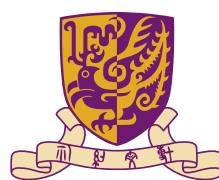


Reducing bacterial resistance with

# IMPACT

Interhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy

Fourth Edition  
Edited by P.L. Ho & S.Y. Wong



**Reducing bacterial resistance with IMPACT –**

**Interhospital Multi-disciplinary Programme on  
Antimicrobial Chemotherapy**

Editors: Pak Leung, HO & Samson Sai Yin, WONG

Fourth Edition 2012

Version 4.0

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## **Foreword**

I am very pleased to see the publication of the new IMPACT Guidelines (2012), now into its fourth edition. The updated IMPACT Guidelines combined the latest scientific evidence and local data on the prevalence and sensitivity patterns of different pathogens. I am confident that the IMPACT Guidelines will continue to serve as an invaluable reference tool for our medical and health professionals in reinforcing the appropriate use of antimicrobial drugs.

We are deeply indebted to the Chairman of the IMPACT Editorial Board, Professor HO Pak-Leung, for his strong leadership, professional expertise, and selfless dedication of his precious time and energy. My heartfelt appreciation also goes to each and every colleague and representative from all medical organizations who contributed to the realization of this new edition of IMPACT.

Antimicrobial resistance threatens the continued effectiveness of many medicines used today to treat the sick. Moreover, it deters important advances being made against major infectious killers, imposing huge costs to individuals and society. The Centre for Health Protection is committed to work hand in hand with medical professionals in Hong Kong to address this important threat.

Dr. Thomas Ho Fai, TSANG  
Controller  
Centre for Health Protection

## **Foreword**

The discovery of penicillin by Alexander Fleming in 1928 marked the advent of the antibiotic era, and for the following 40 years, more than 20 structural classes of new antimicrobial agents were discovered and brought into clinical use. The spate of Nobel prizes awarded to the early pioneers, Waksman, Fleming, Florey, Chain and Domagk, for the development of the first effective antimicrobial agents was a clear evidence of the great importance attributed to these achievements.

Now into the 21<sup>st</sup> century, antimicrobial agents are commonly prescribed for the purposes of treatment of and prophylaxis against infections, in the realms of public health management and travel medicine. At the same time, world-wide emergence of antimicrobial resistance and the spread of resistant microorganisms are among the major challenges plaguing the global community in the healthcare context.

At this moment, smart and rational use of antimicrobial agents is of paramount importance in preventing antimicrobial resistance and salvaging the market-available antibiotics for a longer life span. Common prescribing errors which lead to undesirable clinical outcomes should be avoided. These include treatment of colonization, inappropriate empiric therapy and combination therapy, suboptimal dosing and duration, and mismanagement of apparent antibiotic failure.

Publication of the fourth edition of IMPACT is an opportune moment to share constructive comments from clinicians and other colleagues and insights on the forthcoming battle against antibiotic resistance. The new edition has evolved from the third one by incorporating up-to-date data on epidemiology, prevalence of pathogens and their antimicrobial resistance profiles while maintaining the art of basic sciences throughout the comprehensive review process. I believe the fourth edition of IMPACT would provide a good reference for our clinicians in the use of antimicrobial agents to achieve maximal clinical benefits.

I would like to thank the many people and organizations who have contributed to the successful launching of the fourth edition of IMPACT and look forward to your continued support in the appropriate use of antibiotics as an effective means to control antimicrobial resistance.

Dr P Y Leung  
Chief Executive  
Hospital Authority

## **Preface**

Hong Kong is plighted by a multitude of antibiotic-resistant bacteria. As bacteria including *Staphylococcus aureus*, *Escherichia coli*, *Acinetobacter baumannii* which are causative agents of the major infectious syndromes - skin and soft tissue infections, pneumonia, urinary tract infections, septicaemia - become increasingly resistant to agents that are widely used for their empirical treatment. Clinicians face increasing numbers of “hit and miss” situations in the hospital and in the community. While there is clearly a need for new antibiotics, pharmaceutical investment in antibiotic research has declined in the past decade leading to decreasing number of new antibacterial drugs approved for marketing and a dry pipeline for the near future. This is why the medical profession must be more critical than ever of antibiotic use.

IMPACT recognizes the dangers from antimicrobial resistance, which has reached alarming levels, the tremendous adverse effect it has on quality medical care and the need for a strong, coordinated and multifaceted response. To meet this challenge, the IMPACT editorial board has been broadened and all sections of the document have been revised. As in the previous editions, the content focuses on the clinical situations in which the local epidemiology is unique; highlighting the antimicrobial agents with a strong link to development of multidrug-resistant organisms or that dosing and monitoring are complicated. Where appropriate, comments by the IMPACT group are provided to facilitate a more prudent use of antimicrobial agents. Several new sections have been added, including smart use of antibiotics in outpatient settings, management of antibiotic allergy and tips on laboratory diagnostic tests. To meet the needs of different individuals, the publication is available in two hardcopy sizes (pocket and A4), at the homepages of the partner organizations and made accessible as an Apps to users of mobile phones.

I am grateful to the contributions by our experts in the editorial board. On behalf of the IMPACT group, we thank the Centre for Health Protection for the generous financial support in printing the hard copies and for development of the Apps software.

PL Ho  
Editor  
September 2012



**Part I: Antibiotic resistance - Local scenario**

## **1.1 Background: the problem of antimicrobial resistance in Hong Kong**

1. The emergence of resistance has threatened the successful treatment of patient with infections [1-5].
2. Antimicrobial resistance increases drug costs, length of stay and adversely affects patient's outcome [6].
3. Resistance to all classes of antibiotics has developed to various extents among the common and important nosocomial pathogens (Tables 1.1-1.3).

**Table 1.1 Top eight isolates from clinical specimens in 2011 (data from a regional hospital in Hong Kong)**

Organism	Blood		Respiratory specimens		Urine	
	n=1 517 Non- ICU/HDU rank (%)	n=266 ICU rank (%)	n=6 347 Non- ICU/HDU rank (%)	n=2 309 ICU rank (%)	n=10 834 Non- ICU/HDU rank (%)	n=276 ICU rank (%)
<i>E. coli</i>	1 (29%)	3 (10%)	<i>P. aeruginosa</i> 1 (14%)	<i>E. coli</i> 2 (7%)	<i>E. coli</i> 1 (39%)	2 (26%)
Coagulase-negative staphylococci*	2 (11%)	1 (30%)	<i>H. influenzae</i> 2 (9%)	<i>Enterococcus</i> species 8 (1%)	<i>Enterococcus</i> species 2 (11%)	3 (14%)
<i>K. pneumoniae</i>	3 (9%)	5 (6%)	<i>S. aureus</i> 3 (8%)	<i>Klebsiella</i> species 3 (6%)	<i>Klebsiella</i> species 3 (10%)	4 (8%)
<i>S. aureus</i>	4 (8%)	4 (7%)	<i>Klebsiella</i> species 4 (6%)	<i>Candida</i> species# 1 (8%)	<i>Candida</i> species# 4 (10%)	1 (29%)
<i>Bacillus</i> species*	5 (6%)	2 (18%)	<i>E. coli</i> 5 (3%)	<i>Proteus</i> species 4 (5%)	<i>Proteus</i> species 5 (5%)	7 (2%)
<i>Enterococcus</i> species	6 (4%)	6 (6%)	<i>M. catarrhalis</i> 6 (2%)	-	<i>P. aeruginosa</i> 6 (4%)	5 (6%)
<i>Proteus mirabilis</i>	7 (3%)	-	<i>A. baumannii</i> 7 (2%)	<i>Coagulase negative staphylococci</i> 5 (3%)	<i>Coagulase negative staphylococci</i> 7 (4%)	6 (4%)
<i>P. aeruginosa</i>	8 (2%)	8 (2%)	<i>S. pneumoniae</i> 8 (2%)	-	<i>S. agalactiae</i> (group B) 8 (3%)	-

\*Some of these could be contaminants

#Include both *C. albicans* and non-albican *Candida* species.

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

<b>Bacteria</b>	<b>Intrinsic Resistance</b>	<b>Associated Resistance</b>
MRSA	All beta-lactams, beta-lactam/beta-lactamase inhibitor combinations <sup>a</sup>	Common: erythromycin, clindamycin, aminoglycosides, cotrimoxazole, fluoroquinolones
VREfm (vancomycin-resistant <i>Enterococcus faecium</i> )	Glycopeptides, cotrimoxazole, clindamycin, aminoglycosides	Common: ampicillin, carbapenems, fluoroquinolones, high level aminoglycoside resistance
ESBL-positive <i>Enterobacteriaceae</i> (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 <i>Enterobacteriaceae</i>	All beta-lactams including carbapenem (except monobactam)	Common: fluoroquinolones, aminoglycosides, cotrimoxazole Associated resistance to aztreonam is associated with other co-existing enzymes (AmpC beta-lactamase)
Carbapenem-resistant <i>A. baumannii</i>	All beta-lactams including carbapenem (except monobactam)	Common: fluoroquinolones, aminoglycosides, cotrimoxazole

<sup>a</sup> 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 2010**

Organisms (No. of isolates)	% Non-susceptible																
	Ampicillin	Ampicillin + sulbactam	Amoxicillin + clavulanate	Piperacillin	Ticarcillin + clavulanate	Piperacillin + tazobactam	Cefoperazone + sulbactam	Cefuroxime (I.V.)	Ceftriaxone	Ceftazidime	Cefepime	Gentamicin	Amikacin	Ciprofloxacin	Cotrimoxazole	Imipenem	Nitrofurantoin
<i>Escherichia coli</i> (20 268)	73		29			8	12	30	44		15	32	2	37	46	<1	5
<i>Klebsiella</i> species (6 914)	99		26			41	10	26	24	24	8	8	2	18	26	1	49
<i>Enterobacter</i> species (1 334)	97		96		54	25	12	38	39	24	2	4	1	8	12	0	38
<i>Acinetobacter</i> species (2 088)		32			42	44	28			30	45	29	15	44	37	33	
<i>Pseudomonas aeruginosa</i> (7 092)				5	13		9			5	4	3	1	8		5	
<i>Stenotrophomonas maltophilia</i> ( 90)					33					50				23	4	100	

The results were interpreted according to the CLSI, M100-S20. Most ceftriaxone-nonsusceptible isolates were ESBL-producers.

## 1.2 Methicillin-resistant *Staphylococcus aureus*

Due to the alternation of penicillin binding protein, methicillin-resistant *Staphylococcus aureus* (MRSA) are resistant to penicillins, (including oxacillin, cloxacillin and flucloxacillin), BLBLI, cephalosporins, and carbapenems. Only the new anti-MRSA beta-lactams (e.g. ceftaroline) retain activity against MRSA.

MRSA has been categorized into healthcare-associated (HA-MRSA) and community-associated (CA-MRSA). The Center for Disease Control and Prevention (CDC) classification, which is the most widely accepted, classified HA-MRSA and CA-MRSA epidemiologically [7]. However the border between the two is becoming blurred and surveillance using epidemiological criteria alone has become insufficient (Table 1.4).

### 1.2.1 Healthcare-associated MRSA (HA-MRSA)

1. For *S. aureus* that are susceptible to methicillin, vancomycin is inferior to anti-staphylococcal beta-lactam [8]. However, vancomycin remains the treatment of choice for infection caused by MRSA. The efficacy of vancomycin may be limited by inadequate dosing, poor tissue penetration, slow bactericidal activity and strains with reduced susceptibility to the drug [8, 9].
2. In the recent years, a silent and gradual increase in the vancomycin MIC has been observed. This phenomenon is known as ‘vancomycin creep’ [10, 11]. Since the increment is small and the MIC still falls within the range of ‘sensitive’, it usually goes unnoticed. This phenomenon has also been observed in Hong Kong [12]. 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 [12].
3. The vancomycin creep has been observed in some, but not all centers. This is probably due to difference in the susceptibility testing methods, clonal dissemination of more resistance strain and the intensity of vancomycin usage [12].
4. Vancomycin MIC ≥ 2 µg/ml has been associated with vancomycin treatment failure [13-15]. Therefore, guidelines have recommended isolates with vancomycin MIC ≥ 2 µg/ml be treated with an alternative antibiotic instead of vancomycin [8].
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 MS-MRSA represents HA-MRSA and the increase in isolates was associated with the spread of the clone ST45 possessing SCCmec type IV or V. About 75% of these isolates were recovered from elderly living in residential care homes. This represents that these strains may be more transmissible among the elderly in residential care home and convalescent care settings, serving as a reservoir [16].

### **1.2.2 Community-associated MRSA (CA-MRSA)**

1. CA-MRSA is rapidly emerging in the Hong Kong community [17] and 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 A&E setting [18].
2. During 2009-2011, 2.1% of the 1 487 CA-MRSA cases reported to the DH were invasive infections. The mortality of invasive CA-MRSA infections was 25%. In HK, serious infections and deaths have occurred in otherwise healthy children and adults.
3. Patient infected with CA-MRSA do not have the usual risk factors associated with HA-MRSA. In our locality, ethnic minority, sharing of personal items with other persons have been found to be risk factors while frequent hand washing was CA-MRSA infection [17, 19].
4. PVL (Panton-Valentine leukocidin) toxin is a pore forming cytotoxin that is capable of destroying human monocytes and neutrophils. PVL has been associated with virulence and transmissibility of CA-MRSA. In Hong Kong, 68% of the CA-MRSA causing skin and soft tissue infection possesses PVL toxin.
5. Other than skin and soft tissue infection, PVL toxin is also associated with necrotizing pneumonia, necrotizing fasciitis and meningitis. CA-MRSA has also been reported to co-infect with influenza resulting in fulminant pneumonia [20-22].

**Table 1.4 Characteristics of different types of MRSA**

	CA-MRSA	HA-MRSA	MS-MRSA
Representative strains	ST30/HKU100 lineage Southwest Pacific clone ST59/HKU200 lineage	ST239 (Hungarian/Brazilian clone) Also seen in SE Asia	ST45 (belongs to CC45)
Found in	Community	Hospitals & old age homes	Hospitals & old age homes
SCCmec	IV or V	III / IIIA	IV or V
PVL	+ (~68%)	-	-
Gentamicin	S	R	S
Erythromycin & Clindamycin	Variable		
Cotrimoxazole	S	R	S
Fusidic acid	S	R	S
Minocycline	S	R	
Clinical spectrum	Skin and soft tissue infection	Hospital acquired infections	Bacteraemia
	Necrotizing pneumonia		
	Necrotizing fasciitis		
	Severe sepsis		

CA-MRSA, community-associated MRSA; HA-MRSA, healthcare-associated MRSA; MS-MRSA, multisusceptible MRSA.

### 1.3 Vancomycin-resistant enterococci

1. Vancomycin-resistant *Enterococcus faecalis* (VREfs) and *E. faecium* (VREfm) were first reported in Europe in 1986. Since then, VRE have spread throughout the world and have become a major nosocomial pathogen. In the United States and some European countries, VRE (especially VREfm) have disseminated widely in the hospitals and old age homes [23].
2. In Hong Kong, 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. Two ad hoc studies demonstrated that VRE was carried by <0.1% of patients in high risk areas [24, 25].

3. Since 2009, the epidemiology of VRE in HK is rapidly evolving. This followed the detection of an epidemic strain of VRE<sub>fm</sub> in several public hospitals. By January 2012, the epidemic strain was disseminated to more than ten public hospitals and affecting over a hundred patients and residents of more than ten old age homes. This VRE<sub>fm</sub> clone is becoming endemic in some of our public hospitals and old age homes.
4. Vancomycin resistance in enterococcus is plasmid-mediated. The *vanA* gene is encoded in a transposon Tn1546 and *vanB* encoded in Tn1547. 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 [26].
5. Hospital outbreak caused by VRE has been increasing reported worldwide. Molecular epidemiology study by MLST revealed that this rise is attributed to the spread of a genetic lineage of *Enterococcus faecium* clonal complex-17, CC17, Table 1.5 [26, 27]. CC17 is now the predominant clone seen in hospital outbreaks and has been reported in the Netherlands [28], Spain [29], Germany [30], South America [31] and Taiwan [32].
6. Most of the CC17 *E. faecium* remains susceptible to linezolid. However in a Germany survey, selection of linezolid-resistance epidemic-virulent CC17 strains of enterococcus occurred during Linezolid therapy [30]. It is due to the accumulation of mutations in position 2 576 of the 23s rDNA for at least one of the 23S rRNA 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 [26].

