non mesh hernia repair	Antimicrobial prophylaxis is not indicated
	• Adult hernia mesh repair	• I.V. cefazolin 1 g[3] OR • I.V. cefuroxime 1.5 g
Breast cancer surgery[8] (506)		• I.V. cefazolin 1 g[3] OR • I.V. cefuroxime 1.5 g

Table 6.4 Antimicrobial prophylaxis in contaminated-infected operations

Type of operation	Indications	Recommended drugs[1]
Ruptured viscus[9]	For treatment of established infection	• I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg OR • I.V. amoxicillin-clavulanate 1.2 g[4] (Therapy is often continued for about 5 days)
Bite wound[9]	For treatment of established infection	• I.V. amoxicillin-clavulanate 1.2g[4] OR • P.O. amoxicillin-clavulanate 1g
Traumatic wound[9]	For treatment of established infection	• I.V. cefazolin 1–2 g[3] OR • I.V. cefuroxime 1.5 g OR • I.V. amoxicillin-clavulanate 1.2 g[4]

Footnotes for Tables 6.2–6.4:

[1]The dose of antimicrobial agents recommended in the guidelines is based on adult patient with normal renal function. Special attention should be paid to patient with renal impairment, on renal replacement therapy, or if there is potential drug-drug interaction. Consultation to clinical microbiologist, infectious disease physician and clinical pharmacist is required in complicated cases.

[2]For hospitals or units with a high incidence of postoperative wound infections by MRSA or methicillin-resistant *Staphylococcus epidermidis*, screening for MRSA may be indicated to identify patients for additional preoperative measures such as chlorhexidine bath, 2% mupirocin nasal ointment [Bactroban Nasal] and/or the use of vancomycin as preoperative prophylaxis. Evidence is strongest for cardiothoracic and orthopaedic surgery with implantation (507–508).

[3]Give cefazolin 2 g for patients with body weight greater than 80 kg. For patients allergic to cefazolin, vancomycin 1 g infused over 1 hour should be given after premedication with an antihistamine. Rapid I.V. administration of vancomycin may cause hypotension, which could be especially dangerous during induction of anaesthesia.

[4]Amoxicillin-clavulanate and ampicillin-sulbactam are similar in spectrum coverage and centres may choose to use ampicillin-sulbactam.

[5]Choice of agent(s) depends on the type of open fractures by the Gustilo classification and the likely organisms contaminating the wound. In general, prophylactic antibiotic should be directed against Gram-positive organisms for Gustilo type I and II open fractures; additional Gram-negative coverage should be added for Gustilo type III open fractures. In the setting of faecal or potential clostrial contamination (e.g. soil exposure), a penicillin should be included in the regimen.

[6]The optimal antibiotic and dosing regimens for abortion are unclear. The antimicrobial prophylaxis for abortion stated in Royal College of Obstetricians and Gynaecologists (United Kingdom) (422) clinical guidelines is Level C recommendations and may be suitable. They include: metronidazole 1 g rectally at the time of abortion plus doxycycline 100 mg orally b.d. for 7 days, commencing on the day of abortion; OR metronidazole 1 g rectally at the time of abortion plus azithromycin 1 g orally on the day of abortion.

[7]For transrectal ultrasound (TRUS)-guided biopsy of the prostate, prophylactic regimen is evolving because of increasing fluoroquinolone resistance in *E. coli.* (509). If a fluoroquinolone is used, administer the drug 1–2 hours before the procedure to allow maximum tissue penetration (510). Ensure adequate drug level in the body by giving a full standard dose (500 mg to 750 mg for levofloxacin and ciprofloxacin). If post-biopsy infection develops, antibiotic treatment regimen should include coverage against ESBL-producing organisms given the high prevalence of this resistance mechanism in Hong Kong (Table 1.3).

[8]Amoxicillin-clavulanate may be used if the operation is such that anaerobic coverage is needed, such as in diabetic foot, hernia repair with bowel strangulation or incarcerated/ strangulated hernia or mastectomy with implant or foreign body.

[9]Antimicrobial agents should be considered postoperatively for operations with suppurative, ruptured and gangrenous conditions.

Part VII: Cost and recommended dosage of commonly - used antimicrobial agents

Table 7.1 Preparation and recommended dosing regimens for antibiotics

Agents	Supply source (brand/generic)	Dosage form (unit cost, HK$)	Usual adult regimen (daily dose, route, dosing interval)[1]
Amikacin (163) (Amikin)	Brand	250 mg vial ($41.6) 500 mg vial ($60.6)	I.V. 15 mg/kg (750 mg)[2] q24h or 7.5 mg/kg q12h (max 1.5 g/day)
Amoxicillin	Generic	250 mg cap. ($0.11) 125 mg/5 mL syr. ($0.18/mL)	P.O. 500 mg t.d.s.
Amoxicillin-clavulanate (Augmentin)	Brand / Generic	600 mg vial ($14.5) 1.2 g vial ($8.07) 375 mg tab. ($0.88) 1 g tab. ($ 1.31) 156 mg/5 mL syr. ($0.11/mL) 457 mg/5 mL syr. ($0.36/mL)	I.V. 1.2 g q8h P.O. 375 mg t.d.s. P.O. 1 g b.d. P.O. 312 mg (10 mL) t.d.s. (syr.) P.O. 914 mg (10 mL) b.d. (syr.)
Ampicillin	Generic	500 mg vial ($2.22) 250 mg cap. ($0.28) 500 mg cap. ($0.48) 125 mg/5 mL syr. ($0.44/mL)	I.V. 1 g q6h P.O. 250–500 mg q.i.d.
Ampicillin-sulbactam (Unasyn)	Brand / Generic	750 mg vial ($8.20) 375 mg tab. ($6.92) 250 mg/5 mL syr. ($1.55/mL)	I.V. 1.5–3 g q6h (max 12 g/day) P.O. 375–750 mg b.d.
Azithromycin (Zithromax)	Brand / Generic	500 mg vial ($109) 250 mg tab. ($1.78) 250 mg cap. ($13.1) 200 mg/5 mL syr. ($1.39/mL)	I.V. 500 mg q24h P.O. 500 mg on first day then 250 mg once daily
Cefazolin	Generic	1 g vial ($2.74)	I.V. 1 g q8h
Cefepime (Maxipime)	Brand	1 g vial ($40.2) 2 g vial ($204)	I.V. 1–2 g q12h (max 6 g/day)
Cefoperazone-sulbactam (Sulperazon)	Generic	1 g vial ($5.60)	I.V. 1–2 g q12h (max 8 g/day)