**Table 1.5 Characteristics of vancomycin-resistant *E. faecium*, CC17**

1. Multidrug-resistant, including resistance to: <ol style="list-style-type: none"> <li>a. Ampicillin</li> <li>b. Quinolones</li> </ol>
2. Contains a putative pathogenicity island and the <i>esp</i> gene which encodes for a protein involved in colonization and biofilm formation
3. An association with hospital outbreaks

## 1.4 ESBL-positive *Enterobacteriaceae*

1. ESBLs are enzymes capable of hydrolyzing penicillin, first-, second- and third-generation (extended-spectrum) cephalosporins and aztreonam (except the cephamycins and carbapenems). Most ESBLs can be inhibited by the beta-lactamase inhibitors such as clavulanic acid and tazobactam [33]. (Table 1.6.) TEM, SHV and CTX-M are the three most common family of ESBL seen worldwide.
2. In Hong Kong (Figure 1.1), >90% of strains with an ESBL phenotype produced the CTX-M type enzymes [34, 35]. There is a high rate of resistance towards non-beta-lactam antibiotics, particularly quinolones, cotrimoxazole and aminoglycosides [34, 35]. The high rate of resistance to non-beta-lactam antibiotics therefore limits the choice for management of patients in outpatient setting.
3. ESBL-positive *Enterobacteriaceae* has been considered to be a hospital pathogen in the past. However, community-onset infection has been described in different countries in the recent years. Most of the patients presented with lower urinary tract infection, other presentation includes bacteraemia and intra-abdominal infection [36-39].
4. Rectal colonization with ESBL-positive *Enterobacteriaceae* has been increasingly seen in healthy individuals [40], and this has been postulated to be a risk factor for community-onset ESBL-positive *Enterobacteriaceae* infection. Food animals are a major reservoir of ESBL-positive *E. coli* [41, 42].
5. For two decades, ESBL-positive *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.
6. Recently, the laboratory testing advisory bodies in the US (CLSI) and Europe (EUCAST) have revised their advice and argued that with the lowered cephalosporins breakpoints that both organizations now adopted, it is unnecessary to edit susceptibility categories if an ESBL is found. A group of international experts in this field considered such advice is misguided [43]. It is prudent to continue to seek ESBLs directly and to avoid cephalosporins as treatment.
7. In Hong Kong, if we apply the new ceftazidime breakpoint, three-quarters of the ESBL-positive isolates would be re-classified from resistant to susceptible [44]. Caution with this approach is necessary whilst clinical data are limited [43].

**Table 1.6 Characteristics of ESBL and AmpC beta-lactamase**

	ESBL	AmpC beta-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
Beta-lactamase inhibitor	Inhibited	Not inhibited
Cephameycins: - cefoxitin - cefmetazole	Not hydrolysed	Hydrolysed
Oxymino-beta-lactams - cefotaxime - ceftriaxone - ceftazidime	Hydrolysed	Hydrolysed
Cefepime	Variable	Hydrolysed
Carbapenem	Not hydrolysed	Not hydrolysed
Examples	TEM, SHV and CTX-M	<i>Enterobacter</i> , <i>Citrobacter</i> and <i>Serratia</i> possess inducible beta-lactamase in their chromosomes

## 1.5 Carbapenem-resistant *Enterobacteriaceae*

*Enterobacteriaceae* can acquire resistance to carbapenem through production of carbapenemase, modification of outer membrane permeability and efflux pump (Table 1.7) [45].

1. Carbapenemase, KPC-producing *Klebsiella pneumoniae* was first discovered from a clinical isolate through the ICARE surveillance in North Carolina in 1996 [46, 47] and followed by a substantial spread in New York [48], Israel [49] and Greece [50]. *Enterobacteriaceae* producing KPC has also been described in South America (Colombia, Brazil and Argentina) [51-53] and China [54, 55]. Other than *K. pneumoniae*, the KPC-enzyme has also been described in *Enterobacter* spp. and *Salmonella* spp. [47]. Infection

caused by carbapenem-resistant organisms increases the risk of complications and mortality [56].

2. New Delhi metallo-beta-lactamase 1 (NDM-1, Table 1.8) was first described in 2009 in a Swedish patient of Indian origin. He was hospitalized in India and acquired urinary tract infection caused by a carbapenem-resistant *Klebsiella pneumonia* [57]. Like other Metallo-beta-lactamase (MBL), the enzyme NDM-1 can hydrolyse all beta-lactam except aztreonam. Resistant to aztreonam is usually due to the coexisting ESBL or AmpC beta-lactamase. Majority of the NDM-1 producing organisms harbour other resistance mechanism, rendering it resistant to almost all classes of antibiotics with the possible exceptions of tigecycline and colistin [58, 59].
3. NDM-1 producing *Enterobacteriaceae* has spread across Europe. In a recent survey conducted in 29 European countries, 77 cases were report in 13 countries [58]. Majority of the cases had a history of travel to India subcontinent. Many countries have developed their own national guidelines to deal with the problem of NDM-1 [58].
4. The first case of NDM-1 producing *E. coli* has been described in Hong Kong in October 2009 from an Indian patient with urinary tract infection [60]. Several cases of IMP-4 were found in hospitalized patients since mid-2009 in Hong Kong (Figure 1.2) [61]. The first KPC-2 producing *K. pneumoniae* was described in February 2011 [62].
5. The spread of NDM-1 is probably due to the huge selection pressure created by widespread non-prescription use of antibiotics in India [63] and involvement of promiscuous mobile elements in the gene's dissemination [64].

**Table 1.7 Different classes of carbapenemase**

	<b>Class A</b>	<b>Metallo-beta-lactamase</b>	<b>Oxacillinase</b>
Molecular class	Class A	Class B	Class D
Functional class	2f	3	2d
Chromosomal / plasmid	C and P	C and P	P and C
Examples	KPC# GES SME IMI/NMC#	IMP# VIM# NDM#	OXA-23#* OXA-24 OXA-51#* OXA-58
Found in	<i>Enterobacteriaceae</i>	Non-fermenters and <i>Enterobacteriaceae</i>	Non-fermenters
Inhibited by	Clavulanate and tazobactam	EDTA, divalent cation chelator	Mild inhibition by clavulanate
Active site	Serine	Zinc ion	Serine
Carbapenem	Hydrolysed	Hydrolysed	Hydrolysed
Aztreonam	Hydrolysed	Not hydrolysed	Not hydrolysed
Early beta-lactam	Hydrolysed	Hydrolysed	Hydrolysed
Extended spectrum cephalosporin	Hydrolysed (except SME)	Hydrolysed	Hydrolysed poorly

#Seen in Hong Kong

\*Common in Hong Kong

**Table 1.8 Characteristics of NDM-1 producing organisms**

1. NDM-1 is a MBL (resistant to all beta-lactam except aztreonam)
2. The bla <sub>NDM-1</sub> gene is located in plasmid
3. Resistant to aztreonam is due to coexisting ESBL and Amp C beta-lactamase
4. Associated with other resistance mechanisms (resistant to multiple classes of antibiotics)
5. Only susceptible to tigecycline and colistin
6. The following <i>Enterobacteriaceae</i> can produce NDM-1: <ul style="list-style-type: none"> <li>a. <i>Klebsiella pneumoniae</i> (most common)</li> <li>b. <i>Escherichia coli</i></li> <li>c. Other reported species: <i>K. oxytoca</i>, <i>Citrobacter freundii</i>, <i>Enterobacter cloacae</i>, <i>Morganella morganii</i>, <i>Proteus</i> species and <i>Providencia</i> species</li> </ul>
7. Majority have a travel history and hospitalization in certain parts of the world

8. Transmission:

- a. Indirect faecal-oral inter-human transmission
- b. In both healthcare and community setting

9. Control measure:

- a. Hand hygiene and contact precautions
- b. Laboratory support
- c. Active surveillance [25]

Reference: [15, 23]

## 1.6 Carbapenem-resistant *Acinetobacter baumannii*

Multidrug-resistant *Acinetobacter baumannii* (MRAB) is a widely used, and yet ill-defined and non-specific term (Figure 1.3). 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* [65, 66]. Therefore, resistant to the carbapenems have been defined as a sentinel event [67-69]. Using the term carbapenem-resistant *A. baumannii* (CRAB) allows better communication and surveillance data could be comparable between different centers (Figure 1.3). 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 beta-lactamase [70-73]. Therefore, for surveillance purpose, the term CRAB reflects the current situation more accurately than MRAB.

1. Resistant 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 beta-lactamase [74, 75]. 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 [75].
2. The Metallo-beta-lactamases (MBLs) are Class B beta-lactamases which contain at least one Zinc ion at their active sites (Table 1.7). They are more potent carbapenemases and can hydrolyze all beta-lactamase except the monobactam, aztreonam [75]. However MBL is less commonly seen in *A. baumannii*. Due to the simultaneous presence of resistance determinant often carried on integrons, CRAB has concomitant resistant to other classes of antibiotics [16].

3. In a recent local survey of CRAB, majority of the strains belonged to HKU1 and HKU2 clone [68]. 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 wound was found to be associated with MRAB colonization 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 [70].
4. Imipenem resistance was found to have a significant impact on the mortality on *Acinetobacter* bacteraemia [76], 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.

Figure 1.1 Changes in the incidence density of ESBL positive *E. coli* bacteraemic episodes in a regional hospital in Hong Kong, 2000–2010

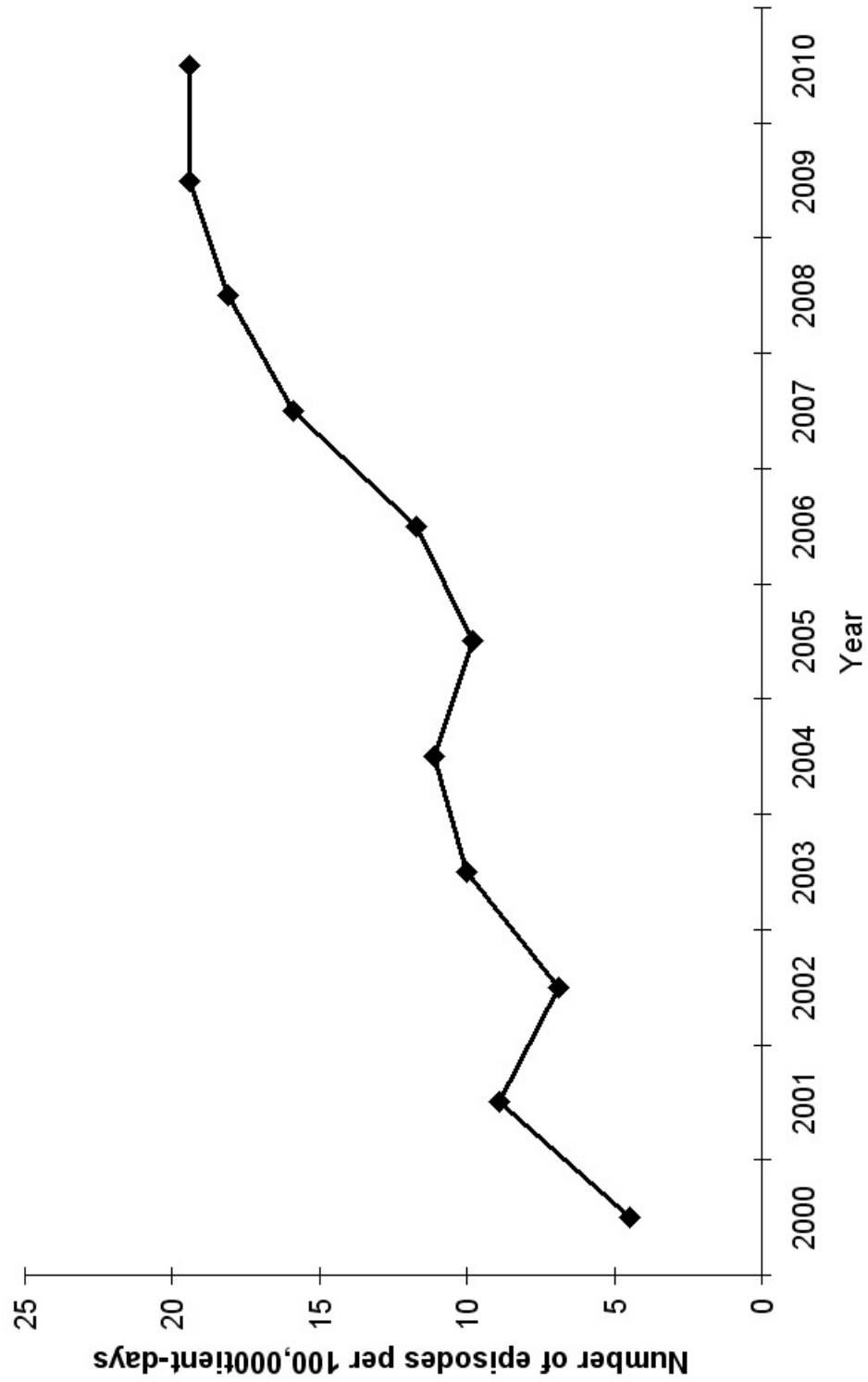




Figure 1.2 Number of carbapenemase-producing *Enterobacteriaceae* confirmed at the PHL, CHP, Jan 2009 to Dec 2011 (A Hong Kong wide surveillance was implemented since the 4th quarter of 2010)