Agents	Supply source (brand/generic)	Dosage form (unit cost, HK$)	Usual adult regimen (daily dose, route, dosing interval)[1]
Ceftazidime (Fortum)	Brand / Generic	500 mg vial ($10.0) 1 g vial ($12.1) 2 g vial ($209)	I.V. 1–2 g q8h (max 6 g/day)
Cefotaxime (Claforan)	Generic	1 g vial ($3.99)	I.V. 1 g q6–8h (max 12 g/day)
Ceftaroline (Zinforo)	Brand	600 mg vial ($344)	I.V. 600 mg q12h
Ceftriaxone (Rocephin)	Brand / Generic	250 mg vial for I.M. injection ($80.8) 1 g vial for I.M. or I.V. injection ($4.85)	I.M. 250 mg once I.M./I.V. 1–2 g/day q12–24h (max 4 g/day)
Cefuroxime (Zinacef)	Brand / Generic	250 mg vial ($14.0) 750 mg vial ($2.94)	I.V. 750 mg–1.5 g q8h (max 6 g/day)
Cefuroxime-axetil (Zinnat)	Brand / Generic	125 mg tab. ($4.01) 250 mg tab. ($0.77) 125 mg/5 mL suspension ($1.24/mL)	P.O. 250–500 mg b.d.
Cephalexin	Generic	250 mg cap. ($0.39)	P.O. 250–500 mg q.i.d.
Ciprofloxacin (Ciproxin)	Brand / Generic	200 mg vial ($60.4) 400 mg vial ($677) 250 mg tab. ($0.41)	I.V. 200–400 mg q12h P.O. 500–750 mg b.d.
Clarithromycin (Klacid)	Brand / Generic	500 mg vial ($118) 250 mg tab. ($0.99) 500 mg tab. ($1.81) 500 mg modified release tab. ($28.4) 125 mg/5 mL suspension ($0.52/mL)	I.V. 500 mg q12h P.O. 250–500 mg b.d.
Clindamycin (Dalacin C)	Brand / Generic	300 mg vial ($9.51) 300 mg ampoule ($9.26) 150 mg cap. ($3.15)	I.V. 600–900 mg q8h (max 4.8 g/day) P.O. 150–450 mg q.i.d.
Cloxacillin	Generic	500 mg vial ($4.14) 250 mg cap. ($0.32) 500 mg cap. ($0.39)	I.V. 500 mg–1 g q6h (max 8 g/day) P.O. 500 mg q.i.d.
Colistin (Colomycin)	Brand	1 million unit vial ($153)	I.V. 1–2 million unit q8h (max 6 million unit/day)

Agents	Supply source (brand/generic)	Dosage form (unit cost, HK$)	Usual adult regimen (daily dose, route, dosing interval)[1]
Daptomycin (Cubicin)	Brand	500 mg vial ($1,389)	I.V. 4 mg/kg (complicated skin and skin structure infections) or 6 mg/kg (*S. aureus* bloodstream infection) q24h
Doxycycline (Vibramycin)	Brand	100 mg tab. ($1.33)	P.O. 100 mg b.d.
Ertapenem (Invanz)	Brand	1 g vial ($230)	I.V. 1 g q24h
Erythromycin (Erythrocin)	Generic	500 mg vial ($583)	I.V. 500 mg q6h (max 4 g/day)
		250 mg tab. ($0.86)	P.O. (tab.) 250–500 mg q.i.d.
		200 mg/5 mL suspension ($0.21/mL)	P.O. (suspension) 400–800 mg q.i.d
Flucloxacillin	Generic	125 mg/5 mL solution ($0.14/mL)	P.O. 250–500 mg q.i.d.
Fosfomycin	Fosfocina[3]	4 g vial ($478)	I.V. 8–12 g/day (100–200 mg/kg/day)
	Monurol	3 g sachet (not in HA formulary) ($30.3)	P.O. 3 g sachet for 1 dose for uncomplicated urinary tract infection
Gentamicin (163)	Generic	80 mg ampoule ($3.72)	I.V. 3.5 mg/kg (180 mg)[2] q24h or 1.2 mg/kg q8h
Imipenem-cilastatin (Tienam)	Brand	500 mg vial ($32.2)	I.V. 500 mg q6h (max 4 g/day)
Levofloxacin (Cravit)	Generic	500 mg infusion bottle ($58.4)	I.V. 500 mg q24h
		100 mg tab. ($0.89)	P.O. 500 mg once daily
		250 mg tab. ($0.66)	
Linezolid (Zyvox)	Brand	600 mg infusion bag ($480)	I.V. 600 mg q12h
		600 mg tab. ($455)	P.O. 600 mg b.d.
		100 mg/5 mL suspension ($15.1/mL)	
Meropenem (Meronem)	Generic	500 mg vial ($19.5)	I.V. 1 g q8h
		1g vial ($32.8)	

Agents	Supply source (brand/generic)	Dosage form (unit cost, HK$)	Usual adult regimen (daily dose, route, dosing interval)[1]
Metronidazole (Flagyl)	Generic	500 mg vial ($4.53) 200 mg tab. ($0.12) 200 mg/5 mL syr. ($1.36/mL)	I.V. 500 mg q8h P.O. 400 mg t.d.s.
Minocycline	Generic	100 mg vial ($86.3) 100 mg cap. ($5.21) 50 mg cap. ($1.98)	I.V. 200 mg loading then 100 mg q12h P.O. 200 mg loading then 100 mg b.d.
Moxifloxacin (Avelox)	Brand	400 mg infusion bottle ($312) 400 mg tab. ($34.4)	I.V. 400 mg q24h P.O. 400 mg once daily
Penicillin G	Generic	1 million unit vial ($6.56)	I.V. 1–2 million unit q4–6h (max 24 million unit/day)
Piperacillin	Generic	4 g vial ($24.7)	I.V. 4 g q6–8h
Piperacillin-tazobactam (Tazocin)	Generic	4.5 g vial ($18.9)	I.V. 4.5 g q6–8h
Teicoplanin (Targocid)	Brand	200 mg vial ($473)	I.V. 6 mg/kg (400 mg) on first day, followed by 3 mg/kg (200 mg) q24h
Ticarcillin-clavulanate (Timentin)	Generic	3.2 g vial ($45.7)	I.V. 3.2 g q4–6h (max 19.2 g/day)
Tigecycline (Tygacil)	Brand	50 mg vial ($476)	I.V. 100 mg loading then 50 mg q12h
Tobramycin (163)	Generic	80 mg vial ($76.7)	I.V. 3.5 mg/kg (180 mg)[2] q24h or 1.2 mg/kg q8h (max 5 mg/kg/day)
Vancomycin (Vancocin)	Generic	500 mg vial ($13.6) 25 mg/mL oral solution (compounding supply from pharmacy)	I.V. 1 g q12h or I.V. 500 mg q6h (i.e. 30 mg/kg/day) P.O. 125 mg q.i.d. (for refractory *C. difficile* colitis)

Note: Unit cost of each preparation updated as of June 2016 in HA.