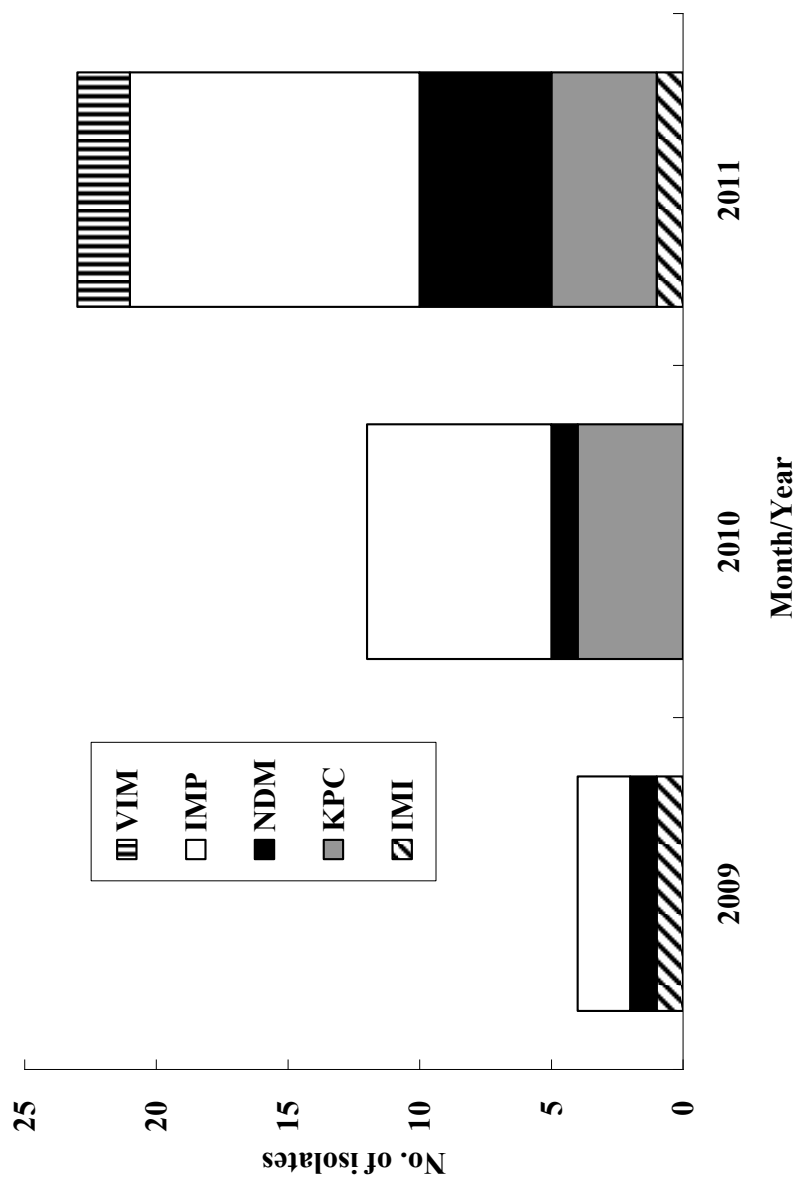
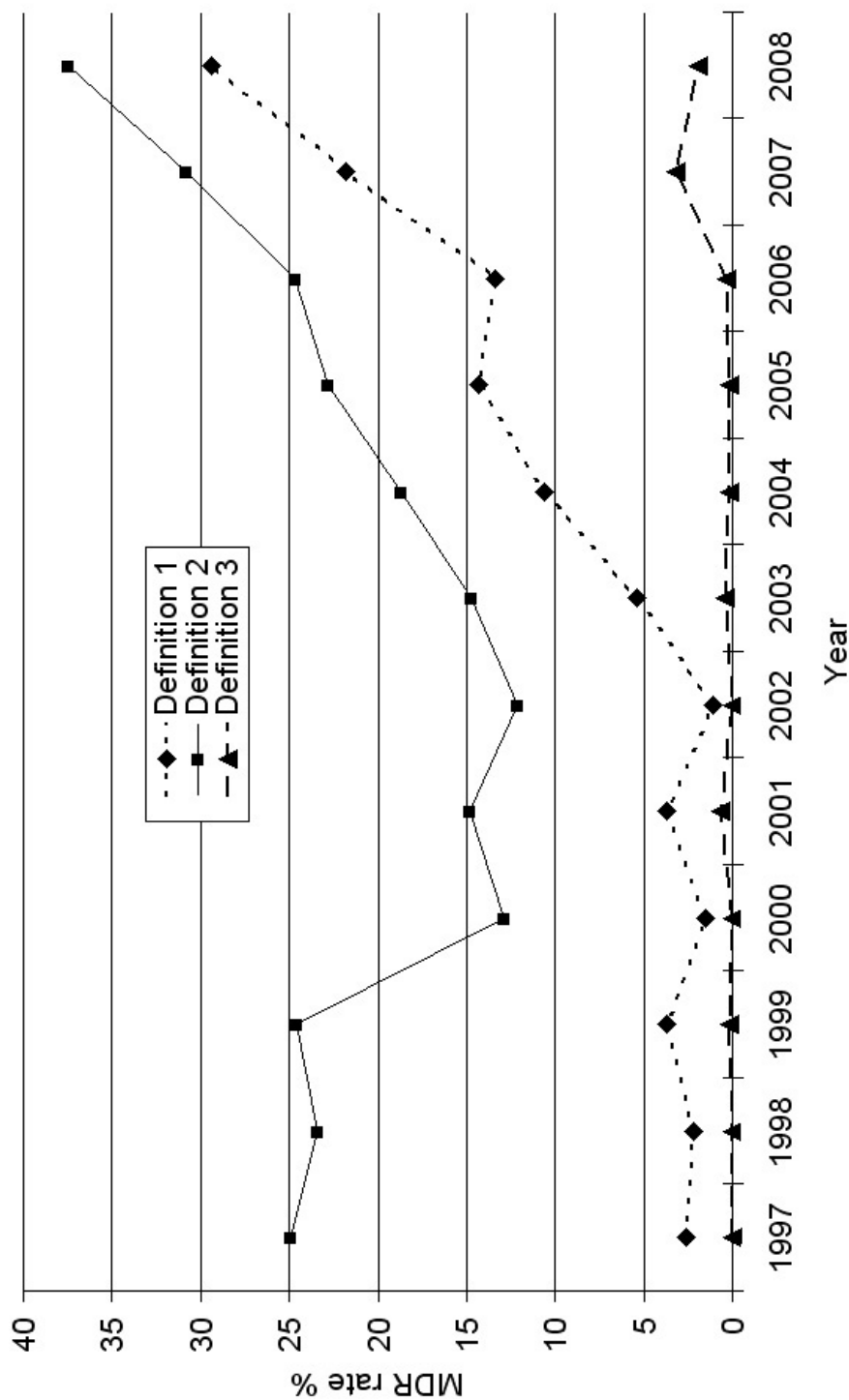


Figure 1.3 Changes in the multidrug-resistant rate of *Acinetobacter baumannii* according to three different definitions, 1997-2008



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 (ceftazideime) and fluoroquinolones (ciprofloxacin)

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

## **Part II: Antimicrobial stewardship programme**

## 2.1 Antimicrobial stewardship programme

- The present summary is based on an article in the Hong Kong Medical Journal [77].

### 2.1.1 What is antimicrobial stewardship programme?

- The term antimicrobial stewardship (ASP) is defined as the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance [78]. In practice, this involves prescribing antimicrobial therapy only when it is beneficial to the patient, targeting therapy to the desired pathogens and using the appropriate drug, dose, and duration. Thus, ASP should not be viewed simply as reduced use or a strategy for cost containment. Instead, by minimizing exposure to drugs, performing dose adjustments, reducing redundant therapy and targeting therapy to the likely pathogens, such activities can be viewed as a strategy to enhance patient safety.
- ASP involves a multidisciplinary, programmatic, prospective, interventional approach to optimizing the use of antimicrobial agents. The multidisciplinary team typically includes clinical microbiologists, infectious disease physicians, infection control practitioners, and clinical pharmacists. Having members from other medical specialties, such as surgery and paediatrics, is also recommended. Multiple approaches have been employed to enforce hospital policies to limit or control antimicrobial use (Table 2.1- 2.3). Under the auspice of ASP, several behavioural methods have been used successfully to effect changes, including problem-based education, consensus guidelines, peer review, concurrent review, data feedback, computer-based reminders, financial incentives, and the use of opinion leaders [79, 80].
- Many professional societies and public health guardians including the World Health Organization, Infectious Diseases Society of America (IDSA), Alliance for the Prudent Use of Antibiotics (APUA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH) are supportive of programmes that promote optimal antimicrobial use [81, 82]. A few have even gone a step forward with action plans [81-84].
- In the real world, multiple factors are involved in the clinical decision making. Local and overseas experience indicate that availability of consultation service by clinical microbiologist / infectious disease physician is the most effective way for improving antimicrobial use [85, 86].

**Table 2.1 Methods to implement antimicrobial control**

<p>1. Administrative control</p> <ul style="list-style-type: none"><li>a. Restriction of hospital formulary through the drug and therapeutics committee</li><li>b. Cascade reporting of sensitivity results</li><li>c. Use of antimicrobial order forms</li></ul> <p>2. Guidelines, education &amp; consultation</p> <ul style="list-style-type: none"><li>a. Written hospital guidelines</li><li>b. Educational efforts aimed at changing prescribing practices of clinicians</li><li>c. Providing consultation from clinical microbiologist / infectious disease physician</li></ul> <p>3. Surveillance</p> <ul style="list-style-type: none"><li>a. Utilisation review with guidelines for rational and appropriate usage</li><li>b. Ongoing monitoring and analysis of antimicrobial agents usage</li><li>c. Ongoing surveillance of antimicrobial susceptibility</li></ul> <p>4. Prospective audit with intervention</p> <ul style="list-style-type: none"><li>a. Monitoring adherence to advice on choice of antimicrobial agents</li><li>b. Usage feedback to clinicians</li></ul>
---

**Table 2.2 Potential barriers to reaching the strategic goals**

Barrier	Countermeasures and improvement strategies
<b>Ownership and accountability</b>	
<ol style="list-style-type: none"> <li>1. Lack of ownership and accountability for recognizing and reporting trends.</li> <li>2. Failure to integrate work of laboratory, infection control, medical, nursing, and intensive care-unit staff.</li> </ol>	<ol style="list-style-type: none"> <li>1. Designate responsibility and accountability for the process.</li> <li>2. Set up a multi-disciplinary team to develop a collaborative system and monitor results.</li> </ol>
<b>Staff knowledge and practice</b>	
<ol style="list-style-type: none"> <li>1. Lack of time for the laboratory and/or infection control staff to generate and analyze data.</li> <li>2. Lack of time for healthcare providers to examine and discuss data and inconsistent or erroneous interpretation of data by staff.</li> </ol>	<ol style="list-style-type: none"> <li>1. Ensure adequacy of laboratory and infection-control staffing and prioritize activities of staff so that data can be generated and analyzed.</li> <li>2. Report data in an easy-to read/interpret format and, when appropriate, include data interpretation in the report.</li> </ol>
<b>Physician attitudes</b>	
<ol style="list-style-type: none"> <li>1. Lack of trust in the hospital administration.</li> </ol>	<ol style="list-style-type: none"> <li>1. Use a data-driven approach to cultivate trust; e.g. communicate regularly with physicians about trends in antimicrobial usage, cost, and resistance; feedback to individual physicians their performance results.</li> </ol>
<b>Expertise</b>	
<ol style="list-style-type: none"> <li>1. Lack of expertise in biostatistics (e.g. presenting trends and analyzing data).</li> </ol>	<ol style="list-style-type: none"> <li>1. Ensure availability of consultants, especially when designing analytic strategy and interpreting trend data.</li> </ol>

Reference: [87]

## **2.2 Switch therapy - conversion from I.V. to P.O.**

In the clinical situation of switch therapy use, oral antimicrobials replace intravenous usage for completion of therapy. Intravenous is almost always employed in serious infections to ensure maximal serum/tissue levels. With few exceptions such as meningitis, infective endocarditis, the majority of patients with infections do not require completion of the antimicrobial course with intravenous therapy. The following criteria have been developed for transition from intravenous to oral antimicrobial [88, 89]:

1. Patient with no clinical indication for I.V. therapy.
2. Patient is afebrile for >24 hours.
3. The WBC count is normalizing (falling towards or  $<10 \times 10^9/L$ ).
4. Signs & symptoms related to infection are improving.
5. Patient is not neutropenic (neutrophil count  $>2 \times 10^9/L$ ).
6. Patient is able to take drugs by mouth (non-NPO).
7. Patient with no continuous nasogastric suctioning.
8. Patient with no severe nausea or vomiting, diarrhea, gastrointestinal obstruction, motility disorder.
9. Patient with no malabsorption syndrome.
10. Patient with no pancreatitis or active gastrointestinal bleeding or other conditions that contraindicated to the use of oral medications.

**Table 2.3 Strategies for optimization of antimicrobial therapy**

Stages in the management of infection	Strategies for optimization
<b>Empirical therapy (ET)</b>	
<ul style="list-style-type: none"> <li>• Document the presence of infection</li> <li>• Likely pathogens?</li> <li>• Likely susceptibility pattern</li> <li>• Community- or hospital-acquired infection?</li> <li>• Monotherapy or combination therapy?</li> </ul> <p style="text-align: center;">↓</p> <p>When culture and susceptibility results are available</p> <p style="text-align: center;">↓</p>	<ul style="list-style-type: none"> <li>• Education [90]</li> <li>• Collection and analysis of local data</li> <li>• Pocket reference guide</li> <li>• Review of prescription of ‘big gun’ antibiotics by ASP team</li> <li>• ASP team to give immediate concurrent feedback (ICF) to prescribers</li> </ul>
<b>Known-pathogen therapy (KPT)</b>	
<ul style="list-style-type: none"> <li>• Narrowest spectrum according to laboratory results</li> <li>• Follow guidelines on the judicious use of ‘big gun’ antibiotics</li> </ul> <p style="text-align: center;">↓</p>	<ul style="list-style-type: none"> <li>• Cascade reporting of sensitivity</li> <li>• Reporting of deviations from guidelines to clinical microbiologist / infectious disease physician</li> <li>• ASP team to give immediate concurrent feedback (ICF) to prescribers</li> </ul>
<b>Switch therapy [91, 92]</b>	
<ul style="list-style-type: none"> <li>• A switch from intravenous to oral therapy</li> <li>• Criteria for switch therapy</li> <li>• Clinical diagnosis compatible with oral therapy</li> <li>• Patient has functioning gastrointestinal tract</li> <li>• Patient is afebrile (for &gt;24 h)</li> <li>• Signs and symptoms related to infection are improving or resolved</li> <li>• The WBC count is normalizing</li> </ul> <p style="text-align: center;">↓</p>	<ul style="list-style-type: none"> <li>• Review of patients on I.V. ‘big gun’ antibiotics by ASP team</li> <li>• Recommendation for ‘switching’ by ASP team</li> </ul>
<b>Stop therapy</b>	
<ul style="list-style-type: none"> <li>• Type of infection</li> <li>• Clinical responses</li> <li>• Follow-up culture results where appropriate</li> </ul>	<ul style="list-style-type: none"> <li>• Education</li> </ul>



## **2.3 Tips on safe use of antibiotics in out-patient setting**

1. Understand the local prevalence of pathogens and associated antibiotic susceptibility profiles. Information on surveillance of antimicrobial resistance at community out-patient setting is available at CHP webpage [93].
2. 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 antibiotics. In some instances, clinical features alone may not reliably discriminate illness into bacterial and viral infections; point-of-care testing (e.g. flu A and B, CRP, WBC) can be helpful in this scenario. 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 [94].
3. It is a good clinical practice to explain to the patient the reasons for giving or not giving antibiotics [95].
4. Whenever appropriate, prescribe the simplest regimen and shortest duration of treatment [96].
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:
  - Practice frequent hand hygiene;
  - Eat or drink only thoroughly cooked or boiled items;
  - Disinfect and cover all wounds;
  - Wear mask if he/she has respiratory symptoms;
  - Young children with symptoms of infection should minimize contact with other children.
7. Take the opportunity to educate patients on proper use of antibiotics:
  - Only take antibiotics prescribed for him/her;
  - Do not share or use leftover antibiotics;
  - Do not save antibiotics for the next illness;
  - 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 [97].

## **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 beta-lactam resistant Gram-positive bacteria (e.g. MRSA, coagulase-negative staphylococci) [98, 99].
2. Treatment of CA-MRSA in severe and extensive SSTI (multiple sites), rapid progression of cellulitis, immunosuppression, extreme of ages, area difficult to drain.
3. Treatment of infections caused by Gram-positive bacteria in patients who have serious allergies to beta-lactam antimicrobial agents (e.g. anaphylactic reaction, Stevens-Johnson syndrome).
4. When *Clostridium difficile* colitis fails to respond to metronidazole therapy or is severe and life-threatening.
5. As prophylaxis for endocarditis following certain procedures inpatients at high risk for endocarditis; according to recommendation from the American Heart Association (e.g. as prophylaxis for genitourinary or gastrointestinal procedures in moderate or high-risk patients allergic to ampicillin/amoxicillin).
6. As prophylaxis for major surgical procedures involving the implantation of prosthetic material or devices in known carriers of MRSA. 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 [100].
7. Addition of rifampicin as single agent or adjunctive not recommended.

### 3.1.2 Situations in which the use of vancomycin is not advised

1. Treatment of MRSA nasal carriage or colonization at other sites such as the isolation of MRSA from
  - Surface swab of superficial wounds
  - Surface swab of chronic ulcers
  - Surface swab of pressure ulcers

2. Routine surgical prophylaxis other than in a patient who has serious allergy to beta-lactam antimicrobial agents.
3. Routine empirical antimicrobial therapy for neutropenic fever (except as recommended by the IDSA 2010 guidelines for the use of antimicrobial agents in unstable neutropenic patients with unexplained fever) [101].
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 of presumed infections in patients whose cultures (blood, joint fluid, peritoneal fluid, pus, etc.), are negative for beta-lactam-resistant Gram-positive bacteria (e.g. MRSA).
6. Systemic or local (e.g. antibiotic lock) prophylaxis against infection (or colonization) of indwelling (central or peripheral) intravascular catheters.
7. As routine prophylaxis, before insertion of Hickman/Broviac catheter or Tenckhoff catheter.
8. As part of the regimen for selective digestive tract decontamination.
9. Primary treatment of *Clostridium difficile* colitis, except when it is severe and life-threatening.
10. Routine prophylaxis for patients on continuous ambulatory peritoneal dialysis or haemodialysis.
11. Treatment (e.g. chosen for dosing convenience) of infection caused by beta-lactam-sensitive Gram-positive bacteria in patients who have renal failure.
12. 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 dosage in special situations and therapeutic drug monitoring**

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. Therapeutic drug monitoring (TDM), Table 3.1

Vancomycin exhibits time-dependent killing. Efficacy can usually be assumed if the trough concentration is sufficiently above the

MIC of the infecting organism (i.e. best if vancomycin levels at site of infection are maintained above MIC throughout the dose interval). MIC of most susceptible organisms (e.g. MRSA) ranges 0.38-1.5 µg/mL.

Routine TDM is not indicated in most patients because vancomycin pharmacokinetics are sufficiently predictable that safe and effective vancomycin dosage regimens can be constructed on the basis of patient's age, weight and estimated renal function.

**Table 3.1 Indications for therapeutic drug monitoring**

(a) Renal impairment
(b) ICU patients co-treated with dopamine and/or dobutamine [102]
(c) Severe burn [103]
(d) Morbid obesity [104]
(e) Spinal cord injury [105]

When TDM is indicated, check only trough level. There is no solid data to support the widely referenced trough range of 5-10 µg/mL and accordingly, serum concentrations have been selected somewhat arbitrarily, based on pharmacology, retrospective studies, case reports and personal opinions. Due to the poor penetration of vancomycin to certain lung tissues, the 2005 American Thoracic Society guideline recommend trough levels of 15-20 µg/mL for treatment of MRSA hospital-acquired pneumonia [106]. Current literature does not support peak concentration measurement [107].