1 Dosage for a 70 kg person with normal renal function. Dosage modification may be necessary for (i) the elderly; (ii) the very obese individuals (in whom the distribution volume of water-soluble drugs may be smaller than expected from body mass); (iii) those with renal failure and/or (iv) liver failure.

[2] Dosage for a typical 50 kg person given. Once daily administration of aminoglycoside is appropriate for most infections with the possible exceptions of neutropenic fever, infective endocarditis and in the presence of severe renal failure.

[3] Named patient basis only.

Table 7.2 Cost comparison of selected I.V. and P.O. antibiotics

Antibiotics	Usual dosage	Cost (HK$/day)
Aminoglycosides		
I.V. gentamicin[1] (3.5 mg/kg/day)	180 mg q24h	11.2
I.V. tobramycin[1] (3.5 mg/kg/day)	180 mg q24h	230
I.V. amikacin[1] (15 mg/kg/day)	750 mg q24h	102
Penicillins		
I.V. ampicillin	500 mg –1 g q6h	9–18
I.V. cloxacillin	500 mg –1 g q6h	17–33
I.V. amoxillin-clavulanate	1.2 g q8h	24
I.V. ampicillin-sulbactam	1.5 g q6h	66
I.V. ticarcillin-clavulanate	3.2 g q6h	183
I.V. piperacillin	4 g q8h	74
I.V. piperacillin-tazobactam	4.5 g q8h	57
	(4.5 g q6h)	(76)
Cephalosporins		
I.V. cefuroxime	750 mg q8h	9
I.V. cefazolin	1 g q8h	8
I.V. ceftriaxone	1 g q12h	10
I.V. cefotaxime	1 g q8h	12
I.V. cefoperazone-sulbactam (Sulperazon)	1 g q12h	11
I.V. cefepime	1 g q12h	80
I.V. ceftazidime	1 g q8h	36
I.V. ceftaroline	600 mg q12h	688
Carbapenems		
I.V. meropenem	500 mg q8h	59
	(1 g q8h)	(98)
I.V. imipenem-cilastatin	500 mg q6h	129
I.V. ertapenem	1 g q24h	230
Fluoroquinolones		
I.V. moxifloxacin	400 mg q24h	312
P.O. moxifloxacin	400 mg once daily	34
I.V. levofloxacin	500 mg q24h	58
P.O. levofloxacin	500 mg once daily	1
I.V. ciprofloxacin	400 mg q12h	1,354
P.O. ciprofloxacin	500 mg b.d.	2

Antibiotics	Usual dosage	Cost (HK$/day)
Macrolides		
I.V. clarithromycin	500 mg q12h	236
I.V. azithromycin	500 mg q24h	109
I.V. erythromycin	500 mg q6h	2,332
Others		
I.V. metronidazole	500 mg q8h	14
I.V. vancomycin	1 g q12h	54
I.V. linezolid	600 mg q12h	960
(P.O. linezolid)	(600 mg b.d.)	(910)

Note: Approximate cost updated as of June 2016 in HA.

[1] Dosage for a typical 50 kg person.

Table 7.3 Cost comparison of systemic antifungal agents

Antifungal agent	Usual dosage	Cost (HK$/day)
P.O. itraconazole (capsule)	200 mg b.d.	9
P.O. itraconazole (solution)	200 mg b.d.	285
I.V. itraconazole	200 mg q12h	1,473
P.O. fluconazole (capsule)	100–400 mg once daily	3–13
P.O. fluconazole (suspension)	100–400 mg once daily	81–323
I.V. fluconazole	200–400 mg q24h	82–165
P.O. posaconazole (suspension)	Prophylaxis: 200 mg t.d.s.	 564
P.O. voriconazole	200 mg b.d.	889
I.V. voriconazole[1]	Loading 6 mg/kg (300 mg) q12h (Day 1) Maintenance 4 mg/kg (200 mg) q12h	1,822–3,644
I.V. anidulafungin	Candidaemia: Loading 200 mg (Day 1) Maintenance 100 mg q24h Oesophageal candidiasis: Loading 100 mg (Day 1) Maintenance 50 mg q24h	 768–1,535 768
I.V. micafungin	Prophylaxis in haematopoietic stem cell transplantation (HSCT): 50 mg q24h Candidaemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses: 100 mg q24h Oesophageal candidiasis: 150 mg q24h	 321 642 964
I.V. caspofungin	Invasive aspergillosis: Loading 70 mg (Day 1) Maintenance 50 mg q24h	 2,000 (70 mg) 2,975 (50 mg)
I.V. amphotericin B (1 mg/kg/day)[1]	50 mg q24h	197
I.V. liposomal amphotericin B (3 mg/kg/day)[1]	150 mg q24h	5,045

Note: Approximate cost updated as of June 2016 in HA.

[1] Dosage for a typical 50 kg person.

Table 7.4 Dosage of antimicrobial agents for central nervous system infections

Antibiotics[1]	Recommended doses	Cost (HK$/day)
I.V. cefotaxime	2 g q4h	48
I.V. ceftriaxone	2 g q12h	19
I.V. cefepime	2 g q8h	612
I.V. meropenem	2 g q8h	197
I.V. ampicillin	2 g q4h	53
I.V. penicillin G	3–4 million unit q4h	118–157
I.V. metronidazole	500 mg q6h	18
I.V. vancomycin	1 g q12h	54
P.O. rifampicin[2]	600 mg once daily	1

Note:

[1] Dosage for a typical body weight ≥70 kg and normal renal function.

[2] Rifampicin should only be used in combination with another antibiotic for meningitis by certain bacteria (e.g. multi-resistant *Streptococcus pneumoniae* or MRSA) with documented sensitivity in susceptibility testing.

Table 7.5 Intra-peritoneal antibiotic dosing recommendations for patients with continuous ambulatory peritoneal dialysis peritonitis

Antibiotics	**Intermittent dosing (once daily)**[1] (Add drug into 1 bag/day unless otherwise specified) (511)
Aminoglycosides	
Amikacin	2 mg/kg
Gentamicin	0.6 mg/kg
Tobramycin	0.6 mg/kg
Cephalosporins	
Cefazolin	15 mg/kg
Cefepime	1 g
Ceftazidime	1–1.5 g
Others	
Ampicillin-sulbactam	2 g q12h
Imipenem-cilastatin	1 g q12h

Note:

[1] In patients with residual renal function, the drug dose should be empirically increased by 25%.

Part VIII: Other issues

8.1. Management of penicillin allergy

8.1.1 Background

1. Studies have shown that 70–90% of patients who gave a history of penicillin allergy could actually tolerate penicillin.
2. It has been estimated that less than 15% of patients with penicillin allergy are still allergic ten years after their last reaction.
3. There is extensive cross-reactivity between drugs in the penicillin family. Patients who are allergic to one penicillin drug must therefore avoid other members of the family.
4. On the other hand, unnecessary avoidance of penicillin in patients who are not actually allergic would result in extra cost and overuse of drugs that should be reserved for treating drug-resistant organisms, such as vancomycin.
5. Certain penicillin drugs are commonly associated with drug rashes. These reactions, although usually mild, can nevertheless result in patient dissatisfaction.
6. Skin testing with major and minor determinants of penicillin, together with benzylpenicillin and amoxicillin, as well as other suspected ß-lactams, can reliably rule out IgE-mediated penicillin allergy.
7. Patients with IgE-mediated ß-lactam allergy can be successfully desensitised just prior to starting treatment.

8.1.2 Dealing with patients with a remote history of penicillin allergy

1. Determine the date of the last reaction, the type of reaction, the timing of the reaction and other extenuating circumstances, such as infectious mononucleosis and other infections (Figure 8.1).
2. Patients who give a history consistent with severe drug allergy, including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug hypersensitivity syndrome must not be given drugs from the same family again.
3. Patients who give a history consistent with an IgE-mediated reaction (urticaria, angioedema, anaphylaxis) should use an alternative agent (see 8.1.5 below). If penicillin is strongly indicated, skin testing can be performed to assess the risk of anaphylaxis (Figure 8.2). If skin testing is not available, rapid oral desensitisation can be performed (Table 8.1) with informed consent just prior to drug administration.
4. Serum specific IgE tests of ß-lactam drugs have such a low sensitivity that they only have a complementary role.

5. Basophil activation tests have a better sensitivity but they are not yet available for clinical service in HK (512).
6. In patients who give a history of minor drug rash, penicillin is not absolutely contraindicated. However, the physician should first consider using an alternative agent to avoid patient dissatisfaction. Under circumstances where the use of penicillin is clinically desirable, the treating physician should carefully explain the rationale and obtain the patient's informed consent. This should be recorded in the patient's medical record. It is also prudent to give a test dose of $1/10^{th}$ of the treatment dose first and observed for one hour, as the history might not be completely reliable in excluding IgE-mediated reactions.

8.1.3 Dealing with patients with a definite history of IgE-mediated penicillin allergy

1. Patient who had reactions that were medically verified as IgE-mediated should use an alternative agent.
2. If penicillin is strongly indicated, desensitisation should be carried out with informed consent just prior to drug administration.

8.1.4 Dealing with patients with a history of cephalosporin allergy

1. Cephalosporins generally have a much lower risk of allergic reactions compared to penicillin because their ß-lactam ring is rapidly broken down in vivo.
2. Cross-reactivity tends to occur between cephalosporins with similar side-chains. It is therefore possible to substitute a cephalosporin with side-chains different from that of the offending drug (Table 8.2).
3. Since cephalosporin allergy is due to side-chain reactivity, skin testing with the classic penicillin agents, together with the native drug can reliably predict the likelihood of IgE-mediated reactions.
4. Therefore, if the patient is allergic to a clearly identified cephalosporin and no satisfactory alternative is available, the physician can choose another cephalosporin with different side-chains. Skin testing should be performed with the classic pencillin agents and the drug to rule out the risk of IgE-mediated reaction. The drug can then be administered after obtaining the patient's informed consent.

8.1.5 Choosing an alternative drug for patients with ß-lactam allergy

1. As cephalosporins have a spectrum of antimicrobial activity similar to penicillin, they are actually good alternatives for patients with penicillin allergy.
2. Unfortunately, product inserts often list penicillin allergy as a contraindication to the use of cephalosporins. This information was based on early experiences with first generation cephalosporins and is no longer up to date. However, there are medico-legal implications when using cephalosporins in patients with penicillin allergy.
3. Second, third and fourth generation cephalosporins have negligible cross-reactivity with penicillin and are good alternatives, as long as one chooses agents that do not share similar side-chains with penicillin G, ampicillin or amoxicillin (Table 8.2). These drugs should be given by graded challenge after a negative skin test with this cephalosporin.
4. Patients with penicillin allergy have a higher risk of becoming allergic to any drug in general. This fact should be communicated to the patient and the rationale for using the alternative agent explained. Informed consent should be obtained and recorded in the medical record.
5. Carbapenems can also be safely used in patients with penicillin and cephalosporin allergy if clinically indicated.
6. Macrolides, fluoroquinolones, lincomycins and aminoglycosides do not cross-react with ß-lactams.
7. Vancomycin should only be considered as a substitute if clinical circumstances dictate its use, i.e. MRSA, *Enterococcus*, etc..

Table 8.1 Oral ß-lactam desensitisation protocol[1]

Dose	Concentration (mg/mL)	Volume (mL)	Time	Reaction
1	0.1	0.3	0:00	
2	0.1	0.6	0:15	
3	0.1	1.2	0:30	
4	0.1	2.5	0:45	
5	0.1	5	1:00	
6	1	1	1:15	
7	1	2	1:30	
8	1	4	1:45	
9	10	0.8	2:00	
10	10	1.6	2:15	
11	10	3.2	2:30	
12	10	6.4	2:45	
13	100	1.2	3:00	
14	100	2.5	3:15	

1. Prepare stock solution of ß-lactam drug that you wish to use at 100 mg/mL.
2. Make serial dilutions at 10 mg/mL, 1 mg/mL, 0.1 mg/mL.
3. Administer doses at 15-minute intervals.
4. Have epinephrine 1:1,000 on stand-by at bedside.
5. Once successfully desensitised, begin treatment immediately.
6. To maintain desensitised state, patient must not interrupt treatment for more than 2 days. Otherwise, patient would need to be desensitised again.