3. Dosage table/nomogram in patients with impaired renal function (Table 3.2)
  - An initial single dose of 15 mg/kg should be given to achieve prompt therapeutic serum concentration. Subsequent daily maintenance dose is to be determined according to dosage table/nomogram.
  - The dosage table/nomogram is not valid for functionally anephric patients on dialysis. For such patients, the dose required to maintain stable concentrations is 1.9 mg/kg/day (~130 mg/day for a 70 kg person).

- For patients with marked renal impairment, it may be more convenient to give maintenance doses of 0.25 g to 1 g every 3-7 days.

**Table 3.2 Dosage table for vancomycin**

Creatinine clearance ( mL/min)	Vancomycin dose (mg/24h)
100	1 545
90	1 390
80	1,235
70	1 080
60	925
50	770
40	620
30	465
20	310
10	155

Adapted from vancomycin package insert, July 2004.

4. Vancomycin in **morbidly obese patients** [104, 107] (Table 3.3)
  - Serum clearance of vancomycin in morbidly obese patients was 2.3-2.5 times higher than that observed in non-obese subjects [104, 108].
  - Studies involving the pharmacokinetic of vancomycin in overweight and obese population have concluded that vancomycin clearance is best correlated with total body weight (TBW) [109]. In a study of 24 morbidly obese patients [104], the mean ( $\pm$ SD) vancomycin dose required to achieve steady state peak 25-35  $\mu$ g/mL and trough 5-10  $\mu$ g/mL were 1.9 g ( $\pm$ 0.5 g) q8h.

**Table 3.3 Calculation of vancomycin dosage for morbidly obese patient**

Steps	Calculation	Scenario: Female/30yr, body weight 200 kg, height 1.8 m, serum creatinine 80 µmol/L
Determine if the patient is morbidly obese	TBW/IBW ratio: 0.8–1.25 = normal >1.25–1.9 = obese >1.9 = morbid obesity	200/70.7 = 2.8
Determine dose of vancomycin	30 mg/kg TBW/day	6 g per day if normal renal function. (administer as I.V. 2 g q8h; infuse each 2 g dose over at least 2 h)
Estimate creatinine clearance (CrCl)	Cockcroft-Gault formula not accurate in morbidly obese patients. The Salazar-Corcoran equation appears to give the least biased estimate of CrCl	
Monitor trough level	Target trough at 5-10 µg/mL	Adjust dosing interval according to trough level

Equations [110] :

- Ideal body weight (IBW)
  - IBW for male = 50 kg + 0.9 kg for each cm over 152 cm (2.3 kg for each inch over 5 feet)
  - IBW for female = 45.5 kg + 0.9 kg for each cm over 152 cm (2.3 kg for each inch over 5 feet)
- Salazar-Corcoran equation (for estimate of creatinine clearance in morbidly obese patients):

Male patient, calculate CrCl as follows:

$$\frac{(137 - \text{age in years}) \times (\text{TBW in kg} \times 0.285) + (12.1 \times \text{height in meter})}{0.58 \times \text{serum creatinine in } \mu\text{mol/L}}$$

Female patient, calculate CrCl as follows:

$$\frac{(146 - \text{age in years}) \times (\text{TBW in kg} \times 0.287) + (9.74 \times \text{height in meter})}{0.68 \times \text{serum creatinine in } \mu\text{mol/L}}$$

<sup>a</sup> TBW, total body weight

## 3.2 Linezolid

1. Indications:
  - a. Indicated for Gram-positive bacteria including MRSA with reduced vancomycin susceptibility MIC  $\geq 2$   $\mu\text{g/mL}$ , vancomycin-resistant *S. aureus* (VRSA at MIC  $\geq 4$   $\mu\text{g/mL}$ ) and VRE and some mycobacteria (including *Mycobacterium tuberculosis*).
  - b. Infections by MRSA in the case of vancomycin failure (e.g. unexplained breakthrough bacteraemia) and/or serious allergy. In these complicated circumstances, the opinion of a clinical microbiologist / infectious disease physician should be sought.
2. Not active against Gram negative bacteria (e.g. *Haemophilus influenzae*, *Moraxella catarrhalis*).
3. Most VRE identified in Hong Kong so far are susceptible to linezolid (both *E. faecalis* and *E. faecium*) at  $\leq 4$   $\mu\text{g/mL}$  and quinupristin/dalfopristin (*E. faecium* only, at  $\leq 1$   $\mu\text{g/mL}$ ) [111]. However, multidrug resistant strains including linezolid-resistant clinical isolates of *Enterococcus faecalis*, *Enterococcus faecium* (VRE), *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 of linezolid includes myelosuppression; thrombocytopenia, anemia and neutropenia reported especially for treatment  $> 2$  weeks [112]; lactic acidosis, peripheral neuropathy, optic neuropathy due to inhibition of intramitochondrial protein synthesis [113]; serotonin syndrome (fever, tremor, agitation and mental state changes), risk with concomitant SSRI [114].
6. Please consult clinical microbiologist / infectious disease physician for the use of linezolid.



### 3.3 Daptomycin

#### 1. Indications

Active against Gram-positive bacteria only with proven in vitro activity against enterococci [including VRE and MRSA with vancomycin MIC  $\geq 2$   $\mu\text{g/mL}$ ].

Approved for use in serious skin and soft tissue infections (SSTI), MRSA bacteraemia and right-sided endocarditis.

2. Not indicated for pneumonia because of poor lung penetration and has not been studied for prosthetic valve endocarditis or meningitis.
3. Dosage: I.V. 4-6 mg/kg per day
4. Side effects of daptomycin include myopathy and rhabdomyolysis especially in patients taking statins. Elevated creatinine kinase in 2.8%. Cases of eosinophilic pneumonia related to the use of daptomycin has also been reported [115].
5. Please consult clinical microbiologist / infectious disease physician for the use of daptomycin.

### 3.4 Tigecycline

1. Indications: MRSA, VRE and other multidrug-resistant organism with in vitro activity, when standard treatment has failed or are contraindicated (e.g. allergy).
2. As for tetracyclines, this drug is not licensed for use in children.
3. Poorly active or not active against the non-fermenters, such as *Stenotrophomonas maltophilia*, *Pseudomonas* species and CRAB.
4. 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 [116].
5. Dosage:
  - I.V. loading dose of 100 mg, then 50 mg every 12 hours.
  - Given as slow I.V. infusion (30-60 minutes).
  - Half maintenance dose (25 mg every 12 hours) for patients with severe liver disease (Child's C).
6. Side effects similar to tetracycline.
7. Please consult clinical microbiologist / infectious disease physician for the use of tigecycline.

### 3.5 Colistin/colomycin

1. Main indication: treatment of multidrug-resistant Gram negative infections (e.g. CRE, pandrug-resistant *A. baumannii*, and *P. aeruginosa*).
2. Poor lung penetration after intravenous administration.
3. For pneumonia cases, use high intravenous dose with possible addition of nebulised colistin [117].
4. Dosage:
  - a. Nebulised 1 million units (80 mg) twice daily
  - b. Intravenous dosage

CrCl (mL/min)	I.V. colomycin dosage and frequency
>50	2 million units q8h
20-50	1 million units q8h
10-20	1 million units q12-18h
<10	1 million units q24h

5. Side effects: significant nephro- and neuro-toxicity
6. Please consult clinical microbiologist / infectious disease physician for the use of colistin.

## 3.6 Fosfomycin

1. Indications
  - a. Indicated for treatment of complicated or uncomplicated cystitis caused by ESBL-positive *Enterobacteriaceae*.
  - b. Systematic review showed 96.8% of ESBL-positive *E. coli* isolates and 81.3% of ESBL-positive *Klebsiella pneumoniae* isolates were susceptible to fosfomycin [118].
2. Inactive against enterococci.
3. Dosage:
  - a. Uncomplicated UTI: 3 g sachet P.O. x 1 dose with / without food
  - b. Complicated UTI: 3 g sachet P.O. every 2-3 days (up to 21 days) on an empty stomach
4. Please consult clinical microbiologist / infectious disease physician for the use of fosfomycin in treatment of infections other than uncomplicated cystitis.

## 3.7 Imipenem/meropenem/ertapenem

### 3.7.1 Indications for using imipenem/meropenem/ertapenem

1. Therapy of infections attributed to ESBL-positive bacteria (such as *E. coli* or *Klebsiella* spp.) such as:
  - Bacteraemia with isolation of ESBL-positive bacteria from blood culture.
  - Deep-seated infection with isolation of ESBL-positive bacteria from normally sterile body site or fluid (CSF, peritoneal fluid, pleural fluid, joint fluid, tissue, pus, etc.).
  - Nosocomial pneumonia, as defined by CDC guidelines, with isolation of ESBL-positive bacteria in a significant quantity, from a suitably obtained, good quality respiratory tract specimens<sup>a</sup>.
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*.)

#### Footnotes

<sup>a</sup> Colonization of the respiratory tract by ESBL-positive bacteria, especially in mechanically ventilated patients is common. Antimicrobial therapy of colonization is not indicated. Isolation of ESBL-positive bacteria at the indicated quantity and specimen type is suggestive of infection rather than colonization (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. Expecterated 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 colonization by ESBL-positive bacteria such as the isolation of these organisms from:
  - Surface swab of superficial wounds
  - Surface swab of chronic ulcers
  - 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/soft tissue infections, etc.
3. As known-pathogen therapy for infections caused by organisms susceptible to other beta-lactams.

### 3.8 Once daily aminoglycosides

1. Once daily aminoglycoside (ODA) dosing is as effective as multiple-daily dosing in most clinical settings. The former dosing probably results in a lower risk of nephrotoxicity than the latter. With ODA, any differences in the relative nephrotoxicity of the aminoglycosides are likely to be small. Nonetheless, there is considerable confusion on the dose and how to monitor serum aminoglycoside levels when using ODA dosing [119].
2. **Dosing to be based on actual body weight** unless the patient is morbidly obese (i.e. 20% over ideal body weight, IBW).

#### **Aminoglycoside dosing weight for morbidly obese patient**

= ideal body weight + 0.4 (actual body weight - IBW).

Formula for calculation of ideal body weight is as follows:

Ideal body weight for male = 50 kg + 0.9 kg for each cm over 152 cm (2.3 kg for each inch over 5 feet)

Ideal body weight for female = 45.5 kg + 0.9 kg for each cm over 152 cm (2.3 kg for each inch over 5 feet)

3. **For patient with impaired renal function**, give the first dose according to body weight as above. Subsequent frequency of administration (of the same dose) to be based on the estimated creatinine clearance of the patient according to the following table.

#### **Cockcroft-Gault formula**

To estimate creatinine clearance, calculate as follows

Creatinine clearance for male patient (mL/min) = (140-age) x 1.2 x ideal body weight (kg) / serum creatinine (mmol/L)

(Female: 0.85 x above value)

(Unit conversion for serum creatinine: mg/dL x 88.4 = mmol/L)

CrCl (mL/min)	Initial dosing interval <sup>a</sup>
>60	q24h
40-60	q36h
20-40	q48h
<20	Follow serial levels to determine time of next dose (level <1 µg/mL)

<sup>a</sup>At present, the dosage of aminoglycoside to use in a ODA strategy has not been clearly determined. Dosages for gentamicin, tobramycin and netilmicin have ranged from 3 to 7 mg/kg, and amikacin dosages have ranged from 11 to 30 mg/kg. On the basis of local experiences and a recent consensus meeting, the following doses are recommended for initial therapy in local Chinese: for gentamicin and tobramycin, 3.5 mg/kg; netilmicin, 4.4 mg/kg and amikacin, 15 mg/kg [119].

4. Therapeutic drug monitoring (TDM) [120-122]

Routine TDM **not** indicated in patients under the following conditions:

- (a) Receiving 24-h dosing regimen,
- (b) Without concurrently administered nephrotoxic drugs (e.g. vancomycin, amphotericin B, cyclosporin),
- (c) Without exposure to contrast media,
- (d) Not quadriplegic or amputee,
- (e) Not in the ICU,
- (f) Younger than age 60 years,
- (g) Duration of planned therapy less than 5 to 7 days.



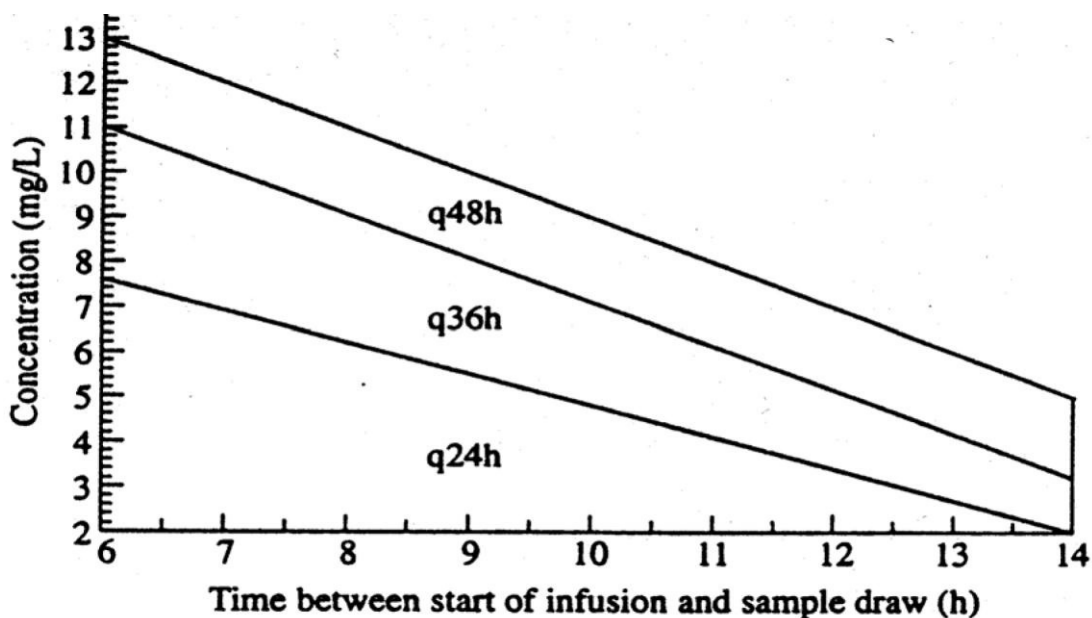
If therapeutic drug monitoring is indicated (e.g. due to impaired renal function), check level and interpret the result as follows:

- a) For once daily (extended-interval) dosing, obtain a single blood sample **after the first dose** between 6-14 h after the start of the infusion. Do not check pre- and post-dose.
- b) Write down the time in number of hours after last dose in request form (e.g. 8 h post-dose). This is essential for result interpretation.
- c) When result becomes available, plot the value on the Hartford normogram (Table 3.4) and work out the appropriate dosing interval by the following table. With this method, the size of each dose need not be reduced.

<b>Post-dose level</b>	<b>Dosing interval</b>
Level falls in the area designated q24h	Dose at an interval of every 24 h
Level falls in the area designated q36h	Dose at an interval of every 36 h
Level falls in the area designated q48h	Dose at an interval of every 48 h
Level on the line	Choose the longer interval
Level off the normogram at the given time	Stop the scheduled therapy, obtain serial levels to determine the appropriate time of the next dose

**Table 3.4 Hartford Hospital once-daily aminoglycoside normogram for gentamicin and tobramycin**

The Hartford normogram has not been validated in the following category of patients: paediatrics, pregnancy, burns (>20%), ascites, dialysis, enterococcal endocarditis.



## 3.9 Antifungal agents

1. Recently, an increasing number of antifungal agents have become available. The mechanism of action for the major antifungal classes is summarized in Table 3.5.
2. It is important to note that there are significant within and between class variations in the antifungal spectrum of the agents (Table 3.6). They also differ in their pharmacokinetic properties (Table 3.7 and 3.8). The need to adjust dosage in renal and hepatic dysfunction is summarized in Table 3.9.
3. Echinocandins are not active or show very limited activity against *Cryptococcus neoformans*, *Trichosporon beigeli*, dematiaceous moulds, *Zygomycetes*, *Fusarium* species and dimorphic fungi (*Blastomyces*, *Histoplasma*, *Coccidioides*) because these fungi do not have the target for the echinocandins to act.
4. Fluconazole show potent 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 3.10 summarized the antifungal agents that have been evaluated in randomized clinical trials (RCT) for the 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 3.11 showed a suggested scheme for choosing antifungals.