Note:

[1]Reference: (513)

Table 8.2 Cross-reacting side chains between ß-lactam antibiotics

	Amoxicillin	Ampicillin	Cefaclor	Cefadroxil	Cefepime	Cefoperazone	Cefotaxime	Cefoxitin	Cefpodoxime	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin	Cephaloridine	Cephalothin	Cephradine	Penicillin G
Amoxicillin		6	6/7	6/7										6/7			6/7	
Ampicillin	6		6/7	6/7										6/7			6/7	
Cefaclor	6/7	6/7		7										7			7	
Cefadroxil	6/7	6/7	7											3,7			3,7	
Cefepime							7		7			7						
Cefoperazone																		
Cefotaxime					7				7			7				3		
Cefoxitin													3		7	7		6/7
Cefpodoxime					7		7					7						
Ceftazidime																		
Ceftibuten																		
Ceftriaxone					7		7		7									
Cefuroxime								3										
Cephalexin	6/7	6/7	7	3,7													3,7	
Cephaloridine								7								7		6/7
Cephalothin							3	7							7			6/7
Cephradine	6/7	6/7	7	3,7										3,7				
Penicillin G								6/7							6/7	6/7		

Numbers denote position of side chains: **3**, similiarity at the cephalosporin 3-position side chain; **7**, similarity at the cephalosporin 7-position side chain; **6/7**, similarity at the penicillin 6-position side chain and the cephalosporin 7-position side chain.
Each number in the matrix indicates side-chain similarity between two drugs. Cross-allergenicity is expected between each similar pair. For example, a patient allergic to amoxicillin would very likely manifest an allergic reaction to ampicillin, cefadroxil, cefaclor, cephalexin, and cephradine. However, the patient would not be expected to exhibit an allergic response to cefepime, cefoperazone, cefotaxime, etc., unless he/she was also allergic to another cephalosporin or penicillin with a similar side chain to the reference drug.

Reference: (514)

Table 8.3 Risk of cross-reactivity between different ß-lactams

Allergic to	Drug of concern	Risk of cross-reactivity
Cephalosporin	Penicillin	8.3%–25.5% in two series (515–516) *Cephalosporin with structures similar or identical to penicillin have 3-fold increase in risk
	Carbapenems	Imipenem 2% and meropenem 1% in one series
Penicillin	Cephalosporins	10.9% with most involving cephalothin and cefamandole (517)
	Carbapenems	Meropenem 0.9%, imipenem 0.9% (518–520)
	All first generation cephalosporins	Odds ratio: first generation cephalosporins 4.2, second generation cephalosporins 1.1 and third generation cephalosporins 0.8 (521)
	Cephalexin	31% in one series with 16 patients (522)
Amoxicillin	Cefadroxil	38% (cefadroxil has identical side chain to amoxicillin) (523)
	Cefamandole	0% for 21 patients (different side chain to amoxicillin) (523)

Figure 8.1 Flow chart on assessment of ß-lactam allergy

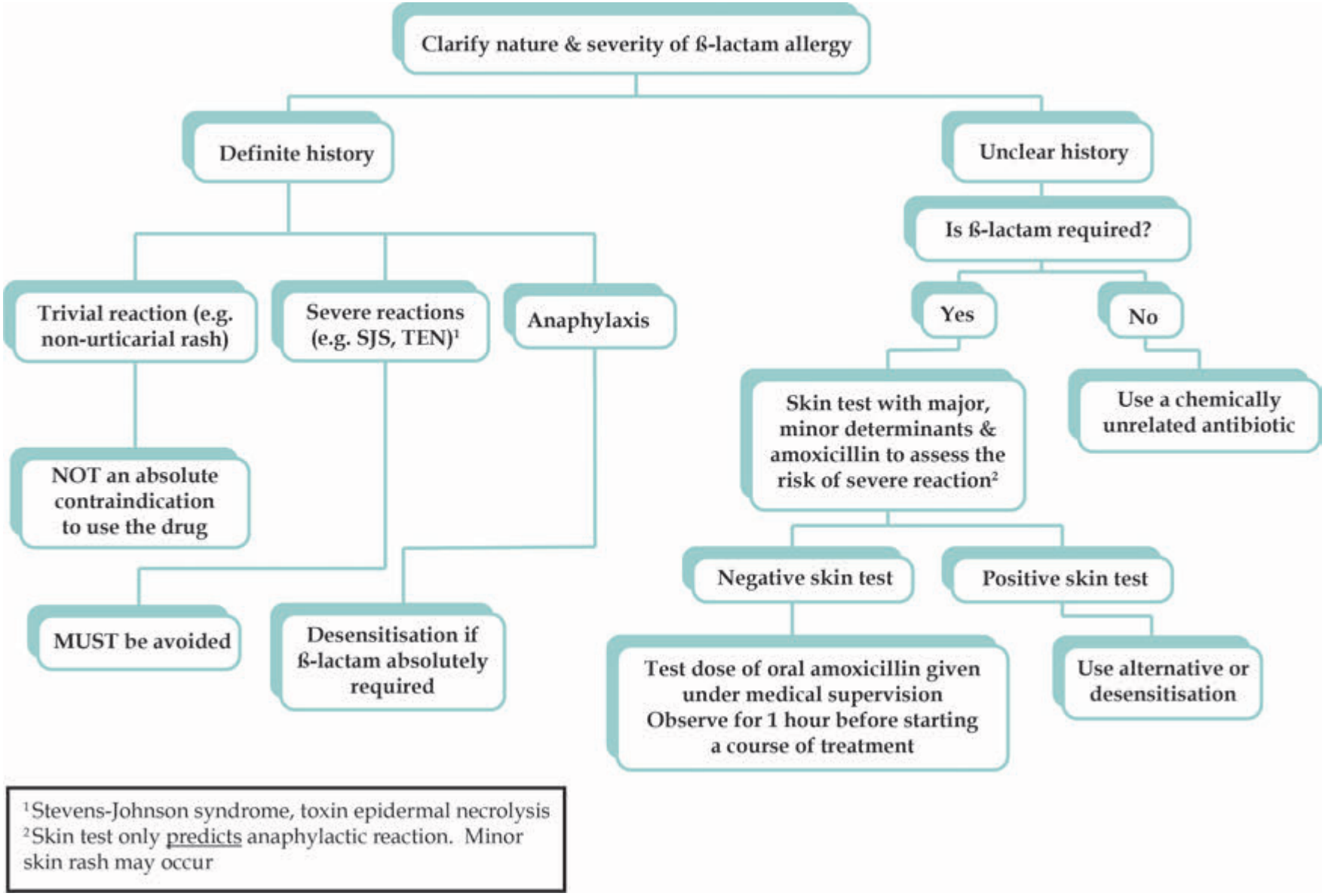


Figure 8.2 ß-lactam skin testing

Stock test solutions:

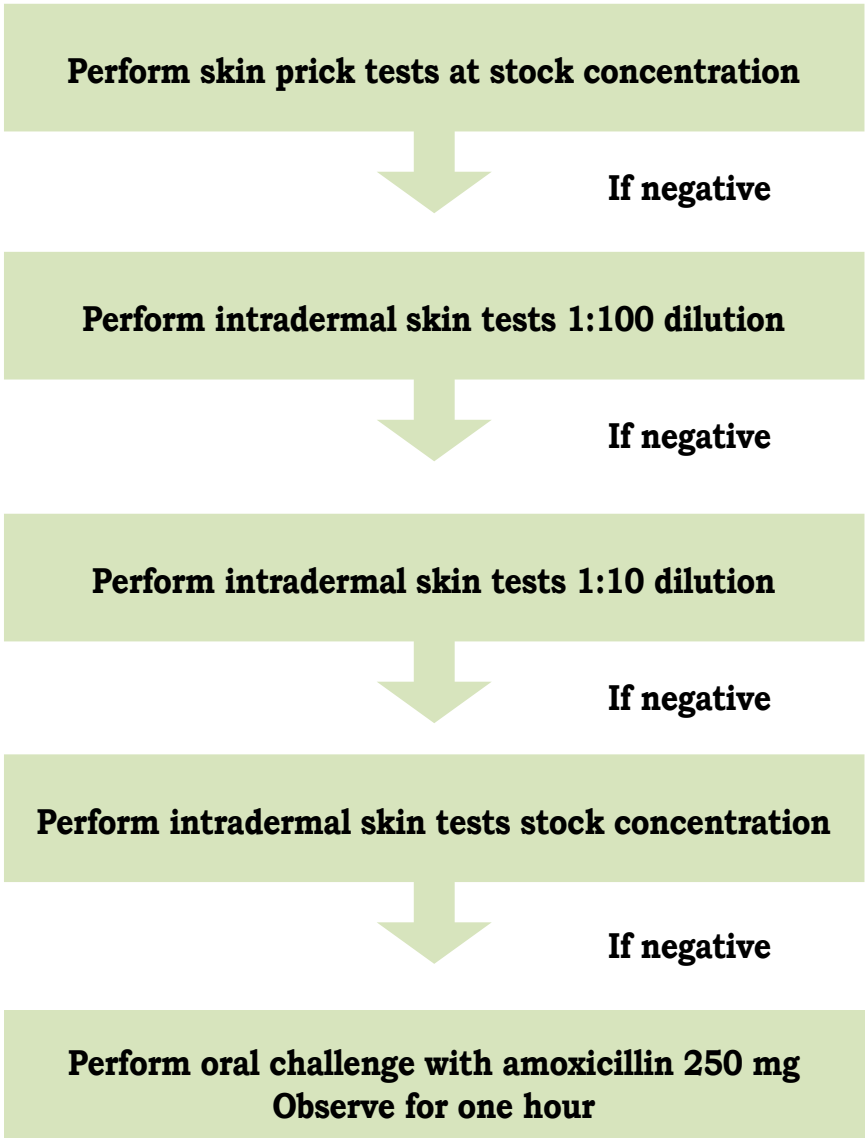
1. Penicilloyl polylysine (PPL) 0.04 mg/mL
2. Minor determinant mix (MDM) 0.5 mg/mL
3. Amoxicillin 20 mg/mL
4. Ampicillin 20 mg/mL
5. Cephalosporins 20 mg/mL

Note that all stock concentrations are in mg/mL

Precautions

This should only be conducted by persons with the proper training. Have epinephrine 1:1,000 on stand-by when performing skin tests.

Procedure



8.2. Tips on laboratory diagnostic tests

8.2.1 Urinary *Legionella* antigen test (UAT)

1. The majority of Legionnaires' disease (LD) is caused by *Legionella pneumophila* serogroup 1 (524). The test kit most commonly used in HA hospitals detects ***L. pneumophila* serogroup 1 ONLY** (Table 8.4).
2. Most of the HA hospitals offering this test can guarantee a turnaround time of 1 day (525).
3. Although more than 80% of patients with LD excrete antigens in urine during day 1 to 3 of symptoms (524), the UAT can remain negative in the first 5 days of the illness. Therefore a negative UAT during the early phase of illness does not exclude LD, and UAT should be repeated (526).
4. The UAT of majority of LD patients will turn negative within 60 days (524). However, the longest documented duration of antigen excretion was 326 days (527). Therefore a positive UAT can indicate either current or past infection.
5. Pneumonia caused by *Streptococcus pneumoniae* and urinary tract infection caused by *E. coli* and *Staphylococcus aureus* can result in false positive UAT (very weak band after 15 minutes). The specificity is around 97.1%. If very weak bands in the first 15 minutes are discounted and re-examined after 45 minutes to look for increased band intensity, the specificity can increase to 100% as false positive bands would not intensify (528). Other causes of false positivity include rheumatoid-like factors, freeze-thawing of urine, and excessive urinary sediments (527).
6. The sensitivity of UAT is variable, ranging from 70% to 80% (527). A Spanish group evaluated the sensitivity of the test during a large *Legionella* outbreak in Spain. They found that severe LD had a higher sensitivity (>80%) (529). Therefore, a negative UAT in a patient with mild atypical pneumonia does not exclude the diagnosis of LD. Other laboratory investigations for diagnosing LD should be performed (paired serology, culture with buffered charcoal yeast extract BCYE agar ± supplements and PCR of lower respiratory tract specimens).