**Table 3.5 Mechanisms of antifungal action**

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

**Table 3.6 General patterns of antifungal susceptibility**

	FLU	ITR	5FC	AMB	VOR	POS	CAS	MFG	AFG
<b>Yeasts</b>									
<i>C. albicans</i>	S	S	S	S	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S	S	S	S	S
<i>C. glabrata</i>	S-DD to R	S-DD to R	S	S-I	S	S	S	S*	S
<i>C. krusei</i>	R	S-DD to R	I-R	S-I	S	S	S	S	S
<i>C. lusitanae</i>	S	S	S	S-R	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S	S	I	S*	S
<i>C. guilliermondii</i>	S	S	S	S	S	S	I	S	S
<i>Cryptococcus neoformans</i>	S	S	S	S	S	S	R	R	R
<i>Trichosporon</i>	R	I	R	I	S	S	R	R	R
<b>Moulds</b>									
<i>Fusarium</i>	R	R	R	++	++	++	R	R	R
<i>Aspergillus</i>	R	+	+	+	++	+++	++	++	++
<i>Pseudallescheria</i>	R	S	R	R	++	++	R	R	R
<i>Zygomycetes</i>	R	+	R	+	R	+	R	R	R
<b>Dimorphic fungus</b>									
<i>H. capsulatum</i>	+	++	R	++	++	++	R	R	R
<i>P. mameffeii</i>	+	++	+	++	++	++	R	R	R

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

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

\*Sporadic cases of breakthrough *C. glabrata* and *C. parapsilosis* infection have been reported in the literature

Reference: [101, 123-133]

**Table 3.7 Comparison of selected pharmacokinetic parameters for the azoles and caspofungin**

Generic name (Trade name)	Fluconazole (Diflucan)	Itraconazole (Sporanox)	Voriconazole (Vfend)	Posaconazole (Noxafil)
Oral bioavailability	>80%	Capsule: 30-55% Solution: 60-80%	90%	> 90%
C <sub>max</sub>	10.2	0.2-0.4 mg/L after 2-4 h of 200 mg oral	2 mg/L after 250 oral	0.28 mg/L after 5 hours
Time to C <sub>max</sub> (hour)	2-4	4-5	1-2	3-5
CSF penetration	50-94%	<1%	20-50%	<1%
Plasma half-life (hour)	22-35	24-42	6-24	35
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
Principal route of elimination	Renal	Hepatic	Hepatic	Hepatic
Active drug in urine (%)	80	<1	2%	14%
Dosage	Oral or I.V. 50-400 mg/day depending on indications	200-400 mg/day	Adult, oral, 200-400 mg 12-hourly for 24 h, then, 100-200 mg 12-hourly; I.V. 6 mg/kg 12 hourly for 24 h, then 4 mg/kg 12 hourly	<i>Aspergillosis / Candida:</i> Adult, oral 200 mg 8-hourly <i>Mucormycosis / Cryptococcus:</i> Adult, oral 400 mg 12 hourly
Renal insufficiency	Reduce dose; removed by haemodialysis	Usual dose. At CFR < 10 ml/min, some recommend decrease dose 50%	No dose adjustment need with oral voriconazole. Avoid I.V. voriconazole in renal failure.	No dose adjustment necessary
Hepatic insufficiency	-	Avoid	Mild to moderate (Child A/B) same loading, reduce maintenance 50% Avoid in severe impairment	-

**Table 3.8 Comparison of selected pharmacokinetic parameters for the azoles and caspofungin**

Generic name (Trade name)	Caspofungin (Cancidas)	Anidulafungin (Eraxis)	Micafungin (Mycamine)
Oral bioavailability	Only I.V.	Only I.V.	Only I.V.
Cmax	10 mg/L end infusion	3.55 to 10.9 mg/L	10 mg/L end infusion
Time to Cmax (hour)	-	-	-
CSF penetration	Unknown (Very low)	Unknown	Undetectable
Plasma half-life (hour)	9-11 (terminal half-life 40-50)	26	11-21
Tissue distribution	Widely distributed; highest concentration in liver.	Widely distributed	Widely distributed
Principal route of elimination	Hepatic	-	Hepatic
Active drug in urine (%)	1%	<1%	<15%
Dosage	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	No dose adjustment needed. Not removed by haemodialysis	No dose adjustment	No dose adjustment Poorly dialysed
Hepatic insufficiency	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 3.9 Need for dosage adjustment in renal and hepatic dysfunction**

		Anidulafungin	Micafungin	Caspofungin	Voriconazole
Renal dysfunction	CrCl (mL/min)				
Mild	50-80	No	No	No	No
Moderate	31-49	No	No	No	Avoid I.V.
Severe	>30	No	No	No	Avoid I.V.
Hepatic dysfunction	Child-Pugh Score				
Mild	5-6	No	No	No	Reduce 50% dose
Moderate	7-9	No	No	Reduce from 50 mg to 35 mg	Reduce 50% dose
Severe	>9	No	?	?	?



**Table 3.10 Randomized control trials conducted on licensed antifungals**

Antifungal Prophylaxis	Neutropenic Fever	Invasive Aspergillosis	Candidemia or Invasive Candidiasis	Esophageal Candidiasis
Voriconazole vs. placebo [134]	Micafungin vs. caspofungin [135]	<u>Posaconazole</u> vs. liposomal amphotericin B ± *caspofungin [136]	Caspofungin vs. amphotericin B [126]	Caspofungin vs. amphotericin B [137, 138]
* <u>Micafungin</u> vs. fluconazole [139, 140]	* <u>Caspofungin</u> vs. liposomal amphotericin B [141, 142]	* <u>Voriconazole</u> vs. amphotericin B [127]	Caspofungin (standard vs. high dose) [143]	Caspofungin vs. fluconazole [144]
* <u>Itraconazole</u> vs. fluconazole [145, 146]	Voriconazole vs. liposomal amphotericin B [147]	Liposomal amphotericin B (standard dose vs. high loading dose) [148]	Anidulafungin vs. fluconazole [149]	Anidulafungin vs. fluconazole [150]
* <u>Posaconazole</u> vs. fluconazole or itraconazole [151-153]	Itraconazole vs. amphotericin B [154, 155]		Micafungin vs. caspofungin [131]	* <u>Micafungin</u> vs. fluconazole [156, 157]
Voriconazole/ posaconazole vs. fluconazole/ itraconazole [158]	Amphotericin B (conventional vs. liposomal) [159-161]		Micafungin vs. liposomal amphotericin B [162-164]	Voriconazole vs. fluconazole [165]
Liposomal amphotericin B vs. placebo inhalation [166]			Voriconazole vs. amphotericin B followed by fluconazole [167]	

\*Agent with superior results for some outcomes is underlined.

**Invasive aspergillosis:** posaconazole superior and safer than liposomal amphotericin B with fewer nephrotoxicity and hepatotoxicity [136]. Voriconazole superior and safer than amphotericin B [127].

**Neutropenic fever:** caspofungin superior and safer than liposomal amphotericin B with fewer nephrotoxicity [141] and comparable [142].

**Antifungal prophylaxis:** micafungin superior to fluconazole in HSCT patients [139] and comparable [140]. Itraconazole superior to fluconazole in acute myelogenous leukaemia (AML) and myelodysplastic syndrome (MDS) patients [145] and HSCT patients [146]. Posaconazole superior to fluconazole/ itraconazole in AML and MDS patients [151].

**Table 3.1.1 A suggested scheme for systemic antifungal agents**

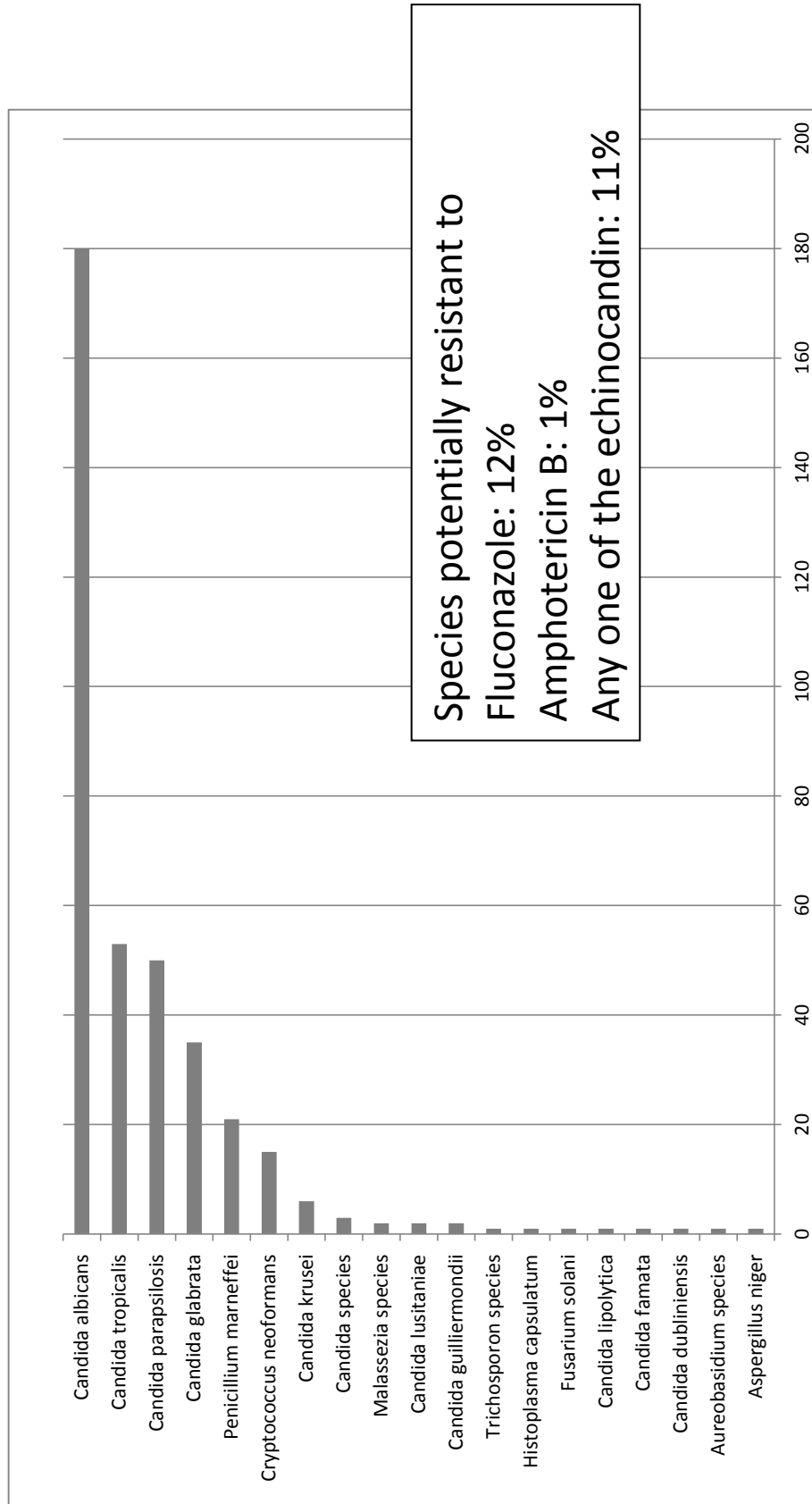
	First-Line	Alternative	Comments
<b>INVASIVE CANDIDIASIS</b>			
Neutropenic or critically ill	Anidulafungin, micafungin, caspofungin, amphotericin B	Voriconazole, posaconazole,	Consider agent other than echinocandin for serious infection due to <i>C. guilliermondii</i> & <i>C. parapsilosis</i>
Stable and nonneutropenic	Fluconazole	Itraconazole	Evidence is mainly for <i>C. albicans</i> . It also works for <i>C. parapsilosis</i> and <i>C. tropicalis</i>
<b>INVASIVE ASPERGILLOSIS</b>			
	Voriconazole	Anidulafungin, micafungin, caspofungin, amphotericin B	*Posaconazole

The diagnosis and treatment of systemic fungal infection is complicated. The newer anti-fungal agents (e.g. posaconazole, micafungin, anidulafungin) should be used at the specific advice of a specialist.

\*Posaconazole: no intravenous formulation available. Steady state level may not be achieved for up to a week, impacting use as initial therapy for invasive aspergillosis.

Reference: [101, 124, 133]

**Figure 3.1 Distribution by species for 377 episodes of fungaemia in HA hospitals, 2010-2011**



**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]
<b>Musculoskeletal infections</b>				
<b>Septic arthritis, adult</b>	<i>S. aureus</i> ; streptococci, <i>N. gonorrhoeae</i>	I.V. cloxacillin + ampicillin	I.V. ceftriaxone or cefazolin (If <i>N. gonorrhoeae</i> is suspected, ceftriaxone is the preferred regimen)	<ul style="list-style-type: none"> <li>Urgent diagnostic tapping for gram stain to guide therapy.</li> <li>If smear reveal Gram-negative cocci or bacilli: ceftriaxone or cefotaxime to replace cloxacillin.</li> <li>Factors suggest <i>N. gonorrhoeae</i> etiology: sexually active teenager/adult ± rash.</li> <li>Consider dilute cloxacillin into larger volume of solution (e.g. 250 ml D5 solution ) to avoid infusion related skin irritation.</li> </ul>
<b>Osteomyelitis, haematogenous, adult</b>	<i>S. aureus</i>	I.V. cloxacillin	I.V. cefazolin or ceftriaxone	<ul style="list-style-type: none"> <li>Occasionally <i>Salmonella</i> spp.</li> <li>Often vertebral.</li> <li>IVDU: <i>S. aureus</i> (vertebral); <i>P. aeruginosa</i> (ribs, sternoclavicular joint).</li> <li>Associated with MRSA bacteraemia: vancomycin [168].</li> </ul>

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<b>Diabetic foot infection</b>				
(a) Previously untreated, no osteomyelitis	<i>S. aureus</i> , beta-haemolytic streptococci	Amoxicillin-clavulanate or ampicillin-sulbactam [169]	Clindamycin or cephalixin	
(b) Chronic, recurrent, limb threatening	Polymicrobial: aerobes + anaerobes	P.O. levofloxacin/ciprofloxacin + P.O. clindamycin or amoxicillin-clavulanate or ampicillin-sulbactam [169]	Piperacillin-tazobactam or imipenem	Cultures from ulcers unreliable. Early radical debridement to obtain tissue for culture; to exclude necrotizing fasciitis and for cure. Ability to insert probe to bone suggest concomitant osteomyelitis.
<b>Skin and soft tissue infections</b>				
<b>Erysipelas or cellulitis</b>	Groups A, B, C, G streptococci (± <i>S. aureus</i> )	(I.V. penicillin or I.V. ampicillin or P.O. amoxicillin) + I.V./P.O. cloxacillin	Cephalexin or amoxicillin-clavulanate or ampicillin-sulbactam	In HK, Group A streptococci : more often resistant to clindamycin (50-80%) [170].

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<b>Necrotizing fasciitis [171]</b>				
1. Following exposure to freshwater; seawater or seafood	<i>Aeromonas hydrophila</i> , <i>A. caviae</i> ; <i>Vibrio vulnificus</i>	I.V. fluoroquinolone + I.V. amoxicillin-clavulanate		Immediate surgical intervention essential. Urgent consult clinical microbiologist.
2. Following cuts and abrasion; recent chickenpox; IVDU; healthy adults	Group A streptococci	I.V. penicillin G + I.V. linezolid [172]		Add high dose IVIG (1–2 g/kg for 1 dose) for streptococcal toxic shock syndrome [173] <sup>a</sup> . In HK, Group A streptococci: more often resistant to clindamycin (50–80%) [170].
3. Following intra-abdominal; gynaecological or perineal surgery [174]	Polymicrobial: <i>Enterobacteriaceae</i> , streptococci, anaerobes	I.V. imipenem or meropenem	I.V. amoxicillin-clavulanate + levofloxacin	
<b>Bite wound</b> (animal or human) [175]	streptococci, <i>S. aureus</i> , anaerobes, <i>Pasteurella multocida</i> (dog), <i>Capnocytophaga</i> spp. (dog), <i>Eikenella</i> spp. (human)	Amoxicillin-clavulanate	Penicillin V or ampicillin + cloxacillin	<ul style="list-style-type: none"> <li>• Risk of infection after dog bite = 80%.</li> <li>• Monotherapy with penicillin, cloxacillin or first generation cephalosporin inadequate.</li> <li>• Penicillin allergy: Clindamycin plus (levofloxacin /moxifloxacin).</li> </ul>



	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<b>Central nervous system infections</b>				
<b>Brain abscess</b>	Usually polymicrobial with aerobes and anaerobes	Ceftriaxone + metronidazole	Cefotaxime + metronidazole	<ul style="list-style-type: none"> <li>• Urgent consult neurosurgical.</li> <li>• Exclude primary focus in middle ear, mastoid, paranasal sinuses, dental and lung.</li> </ul>
<b>Meningitis [176]</b>	<i>S. suis</i> , <i>S. pneumoniae</i> , <i>N. meningitidis</i> , Group B streptococcus	[Ceftriaxone or cefotaxime] plus vancomycin	Meropenem plus vancomycin	<ul style="list-style-type: none"> <li>• If impaired cellular immunity e.g. high dose steroid, add ampicillin to cover <i>Listeria</i> spp.</li> <li>• If rapid test (e.g. Gram smear, antigen detection) or other clues suggest <i>S. pneumoniae</i>, add vancomycin until sensitivity data available. For pen-R <i>S. pneumoniae</i> (MIC <math>\geq 2</math>), 77% and 5% are respectively intermediate and resistant to Ceftriaxone [177, 178].</li> <li>• 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 [179].</li> </ul>

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<b>Intra-abdominal and GI system infections (community-acquired)</b>				
<b>Secondary peritonitis</b> (PPU, other bowel perforation, ruptured appendicitis, diverticulitis)	<i>Enterobacteriaceae</i> , <i>B. fragilis</i> , other anaerobes, enterococci	Cefuroxime + metronidazole	Amoxicillin-clavulanate or ampicillin-sulbactam	<ul style="list-style-type: none"> <li>• Surgical intervention essential.</li> <li>• BL/BLIs cover anaerobes including <i>B. fragilis</i>.</li> </ul>
<b>Cholangitis, cholecystitis or other biliary sepsis</b>	<i>Enterobacteriaceae</i> , enterococci, <i>Bacteroides</i>	Amoxicillin-clavulanate or ampicillin-sulbactam	Ticarcillin-clavulanate or (cefuroxime + metronidazole)	<ul style="list-style-type: none"> <li>• Adequate biliary drainage essential.</li> <li>• BL/BLIs cover most <i>Enterobacteriaceae</i>, enterococci and anaerobes.</li> </ul>

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<b>Liver abscess</b> (community-acquired)	<i>Klebsiella pneumoniae</i> and other <i>Enterobacteriaceae</i> , <i>Bacteroides</i> , enterococci, <i>Entamoeba histolytica</i> , <i>Streptococcus milleri</i>	Ceftriaxone + metronidazole (for <i>E. histolytica</i> )	Amoxicillin-clavulanate + metronidazole (for <i>E. histolytica</i> )	<ul style="list-style-type: none"> <li>For all cases: serology for <i>E. histolytica</i>.</li> <li>CT guided or open drainage for large abscess.</li> <li>For amoebic infection: Metronidazole for 10 days then followed by diloxanide.</li> <li>Ophthalmological assessment to rule out endophthalmitis if pus aspirate grew <i>Klebsiella pneumoniae</i>. Endogenous endophthalmitis in patient with <i>Klebsiella</i> liver abscess occurred in 3% to 10.4%, esp. if DM [180-185].</li> <li>Ceftriaxone is the drug of choice for better CNS penetration if concomitant CNS involvement is likely to occur.</li> </ul>
<b>Mild to moderate gastroenteritis</b>	Food poisoning ( <i>B. cereus</i> , <i>S. aureus</i> , <i>C. perfringens</i> ), <i>Salmonella</i> spp., <i>E. coli</i> , <i>Campylobacter</i> spp., <i>Aeromonas</i> spp.	Routine antibiotic therapy not recommended		Fluid and electrolytes replacement.

Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<p><b>Moderate to severe gastroenteritis</b> (presume bacterial) in persons with immunosuppressive disease (e.g. for HIV +ve; high dose steroid when laboratory results not available)</p>	<p><i>Salmonella</i> spp, <i>Campylobacter</i> spp.</p> <p>Fluoroquinolone</p>		<p>Fluoroquinolone resistance among <i>Campylobacter</i> increasing. If symptoms not improving or worsening when diagnosis of <i>campylobacter</i> gastroenteritis is made; stop fluoroquinolone and prescribe a course of oral macrolide for 5-7 days.</p>
<p><b>Severe gastroenteritis</b> (laboratory results not available)</p>	<p>≥6 unformed stool /day, fever ≥38.5°C; tenesmus; blood or faecal WBC +ve</p> <p>Fluoroquinolone</p>		<p>Add metronidazole if suspect <i>Clostridium difficile</i> infection; replace fluid and electrolytes; avoid antimotility agents. Please refer to KPT if suspected <i>Clostridium difficile</i> infection.</p>
<p><b>Cardiovascular infections</b></p> <p><b>Subacute infective endocarditis</b> (CRHD, degenerative or congenital valvular diseases) [186-189]</p>	<p><i>S. viridans</i>, <i>HACEK</i>, enterococci</p> <p>I.V. ampicillin 2 g q4h + gentamicin 1 mg/kg q8h</p>		<p>Obtain at least 3 sets of blood cultures by 3 different venepuncture over 24 h (label '? IE' in laboratory form); then start I.V. antibiotics [190]. <i>HACEK</i>: Ceftriaxone</p>

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<b>Acute infective endocarditis</b> (IVDU) [186-189]	<i>S. aureus</i>	I.V. cloxacillin 2 g q4h + gentamicin 1 mg/kg q8h for the first 5 days	I.V. cefazolin 2 g q8h	<ul style="list-style-type: none"> <li>• Usually tricuspid valve infection ± metastatic lung abscesses.</li> <li>• Blood culture q30min × 3 sets (label 'IE' in laboratory form); then start I.V. antibiotics immediately [190].</li> </ul>
<b>Gynaecological infections</b>				
<b>Pelvic inflammatory disease</b> (or upper genital tract infection) [191, 192]	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , <i>Enterobacteriaceae</i> , anaerobes	Inpatient: I.V. cefoxitin 1-2 g q6h or (I.V. amoxicillin-clavulanate + doxycycline) or (I.V. ceftriaxone + doxycycline ± metronidazole) [191, 192]	Inpatient: I.V. clindamycin 600-900 mg q8h + gentamicin [193]	<p>Coverage of anaerobes important in tubo-ovarian abscess, co-existing bacterial vaginosis, HIV +ve [194].</p> <p>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 [191, 192].</p> <p>Due to high prevalence of gonococcal resistance, oral ceftibuten, fluoroquinolones not suitable for empirical treatment of acute PID [195, 196].</p>
<b>Breast abscess</b>	Usually <i>S. aureus</i> (± anaerobes in non-puerperal abscess)	I.V./P.O. cloxacillin (+ P.O. metronidazole if anaerobes likely)	Cefazolin or amoxicillin-clavulanate or ampicillin-sulbactam	I & D essential; send pus for Gram smear and culture.

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<b>Head and neck infections</b>				
<b>Odontogenic or neck infection</b>	Oral anaerobes	(I.V. penicillin + P.O. metronidazole) or I.V./P.O. clindamycin	Amoxicillin-clavulanate or ampicillin-sulbactam	
<b>Urinary tract infections</b>				
<b>Cystitis [197, 198]</b>	<i>E. coli</i> ; <i>S. saprophyticus</i> , Group B streptococcus	P.O. nitrofurantoin or amoxicillin-clavulanate	P.O. levofloxacin	Encourage fluid intake. Increasing numbers of fluoroquinolone-resistant <i>E. coli</i> in the community have already been found, thus restricting the empirical use of fluoroquinolones as suggested in IDSA and EAU guidelines [197, 199].
<b>Acute pyelonephritis [197, 198]</b>	<i>Enterobacteriaceae</i> , enterococcus, ( <i>Pseudomonas</i> in catheter-related, obstruction, transplant)	I.V. amoxicillin-clavulanate	(Piperacillin-tazobactam if suspect <i>P. aeruginosa</i> ) or Imipenem or Meropenem	Blood culture and 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]
<b>Respiratory tract infections</b>				
<b>Acute bacterial exacerbation of COPD</b> (AECB) [200-203]	Respiratory viruses, <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i>	I.V./P.O. amoxicillin-clavulanate	Cefotaxime or a new anti-Gram positive fluoroquinolone <sup>b</sup> for multi-resistant <i>S. pneumoniae</i> with penicillin (MIC >8 µg/mL)	<ul style="list-style-type: none"> <li>• Latest GOLD 2011 Recommendation: Antibiotics should be given to patients with: <ul style="list-style-type: none"> <li>a. Following three cardinal symptoms: increased dyspnoea, increased sputum volume, increased sputum purulence;</li> <li>b. Increased sputum purulence and one other cardinal symptom;</li> <li>c. Requiring mechanical ventilation</li> </ul> </li> </ul>
	Appropriate use of antibiotics in AECB is imperative to help control the emergence of multidrug resistant organisms			<ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i> (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.i.d. if co-infection by ampicillin-resistant <i>H. influenzae</i>) [202].</li> <li>• Penicillin allergy or at risk of <i>P.aeruginosa</i> : P.O. levofloxacin</li> </ul>

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<b>Acute bacterial exacerbation or pneumonia in patient with bronchiectasis</b>	<i>P. aeruginosa</i> <i>H. influenzae</i> , <i>M. catarrhalis</i> , <i>S. pneumoniae</i>	P.O. levofloxacin/ ciprofloxacin or I.V. ticarcillin- clavulanate or I.V. cefoperazone+ sulbactam	I.V. piperacillin tazobactam	For <i>P. aeruginosa</i> , levofloxacin should be given at high dose (e.g. P.O. 500-750 mg once daily).
<b>Aspiration pneumonia</b>	Oral anaerobes: <i>Bacteroides</i> , <i>Peptostreptococci</i> , <i>Fusobacterium</i> , <i>S. milleri</i>	I.V./P.O. amoxicillin- clavulanate or (I.V. ceftriaxone + P.O. metronidazole)	I.V. ticarcillin- clavulanate or cefoperazone+ sulbactam	Penicillin allergy: Levofloxacin plus (clindamycin or metronidazole)
<b>Community-acquired pneumonia (CAP)</b>				
1. CAP, not hospitalized	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. pneumoniae</i> , <i>C. pneumoniae</i> , <i>C. psittaci</i> (influenza A, <i>M. tuberculosis</i> )	P.O. amoxicillin- clavulanate (eg 1 g b.i.d.) ± a macrolide or P.O. high dose amoxicillin (at least 1.5 g/day) + a newer macrolide	Levofloxacin	Penicillin allergy: Levofloxacin Meta-analysis of 127 studies (n=33 148): <i>S. pneumoniae</i> (73%); <i>H. influenzae</i> (14%); <i>S. aureus</i> (3%); Gram-negative rods (2%). In Hong Kong, macrolide/azalide, tetracycline or cotrimoxazole should not be used alone for empiric treatment of CAP. Locally, 50–70% pen-S and pen-R <i>S. pneumoniae</i> isolates (both community and hospital isolates) are multi-resistant to these agents [1, 204, 205].



Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<p><b>Community-acquired pneumonia (CAP)</b></p> <p>2. CAP, hospitalized in general ward [206-208]</p>	<p>As above</p> <p>I.V./P.O. amoxicillin-clavulanate ± a macrolide</p> <p>(Macrolide-resistant <i>M. pneumoniae</i> is emerging in Hong Kong. Such organisms may be treated with doxycycline.)</p>	<p>Ceftriaxone ± a macrolide</p>	<p>Modifying factors: bronchiectasis: either (ticarcillin-clavulanate or piperacillin-tazobactam or cefepime) + a macrolide; or fluoroquinolone + an aminoglycoside</p> <p>Rapid test for diagnosis of Legionella infection:                      -Urine antigen for <i>Legionella pneumophila</i> serogroup 1 (sensitivity 70%, specificity 100%), or                      -Detection of nucleic acid of <i>Legionella</i> species from respiratory specimens by a validated assay (e.g. PCR) in <u>selected cases</u>.</p>

Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<p>3. CAP, hospitalized in ICU or serious pneumonia [206-208]</p>	<p>As above + <i>Enterobacteriaceae</i></p>	<p>I.V. piperacillin-tazobactam or ceftriaxone + a macrolide</p>	<p>Ticarcillin-clavulanate and ceftazidime are not useful against penicillin-non-susceptible <i>S. pneumoniae</i>.</p> <p>Rapid test for diagnosis of <i>Legionella</i> infection:</p> <ul style="list-style-type: none"> <li>-Urine antigen for <i>Legionella pneumophila</i> serogroup 1 (sensitivity 70%, specificity 100%), or</li> <li>-Detection of nucleic acid of <i>Legionella</i> species from respiratory specimens by a validated assay (e.g. PCR) in <u>all cases</u>.</li> </ul> <p>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 <i>S. aureus</i>: shock, haemoptysis, leucopenia, multilobular infiltrates, etc.), then add I.V. linezolid 600 mg q12h (preferred) or I.V. vancomycin 1 g q12h</p> <p>With concern for influenza: add oseltamivir 75 mg b.i.d.</p>

Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
<b>Hospital-acquired pneumonia (HAP)</b>			
HAP, onset <4 days after admission + no previous antibiotics [209]	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i> , <i>S. aureus</i>	I.V./P.O. amoxicillin-clavulanate	Penicillin allergy such as severe reactions, Steven-Johnson syndrome
HAP, onset ≥4 days after admission + had antibiotics recently, OR onset ≥5 days after admission OR mechanical ventilation [209]	MRSA; <i>P. aeruginosa</i> , <i>Acinetobacter</i> , <i>Klebsiella</i> spp., <i>Enterobacter</i> spp.	I.V. cefoperazone-sulbactam or cefepime	<ul style="list-style-type: none"> <li>• With ESBL concern: I.V. imipenem/ meropenem</li> <li>• With MRSA concern: Add vancomycin</li> </ul>
		Ticarcillin-clavulanate or piperacillin-tazobactam	

**Footnote**

**<sup>a</sup> Classification and definition of group A streptococcal toxic shock syndrome [210]**

*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  $\leq 90$  mm Hg in adults or  $< 5$ th percentile for age in children, and

Criteria IIB:  $\geq 2$  of the following signs:

- (a) Renal impairment: creatinine  $\geq 177$   $\mu\text{mol/L}$  for adults or  $> 2\times$  the upper limit of normal for age. In patients with pre-existing renal disease, a  $\geq 2$ -fold elevation over the baseline level.
- (b) Coagulopathy: platelets  $\leq 100,000/\text{mm}^3$  or DIC defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products.
- (c) Liver involvement: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels  $> 2\times$  the upper limit of normal for age. In patients with pre-existing liver disease a  $\geq 2$ -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 generalized oedema, or pleural or peritoneal effusions with hypoalbuminaemia.
- (e) A generalized erythematous macular rash that may desquamate.
- (f) Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene.

**b** Caution required as unique groups of COPD patients appears to be the main reservoir of levofloxacin-resistant *S. pneumonia* [211]. Suboptimal dose of levofloxacin has been associated with levofloxacin-resistant *S. pneumonia* [211]. Ofloxacin and ciprofloxacin should **not** be used for treatment of pneumococcal infection. Levofloxacin is the L-isomer of the racemate, ofloxacin. The MICs of most pneumococci in Hong Kong are close to the breakpoint of levofloxacin. In patients with acute purulent exacerbation of chronic bronchitis, failures appeared to be common in those with pneumococci (failures in 65%, 13/20) [212]. The recommended dose for levofloxacin is 500 mg once daily that for moxifloxacin is 400 mg once daily. Opinion from clinical microbiologist suggested if use of fluoroquinolone is contemplated.