Table 8.4 Key points in the use of UAT

1. Can detect ***L. pneumophila* serogroup 1** ONLY.
2. Short turnaround time (within 1 day).
3. UAT can be negative within the first 5 days.
4. A positive UAT result usually turns negative within 60 days.
5. Sensitivity: 70–80%
   Specificity: approaches 100%
6. Negative UAT does not exclude LD
7. False positive UAT:
   - Pneumonia caused by *S. pneumoniae*
   - Urinary tract infection caused by *E. coli*, *S. aureus*
   - Rheumatoid-like factors
   - Freeze-thawing of urine
   - Excessive urinary sediments

8.2.2 Diagnosis of catheter-associated bloodstream infection (CABSI)

1. The presence of bacteria in the blood stream is detected by the continuous-monitoring blood culture system in HA hospitals. The automatic device continuously measures the metabolic product produced by microorganisms. When a certain cutoff value is reached, the monitoring machine would indicate positivity of the blood culture bottle of interest, where the bottle would then be removed and subcultured. The time to positivity (TTP) would be affected by the initial bacterial inoculum, i.e. the higher the inoculum, the shorter the TTP (530–531).
2. In vitro studies have noted a linear relationship between the bacterial inoculum size and TTP of blood culture (532). The TTP in patients with bacteraemia is variable, ranging from <7 hours to >20 hours, depending on the infecting organism and severity of the disease (Table 8.5).
3. The differential time to positivity is a reliable and simple technique to diagnose CABSI without the need for removal of the catheter (533). A high central to peripheral blood culture colony ratio is indicative of CABSI. When blood is drawn simultaneously from central venous catheter and peripheral, **catheter blood culture** positive **2 hours** earlier than **peripheral blood culture** is highly indicative of CABSI (532,534). (Information of TTP can usually be obtained from the microbiology laboratory) (Table 8.6).
4. In a meta-analysis, the sensitivity and specificity of differential time to positivity in diagnosing CABSI is 89% and 87% respectively (533).

Table 8.5 TTP of blood culture of different organisms

Organism	Time to positivity	Reference
Staphylococcus aureus	19.9 ± 19.4 h	(535–536)
Methicillin-sensitive *Staphylococcus aureus* (MSSA)	15h (14.1 ± 9.8) h	
Methicillin-resistant *Staphylococcus aureus* (MRSA)	17h (28.6 ± 26.1) h	
Coagulase-negative *Staphylococcus*	CFU <10 : >20 h CFU >100 : ≤16 h	(533)
S. pneumoniae	14 h	(537–538)
E. coli	9.7 – 11.2 h	(539)
ESBL-pos *E. coli*	8.3 h	(531)
Klebsiella pneumoniae	<7 h	(540)
Acinetobacter baumannii	10.4 ± 7.9 h	(541)
Drug-sensitive strain	14.5 ± 9.5 h	
Drug-resistant strain	8.6 ± 3.2 h	
Candida	25.9 ± 24.9 h	(542)

Table 8.6 Diagnosing CABSI by differential time to positivity

1. Blood culture performed with aerobic and anaerobic blood culture bottle from central venous catheter and peripheral site respectively.
2. Approximately **equal volume** of peripheral blood and catheter blood (from ALL lumens) should be drawn **simultaneously** under aseptic technique.
3. Label clearly "Suspected catheter associated blood stream infection" to alert laboratory staff so that all bottles are incubated into the continuous monitoring blood culture system at the same time.
4. The time for blood culture broth to turn positive is recorded. (The TTP can be obtained from microbiology laboratory)
5. If catheter blood TTP is >**2 hours early** than peripheral blood TTP, then the patient is likely to have CABSI.
6. The differential time to positivity is valid only if:
   - The **volume** of peripheral blood injected into the blood culture bottles is approximately **equal** to the catheter blood
   - Blood culture are taken **simultaneously**
   - Blood culture are incubated into the blood culture system **at the same time**

8.2.3 Prosthetic joint infection

1. Multiple intraoperative specimens (5 to 6 specimens) should be obtained during revision surgery of an infected prosthetic hip joint, since isolation of an indistinguishable organism from 3 or more independent specimen is highly predictive of infection. Use of separate instruments to obtain the specimen could reduce the chance of false positivity and cross-contamination (543).
2. Slow-growing, fastidious organisms and biofilm-forming sessile phase bacteria may be difficult to detect in routine bacterial culture. Seven days of culture can detect up to 70% of the infections, while prolonged bacterial culture for 2 weeks can detect the remainder (544).
3. BACTEC blood culture bottles could be used for the diagnosis of prosthetic joint infection. Intraoperative specimens (synovial fluid or homogenised infected tissue) could be injected into BACTEC blood culture bottles and incubated in an automated monitoring machine (545–547). BACTEC was found to have high sensitivity and specificity in diagnosing prosthetic joint infections, compared to conventional laboratory culture methods (547). BACTEC was also found to have the shortest TTP comparing with different laboratory enrichment methods (547).

8.2.4 Culture of sterile body fluid

1. Use of BACTEC blood culture bottles can increase the sensitivity for recovery of microorganisms from sterile body fluids (548–551). It can also reduce the time to detection and increase the yield of isolation of fastidious organisms (549–551).
2. Continuous ambulatory peritoneal dialysis peritonitis may be difficult to diagnose, especially when caused by fastidious organisms, when the dialysate contains very low number of organisms or when prior antibiotics have been given. Using BACTEC and BacT/ALERT bottles to culture the dialysate fluid can increase the sensitivity for recovering microorganisms, especially fastidious bacteria (550,552). Direct inoculation of ascitic fluid into blood culture bottles at the bedside was found to have a significantly higher sensitivity and shorter time for detection of bacterial growth (553).
3. The use of BACTEC and BacT/ALERT blood culture bottles could increase the yield of microorganisms from pleural fluid (550,552).

8.3 Tuberculosis (TB)

1. TB usually involves the lung but can practically affect any other body organs. It transmits mainly through the infectious airborne droplet nuclei generated during coughing, singing, speaking or sneezing by a patient with pulmonary TB, especially in the presence of open lung cavities or positive sputum smears (554).
2. Active disease develops months or years after infection in only about one in ten of infected individuals. There is a higher risk of developing active disease with recent infection, impaired systemic immunity (notably HIV infection, diabetes mellitus, chronic renal failure, leukaemia, immunosuppressive therapy, alcoholism, malnutrition, ageing) or local defence (notably silicosis, smoking). Early diagnosis of active disease and prompt initiation of effective treatment remains the key strategy to control this airborne infection at source.
3. Up to one-third of the local (and global) population has been infected with TB. To maximise cost-effectiveness and optimise benefit vs risk, screening and treatment of latent TB infection (asymptomatic and non-infectious) are normally targeted at high risk groups (555). Tuberculin skin test and interferon-gamma release assays (IGRAs) are tests for TB infection only, and they CANNOT either rule in or rule out active TB disease.