## 4.2 Guidelines on the use and choice of antibiotics in severe acute pancreatitis

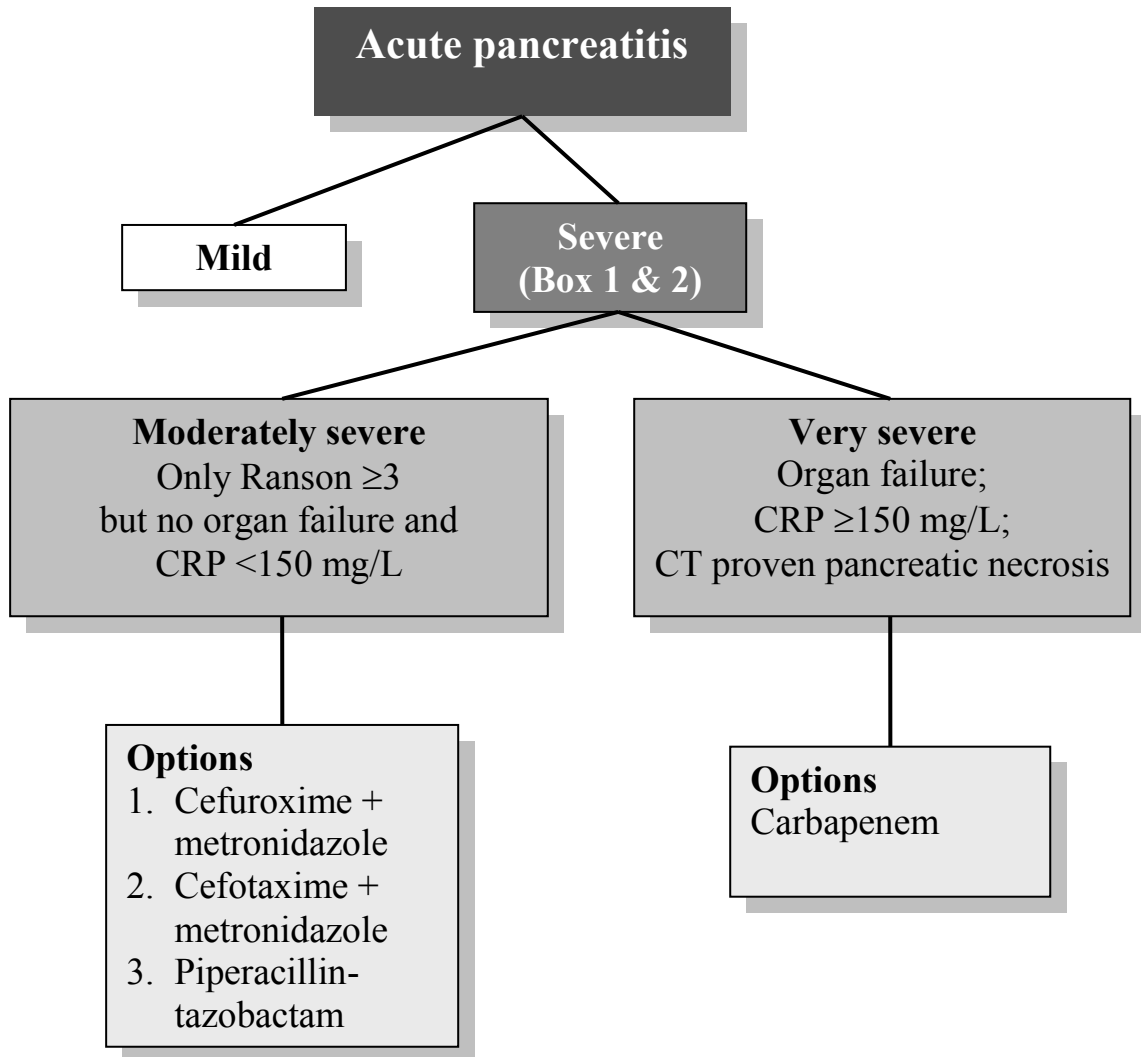
- 1. Criteria for severity assessment of acute pancreatitis** (Table 4.2). Most acute pancreatitis is mild. Severe acute pancreatitis (SAP) occurs in about 5-13% of all patients with mortality rates of 30% [213, 214]. SAP is commonly defined as having any of the following 4 criteria: (a) organ failure; (b) local complication such as necrosis, pseudocyst, or abscess; (c) Ranson score  $\geq 3$ ; or (d) at least 8 of the APACHE II criteria [215]. Of all markers available, CRP is the single most useful parameter in predicting the severity of acute pancreatitis [216].
- 2. Infection risk and antibiotic prophylaxis:** Pancreatic or peripancreatic infection occurs in 30-40% patients who have >30% pancreatic necrosis in CT staging. In patients with necrosis involving more than one-half of the pancreas, the incidence of subsequent infection is as high as 40–70%. Infection typically occurs in the second or third week after presentation [217]. Infection usually occurs at least 10 days after the onset of SAP. In patients with severe acute pancreatitis, the early data suggests that prophylactic antibiotic reduce infection and mortality [218-222], but the most recent double blind randomized studies, published in 2004, 2007 and 2009 cannot confirm a beneficial effect in reduction of mortality [213, 223, 224]. Inconsistent conclusion was also noted in two recently published meta-analysis [225, 226]. Further investigation has to be performed in this area.
- 3. Choice of antibiotics** (Figure 4.1): However, if antibiotic is to be given, the agents should be able to penetrate into pancreatic tissue. Good pancreatic tissue concentrations have been documented for cefotaxime, piperacillin, imipenem and metronidazole [227]. In terms of activity, it seems reasonable to provide coverage for the enteric Gram-negative bacilli and anaerobes. Carbapenem group of antibiotic should be reserved for the most severe form of disease (i.e. SAP with highly suspected or documented pancreatic necrosis).
- 4. Duration of prophylactic antibiotics: 5 to 14 days** depending on disease severity and patient progress [218-222, 227-229]. Excessive and prolonged antibiotic use in this setting is known to cause fungal super-infection and emergence of antibiotic-resistant bacteria, and should be avoided [230, 231].

5. Consider CT or US guided-FNA of necrotic area for culture if secondary pancreatic infection is suspected and if fever or leukocytosis persist or develops beyond 7-10 days.

**Table 4.2 Criteria for severity assessment of acute pancreatitis**

Box 1. Ranson's criteria	Box 2. Organ failure
<p>One point for each of:</p> <p><b>At admission</b></p> <ul style="list-style-type: none"> <li>• Age &gt; 55 years</li> <li>• WBC &gt;16 000/<math>\mu</math>L</li> <li>• Glucose &gt;11.1 mmol/L (&gt;200 mg/dL)</li> <li>• LDH &gt;350 IU/L</li> <li>• AST &gt;250 IU/L</li> </ul> <p><b>During initial 48 hours</b></p> <ul style="list-style-type: none"> <li>• Haematocrit decrease &gt;10%</li> <li>• BUN increase &gt;1.8 mmol/L (&gt;5 mg/dL)</li> <li>• Calcium &lt;2 mmol/L (&lt;8 mg/dL)</li> <li>• PaO<sub>2</sub> &lt;60 mm Hg</li> <li>• Base deficit &gt;4 mEq/L</li> <li>• Fluid sequestration &gt;6 L</li> </ul>	<ul style="list-style-type: none"> <li>▪ CVS: shock (SBP &lt;90 mm Hg or mean arterial pressure &lt;70 mm Hg or inotropic support)</li> <li>▪ Resp: PaO<sub>2</sub> &lt;60 mm Hg or ventilator dependent</li> <li>▪ Renal: Urea &gt;7.4 mmol/L or Creatinine &gt;250 <math>\mu</math>mol/L or requiring renal replacement</li> <li>▪ Gastrointestinal: bleeding &gt;500 mL in 24 hours</li> </ul>

**Figure 4.1 Prophylactic use of antibiotic in acute pancreatitis**





## 4.3 Management of community-acquired pneumonia

### 4.3.1 General considerations and principles

1. A number of guidelines on the management of community-acquired pneumonia (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 [206-208].
2. All agreed that *S. pneumoniae* is the most common pathogen in CAP including those without an identifiable etiology. 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 within 8 hours of hospitalization. Prior studies indicated that compliance with this recommendation is associated with a significant reduction in mortality [232].
4. **Factors to be considered in choosing empirical therapy for CAP:**
  - (a) **Place of therapy** (outpatient, inpatient ward, or intensive care unit).
  - (b) **Role of atypical pathogens** (e.g. *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* spp.) is increasingly being recognized. ATS guidelines even suggested that all patients should be treated for the possibility of atypical pathogen infections [206].
  - (c) **Presence of modifying factors** including risk factors for DRSP (e.g. age >65 years., beta-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 Hong Kong, high prevalence of macrolide resistance has been reported among *mycoplasma pneumoniae* strains in recent years [233-236].

- (e) **Emerging pathogens** including those of regional significance such as CA-MRSA (association with necrotizing 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) [237, 238].
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 oral therapy can be made.

### 4.3.2 Management of community-acquired pneumonia 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 [239, 240]. At higher level of resistance (penicillin MIC 2-4 µg/mL), recent evidence suggests that risk of mortality or suppurative complications were increased [241, 242]. In one study [243], the observed increase in mortality was confined to patients with pneumococcal isolates with penicillin MIC of ≥4 µg/mL.
2. It is important to note that different breakpoints are used for interpretation of penicillin susceptibility (Table 4.3) [244, 245].

**Table 4.3 Interpretation of penicillin susceptibility for *S. pneumoniae* (CLSI, Jan 2012)**

Period , Syndrome, Route of administration	Penicillin or Amoxicillin MIC (µg/mL)		
	Susceptible	Intermediate	Resistant
Meningitis, I.V. Penicillin	≤ 0.06	-	≥ 0.12
Non-Meningitis, I.V. Penicillin	≤ 2	4	≥ 8
Non-Meningitis, Oral (high dose) Amoxicillin or Amoxicillin-clavulanic acid	≤ 2	4	≥ 8

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. beta-lactams. Comparative anti-pneumococcal activities of commonly used beta-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 beta-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  $\geq 4$   $\mu\text{g}/\text{mL}$ ) makes it important that they 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  $\geq 4$   $\mu\text{g}/\text{mL}$ ).

### 4.3.3 Regional considerations for *S. pneumoniae*

References: [1, 2, 177, 178, 204, 246-249]

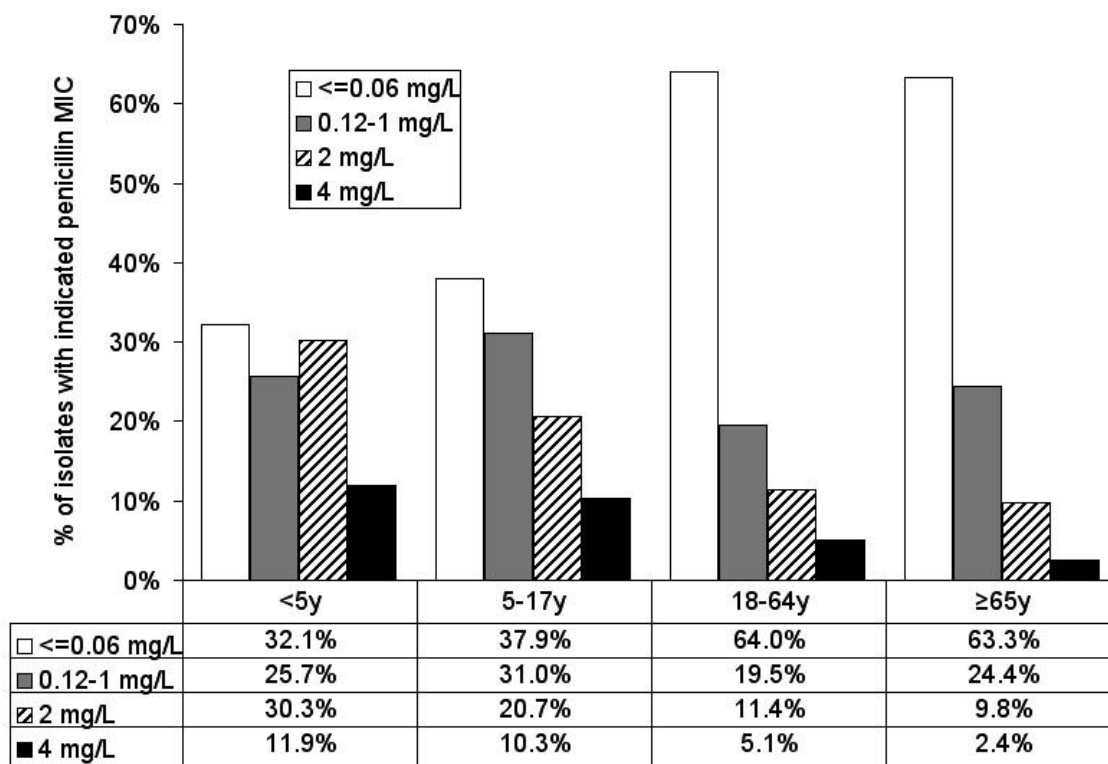
1. In Hong Kong, reduced susceptibility to penicillin (Figure 4.2) and resistance to macrolides were high in both hospital [178, 204] and community settings [246, 247].
2. Erythromycin resistant isolates are also resistant to the newer macrolides/azalides such as clarithromycin and azithromycin [250]. In 2005-2011, the age group-specific rates of macrolide resistance among 844 invasive pneumococcal isolates were as follows: 79.8% in <5 years, 75.9% in 5-17 years, 61.6% in 18-64 years and 58.9% in  $\geq 65$  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%). Hong Kong is one of the rare exceptions in which fluoroquinolone resistance (levofloxacin MIC  $\geq 8$   $\mu\text{g/mL}$ ) is emerging among the *S. pneumoniae*, especially among respiratory isolates from elderly patients with chronic lung diseases [178].
4. In view of the above, adherence to the CDC guidelines on the use of the fluoroquinolones seems appropriate. Moreover, tuberculosis is prevalent in Hong Kong 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 tuberculosis; (2) increased fluoroquinolone resistance among *Mycobacterium tuberculosis* [251, 252]. Hence, this class of agents is not recommended as first line (or routine) therapy in Hong Kong for CAP. In this regard, extra-care need to be exercised in using fluoroquinolones in patients with risk factors for fluoroquinolone-resistant *S. pneumoniae* [211]:
  - Presence of COPD;
  - Nosocomial pneumococcal infection;
  - Residence in old age home;
  - Past exposure to fluoroquinolones; and
  - 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. pneumonia* [205]. If a respiratory fluoroquinolone is indicated, there is evidence to suggest that the more potent ones (e.g. gemifloxacin, moxifloxacin, gatifloxacin) are less likely to lead to development of resistance.

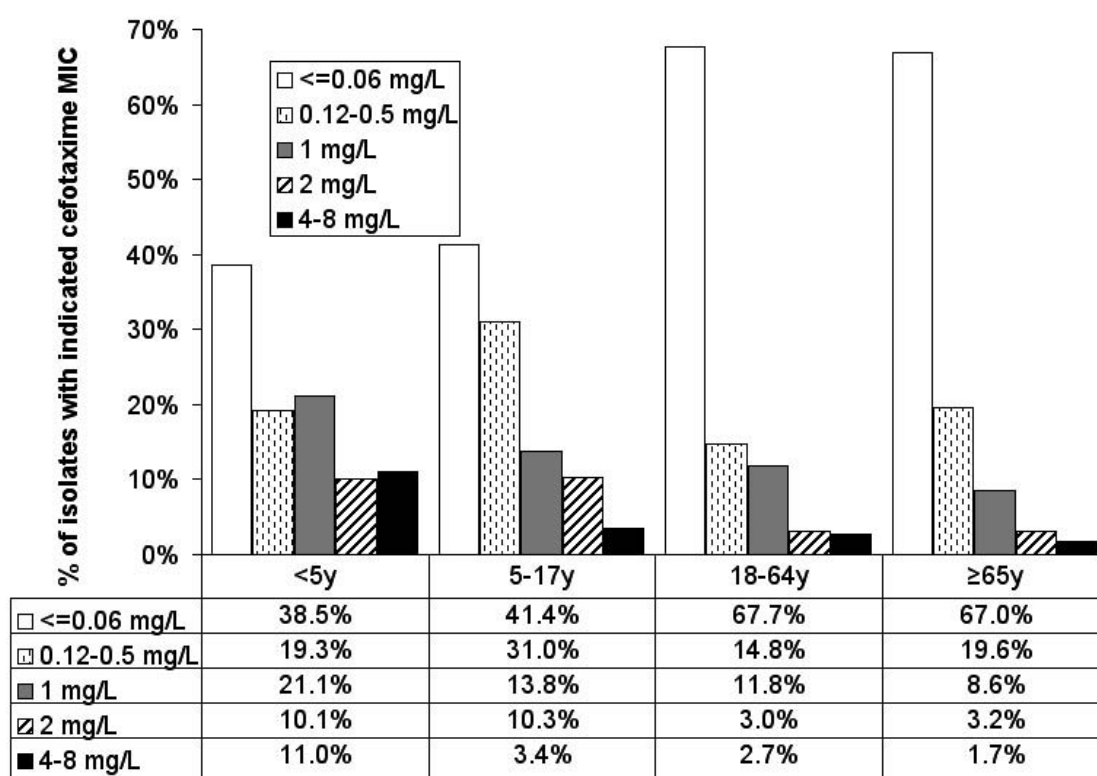
6. Penicillin G (I.V.) or ampicillin (P.O./I.V.) or amoxicillin (P.O./I.V.) are generally viewed as the beta-lactam drugs of choice for treating infections with penicillin-susceptible and penicillin-intermediate strains of *S. pneumoniae*. The following beta-lactams are not recommended because of poor 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 oral amoxicillin (high dose).
8. Penicillins combined with beta-lactamase inhibitors (ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam) are active against beta-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 beta-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 844 invasive pneumococcal isolates to penicillin and cefotaxime according to patient age groups, 2005-2011, Hong Kong**

**(A) Penicillin**



**(B) Cefotaxime**



**Table 4.4. Comparative activities of commonly used beta-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 (mg/L) for intravenous 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.