4. The typical site-specific symptoms, e.g. chronic cough +/– blood-streaked sputum for lung parenchymal involvement, and systemic symptoms, like chronic, often low-grade fever, night sweating, weight loss, are rather non-specific and may be absent altogether. Atypical presentations can also occur, e.g. acute onset of pneumonia or meningitis. TB may thus mimic or be mimicked by many other diseases. As TB is still a common disease in HK, it is useful to keep this differential diagnosis in mind, especially for chronic septic or lung conditions where an alternative cause has not been established.
5. Chest X-ray has reasonably good sensitivity for pulmonary TB and interval changes are useful to assess activity or response to alternative treatment. However, bacteriological work-up (AFB smear, culture & drug susceptibility tests and/or rapid molecular tests) is essential for confirming the diagnosis and detection of drug resistance. Rapid identification of positive mycobacterial isolates is required to differentiate *Mycobacterium tuberculosis* complex from non-tuberculous mycobacteria (NTM), infection or colonisation by which is increasingly seen nowadays, especially in patients with underlying lung diseases and/or compromised general immunity. Empirical trial of TB drugs may be considered if TB remains a likely possibility after exhaustive diagnostic workup for possible differential diagnoses.
6. TB disease requires combination drug therapy. The standard short-course TB treatment regimen consists of isoniazid and rifampicin given for six months, supplemented in the first two months with pyrazinamide and either ethambutol or streptomycin (556). Directly observed therapy is currently recommended to promote drug adherence, which is absolutely essential for ensuring treatment success and preventing progressive acquisition of drug resistance.
7. The standard TB regimen is given with the assumption that the patient does not have multidrug-resistant TB (MDR-TB), which is defined by bacillary resistance to both isoniazid and rifampicin. Although the prevalence of MDR-TB in HK is low (around 1%), clinical vigilance is still required, especially for patients with history of residence/ prolonged stay in areas with high prevalence of TB drug resistance, previous history of treatment and/or poor response to treatment. As MDR-TB is increasingly seen among new TB patients without any known risk factors across a wide age spectrum, caution is also required in high risk institutional environments, where secondary transmission to vulnerable contacts is a key concern. Rapid molecular tests often help to establish a timely diagnosis and inform the initial choice of drugs under such situations.

8. Fluoroquinolones are essential in the treatment of MDR-TB. They should not be used as a convenient substitute for ethambutol or streptomycin, as fluoroquinolone resistance may easily develop in case of unrecognised MDR-TB. The use of a fourth drug, ethambutol or streptomycin, in the standard TB regimen may not be necessary if resistance to isoniazid can be excluded. When it is considered necessary to use a fluoroquinolone to replace ethambutol/ streptomycin as the fourth drug, it would be worthwhile to screen for MDR-TB/rifampicin resistance by suitable rapid tests.
9. MDR-TB is much more difficult to treat, especially for extensively drug-resistant TB (XDR-TB) with additional bacillary resistance to fluoroquinolone and at least one of the second-line injectable drugs. It is best managed in centres with relevant experience and adequate laboratory support for both phenotypic and genotypic drug susceptibility testing. The newer-generation fluoroquinolones (levofloxacin or moxifloxacin) and second-line injectable drugs (if susceptible) are core drugs, which must be used together with an adequate number of other likely effective first-line or second-line accompanying drugs to prevent further acquisition of drug resistance. High dose isoniazid may be considered in case of low-level isoniazid resistance. Linezolid, in suitable dosage and dosing frequency to minimise toxicity, often plays an important role in the treatment of fluoroquinolone-resistant MDR-TB and XDR-TB. Novel drugs, such as delamanid and bedaquiline, may also need to be considered when drug choices are strictly limited.

Abbreviations

ABECB	Acute bacterial exacerbation of chronic bronchitis
AMR	Antimicrobial resistance
ASP	Antimicrobial stewardship programme
b.d.	Twice a day
CABSI	Catheter-associated blood stream infection
CA-MRSA	Community-associated methicillin-resistant *Staphylococcus aureus*
CAP	Community-acquired pneumonia
cap.	Capsule
CBA	Colistin base activity
CC17	Clonal complex17
CDC	Centers for Disease Control and Prevention
CFU	Colony-forming unit
CHP	Centre for Health Protection
CLSI	Clinical laboratory standards institute
CPE	Carbapenemase-producing *Enterobacteriaceae*
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CRE	Carbapenem-resistant *Enterobacteriaceae*
CSF	Cerebrospinal fluid
DRSP	Drug-resistant *Streptococcus pneumoniae*
ESBL	Extended-spectrum β-lactamase
FDA	Food and Drug Administration
g	Gram
HA	Hospital Authority
HACEK	*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* species
HA-MRSA	Healthcare-associated methicillin-resistant *Staphylococcus aureus*
HAP	Hospital-acquired pneumonia
HDU	High dependency unit
HIV	Human immunodeficiency virus
HK	Hong Kong
HSCT	Haematopoietic stem cell transplantation

I.M.	Intramuscular
I.V.	Intravenous
ICU	Intensive care unit
IU	International units
IVDU	Intravenous drug user
kg	Kilogram
LD	Legionnaires' disease
MDR-TB	Multidrug-resistant tuberculosis
µg	Microgram
mg	Milligram
MIC	Minimal inhibitory concentration
mL	Millilitre
MRAB	Multidrug-resistant *Acinetobacter baumannii*
MRMP	Macrolide-resistant *Mycoplasma pneumoniae*
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS-MRSA	Multi-susceptible methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
NDM	New Delhi metallo-ß-lactamase
P.O.	Per oral
PCR	Polymerase chain reaction
PID	Pelvic inflammatory disease
PVL	Panton-Valentine leukocidin
q.i.d.	Four times daily
SAP	Severe acute pancreatitis
spp.	Species
syr.	Syrup
t.d.s.	Three times daily
tab.	Tablet
TB	Tuberculosis
TTP	Time to positivity
UAT	Urinary *Legionella* antigen test
VRE	Vancomycin-resistant enterococci
VREfm	Vancomycin-resistant *Enterococcus faecium*
WBC	White blood cell
XDR-TB	Extensively drug-resistant tuberculosis

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