**Part V: Guidelines for known-pathogen therapy**

**Table 5.1 Guidelines for known-pathogen therapy**

	Drug of choice	Alternatives	Remarks
<b><i>Acinetobacter baumannii</i></b>	I.V. ampicillin-sulbactam + an aminoglycoside	<ul style="list-style-type: none"> <li>▪ Cefoperazone-sulbactam + an aminoglycoside (mixed infection with <i>P. aeruginosa</i>)</li> <li>▪ Fluoroquinolone + an aminoglycoside (if allergic to penicillin)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Sulbactam is highly active against <i>Acinetobacter</i>.</li> <li>▪ Resistance rates in 2010: ampicillin-sulbactam (24%), cefoperazone-sulbactam (24%), imipenem (37%), gentamicin (32%), amikacin (25%), ciprofloxacin (50%)</li> </ul>
<b><i>Clostridium difficile</i></b>	P.O. metronidazole [253, 254]	P.O. vancomycin (if metronidazole fails as documented microbiologically)	<ul style="list-style-type: none"> <li>• Mild/moderate disease, clinical efficacy: metronidazole = P.O. vancomycin. Relapse rate: metronidazole = P.O. vancomycin</li> <li>• Severe disease: P.O. vancomycin</li> <li>• If ileus or toxic megacolon: I.V. metronidazole + P.O. vancomycin</li> <li>• Metronidazole remains the drug of choice for relapse.</li> </ul>

	Drug of choice	Alternatives	Remarks
<b>Enterobacter cloacae complex</b>	<ul style="list-style-type: none"> <li>• P.O./I.V. levofloxacin/ ciprofloxacin for urinary tract infection</li> <li>• I.V. cefepime ( ± an aminoglycoside) for severe infection</li> </ul>	<ul style="list-style-type: none"> <li>• Carbapenem (for severe infection and/or ESBL-positive strain)</li> </ul>	<ul style="list-style-type: none"> <li>• Cefepime is highly active in vitro against almost all <i>Enterobacter</i> isolates.</li> <li>• Emergence of <i>AmpC</i> derepressed mutants emerge in 20-40% of infections treated with the second or third generation cephalosporins. Use of these agents for serious infections (other than UTI) is not recommended.</li> <li>• One study in Hong Kong found high prevalence of ESBL production among <i>E. hormaechei</i> (a member of the <i>E. cloacae</i> complex) [255].</li> <li>• Resistance rate in 2010: levofloxacin (8%), gentamicin (4%), amikacin (1%)</li> </ul>

	Drug of choice	Alternatives	Remarks
<b><i>E coli</i></b> <b>(ESBL-neg)</b>	<ul style="list-style-type: none"> <li>• P.O./I.V. ampicillin-sulbactam or amoxicillin-clavulanate (add an aminoglycoside if rapid bactericidal action desirable on clinical grounds)</li> </ul>	<ul style="list-style-type: none"> <li>• Cefuroxime (if resistant to amoxicillin-clavulanate), add metronidazole (if mixed infection with anaerobes likely).</li> <li>• Piperacillin-tazobactam + an aminoglycoside (if <i>P. aeruginosa</i> or <i>Acinetobacter</i> are co-pathogens)</li> </ul>	
<b><i>Haemophilus influenzae</i></b>	<ul style="list-style-type: none"> <li>• P.O. amoxicillin or P.O./I.V. ampicillin-sulbactam or amoxicillin-clavulanate</li> </ul>	<ul style="list-style-type: none"> <li>• Fluoroquinolones (if allergic to penicillin)</li> </ul>	<ul style="list-style-type: none"> <li>• Amoxicillin-clavulanate also provides good coverage for <i>M. catarrhalis</i> and <i>S. pneumoniae</i>.</li> </ul>
<b><i>Klebsiella pneumoniae</i></b> <b>(ESBL-neg)</b>	<ul style="list-style-type: none"> <li>• P.O./I.V. ampicillin-sulbactam or amoxicillin-clavulanate (add an aminoglycoside if rapid bactericidal action desirable on clinical grounds)</li> </ul>	<ul style="list-style-type: none"> <li>• Cefuroxime (if resistant to amoxicillin-clavulanate), add metronidazole (if mixed infection with anaerobes likely).</li> <li>• Piperacillin-tazobactam + an aminoglycoside (if <i>P. aeruginosa</i> or <i>Acinetobacter</i> are co-pathogens)</li> </ul>	<ul style="list-style-type: none"> <li>• Ampicillin-sulbactam less satisfactory because of poor inhibitory activity of sulbactam for SHV-1 beta-lactamase.</li> </ul>

	Drug of choice	Alternatives	Remarks
<p><b><i>E. coli</i> / <i>K. pneumoniae</i> (ESBL-pos)</b></p>	<ul style="list-style-type: none"> <li>• P.O. cotrimoxazole or amoxicillin-clavulanate or P.O. nitrofurantoin or P.O. levofloxacin or ciprofloxacin for urinary tract infection</li> <li>• Carbapenem for bacteraemia or other serious infection</li> </ul>	<ul style="list-style-type: none"> <li>• Fluoroquinolone (add an aminoglycoside for serious infection and also if rapid bactericidal effect is desirable clinically).</li> <li>• Piperacillin-tazobactam + an aminoglycoside</li> </ul>	<ul style="list-style-type: none"> <li>• Carbapenem has been shown to be effective clinically and is currently the beta-lactam agent of choice for serious infection by ESBL-pos <i>E. coli</i> / <i>Klebsiella</i> spp. Data for beta-lactam/beta-lactamase inhibitor combinations limited and should be used cautiously.</li> <li>• Insufficient clinical data to justify ceftazidime or cefepime as treatment for bacteraemia or other serious infections caused by ESBL-pos <i>E. coli</i> / <i>K. pneumoniae</i> with low MIC or large inhibition zone diameters.</li> </ul>

	Drug of choice	Alternatives	Remarks
<b><i>Pseudomonas aeruginosa</i></b>	I.V. piperacillin or ticarcillin-clavulanate or piperacillin-tazobactam + an aminoglycoside	<ul style="list-style-type: none"> <li>▪ Cefoperazone-sulbactam + an aminoglycoside (mixed infection with <i>Acinetobacter</i>).</li> <li>▪ Levofloxacin/ciprofloxacin + an aminoglycoside (if allergic to penicillin).</li> </ul>	<ul style="list-style-type: none"> <li>▪ Combination therapy recommended (for synergism) for all serious infection except for uncomplicated catheter-related bacteraemia.</li> <li>▪ Piperacillin-tazobactam used instead of ceftazidime due to rapid rise in <i>AmpC</i> type and ESBL-producers in <i>Enterobacteriaceae</i>.</li> <li>▪ In a parallel evaluation of 7 000 <i>P. aeruginosa</i> isolates, no difference was found in the susceptibility between piperacillin-tazobactam and piperacillin i.e. 93.9% vs 93% [256].</li> </ul>

	Drug of choice	Alternatives	Remarks
<b>Methicillin-sensitive S. aureus</b>	P.O./I.V. cloxacillin or amoxicillin-clavulanate or ampicillin-sulbactam or first generation cephalosporin	<ul style="list-style-type: none"> <li>Cefazolin (if allergic to penicillin, but limited to those with minor allergy such as rash alone)</li> <li>Clindamycin (if allergic to penicillin)</li> </ul>	
<b>Methicillin-resistant S. aureus</b>	I.V. vancomycin (bacteraemia or other invasive infections)	<ul style="list-style-type: none"> <li>Linezolid or daptomycin if (1) vancomycin allergy - extensive rash, other than red-man syndrome develop after vancomycin), or (2) bacteraemia caused by MRSA with vancomycin <math>\geq 2</math> mg/L</li> </ul>	<ul style="list-style-type: none"> <li>Cotrimoxazole, fusidic acid or rifampicin are useful adjuncts for deep-seated infections (e.g. osteomyelitis) but these agents should not be administered as monotherapy.</li> <li>Most abscesses or uncomplicated SSTI caused by CA-MRSA could be treated with drainage <math>\pm</math> oral cotrimoxazole or oral doxycycline.</li> </ul>

	Drug of choice	Alternatives	Remarks
<b><i>Stenotrophomonas maltophilia</i></b>	P.O./I.V. cotrimoxazole + I.V. ticarcillin-clavulanate	<ul style="list-style-type: none"> <li>▪ Cotrimoxazole + fluoroquinolone</li> </ul>	<ul style="list-style-type: none"> <li>▪ Cotrimoxazole + ticarcillin-clavulanate is synergistic in vitro. Cotrimoxazole is a key component in therapy.</li> <li>▪ Combination therapy recommended for synergy and to prevent resistance.</li> </ul>



Drug of choice	Alternatives	Remarks
<p><b><i>Streptococcus pneumoniae</i><sup>a</sup></b></p> <p>For infections outside the central nervous system:</p> <ul style="list-style-type: none"> <li>• Penicillin-sensitive: I.V. penicillin G (4 to 8 MU/day, q6h)</li> <li>• Penicillin-intermediate: I.V. penicillin G (high dose, 12 to 18 MU/day, q4h)<sup>a</sup></li> <li>• Penicillin-resistant: I.V. cefotaxime or ceftriaxone</li> </ul>	<ul style="list-style-type: none"> <li>• Beta-lactam/beta-lactamase inhibitor combination with the exception of cefoperazone-sulbactam (for mixed infections).</li> <li>• Erythromycin or clindamycin (if allergic to penicillin).</li> </ul>	<ul style="list-style-type: none"> <li>• Most pneumococcal pneumonia can be treated with high dose amoxicillin or high dose amoxicillin-clavulanate.</li> <li>• For pure pneumococcal infection, penicillin G instead of amoxicillin-clavulanate is preferred, switch therefore recommended.</li> <li>• &gt;70% resistant to erythromycin. Cross-resistance to clindamycin very common.</li> <li>• Resistance to erythromycin = resistance to other newer macrolides (clarithromycin, azithromycin, roxithromycin).</li> </ul>

<sup>a</sup> CLSI (NCCLS) 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 intravenous antimicrobial agent is needed for surgical prophylaxis in the great majority of cases. Published evidence shows that antimicrobial prophylaxis after wound closure is unnecessary and could lead to emergence of resistant bacteria. 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 anesthesia) to achieve an adequate tissue concentration at the time of initial incision. This can be facilitated by having the anesthesiologist 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 (intra-operatively) if the operation is still continuing after two half-lives of the initial dose or massive intra-operative blood losses occur.

References: [257-336]

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

Antimicrobial agent	Standard* intravenous 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

\*In patient with normal renal function and not morbidly obese.

**Table 6.2 Antimicrobial prophylaxis in clean operations**

Type of operation	Indications	Recommended drugs <sup>c</sup>
Cardiac <sup>a</sup>	<ul style="list-style-type: none"> <li>• Prosthetic valve</li> <li>• Coronary artery bypass</li> <li>• Pacemaker implant</li> <li>• Open heart surgery</li> </ul>	<ul style="list-style-type: none"> <li>• I.V. cefazolin 1 g<sup>b</sup> then every 4 hours.</li> </ul> <p><b>Note:</b> The duration of antimicrobial prophylaxis should <u>not</u> be longer than 48 hours.</p>
Thoracic <sup>a</sup>	<ul style="list-style-type: none"> <li>• Pulmonary resection</li> <li>• Closed tube thoracostomy for chest trauma</li> </ul>	<ul style="list-style-type: none"> <li>• I.V. cefazolin 1 g<sup>b</sup> OR</li> <li>• I.V. cefuroxime 1.5 g OR</li> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>c</sup></li> </ul>
Vascular	<ul style="list-style-type: none"> <li>• Abdominal aortic operations</li> <li>• Prosthesis</li> <li>• Groin incision</li> <li>• Lower extremity amputation for ischaemia</li> </ul>	

Type of operation	Indications	Recommended drugs <sup>c</sup>
Neurosurgery <sup>a</sup>	<ul style="list-style-type: none"> <li>• Craniotomy</li> <li>• V-P shunt</li> </ul>	<ul style="list-style-type: none"> <li>• I.V. cefazolin 1 g<sup>b</sup></li> <li>OR</li> <li>• I.V. cefuroxime 1.5 g</li> </ul>
	<ul style="list-style-type: none"> <li>• Re-exploration or microsurgery</li> </ul>	<ul style="list-style-type: none"> <li>• I.V. cefuroxime 1.5 g</li> <li>OR</li> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup></li> </ul>
Orthopaedic & Traumatology <sup>a</sup>	<ul style="list-style-type: none"> <li>• Total joint replacement with prosthesis</li> <li>• Internal fixation of closed fractures</li> </ul>	<ul style="list-style-type: none"> <li>• I.V. cefazolin 1 g<sup>b</sup></li> <li>OR</li> <li>• I.V. cefuroxime 1.5 g</li> </ul> <p><b>Note:</b> Antimicrobial agents should be completely infused before inflating the tourniquet.</p>
	<ul style="list-style-type: none"> <li>• Open fractures with soil contamination or farm injuries (Antibiotic selection depends on the likely organisms contaminating the wound. Wound cultures and sensitivity testing are useful for informing subsequent choice of antimicrobials) [337-339]</li> </ul>	<ul style="list-style-type: none"> <li>• (I.V. amoxicillin-clavulanate ± gentamicin) or (I.V. ceftriaxone 2 g or other third generation cephalosporin ± I.V. Penicillin G for better anaerobic coverage )</li> </ul> <p><b>Note:</b> The recommended duration is 3 days for Gustilo-Anderson grade I and II open fractures and up to 5 days for grade III wounds</p>
Thyroid & parathyroid glands		<ul style="list-style-type: none"> <li>• Antimicrobial prophylaxis is not indicated</li> </ul>

**Table 6.3 Antimicrobial prophylaxis in clean-contaminated operations**

Type of operation	Indications	Recommended drugs <sup>c</sup>
Oral- Pharyngeal/ Nasal	<ul style="list-style-type: none"> <li>• Tonsillectomy</li> <li>• Maxillofacial</li> <li>• Rhinoplasty</li> <li>• Turbinate/Septoplasty</li> </ul>	<ul style="list-style-type: none"> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup></li> </ul> OR If <i>pseudomonas</i> is suspected: <ul style="list-style-type: none"> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup> + I.V. gentamicin</li> </ul> OR <ul style="list-style-type: none"> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup> + I.V. ceftazidime 1-2 g</li> </ul>
Ear	<ul style="list-style-type: none"> <li>• Myringotomy</li> <li>• Tympanostomy Tube Insertion</li> </ul>	<ul style="list-style-type: none"> <li>• Quinolone or Softradex eardrop</li> </ul>
Upper Gastro-Intestinal Tract	Gastro-duodenal (high risk): <ul style="list-style-type: none"> <li>• Obstruction</li> <li>• Haemorrhage</li> <li>• Gastric ulcer</li> <li>• Malignancy</li> <li>• H<sub>2</sub> blocker</li> <li>• Proton pump inhibitor</li> <li>• Morbid obesity</li> <li>• Gastric bypass</li> <li>• Percutaneous endoscopic gastrostomy</li> </ul>	<ul style="list-style-type: none"> <li>• I.V. cefuroxime 1.5 g</li> </ul> OR <ul style="list-style-type: none"> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup></li> </ul>
	<ul style="list-style-type: none"> <li>• Oesophageal operation with manipulation of pharynx</li> </ul>	<ul style="list-style-type: none"> <li>• I.V. cefuroxime 1.5 g</li> </ul> OR <ul style="list-style-type: none"> <li>• I.V. cefazolin 1 g<sup>b</sup> ± metronidazole 500 mg</li> </ul>

Type of operation	Indications	Recommended drugs <sup>c</sup>
Hepato-Biliary System  Laparoscopic Gall Bladder Surgery	High risk: <ul style="list-style-type: none"> <li>• Age more than 70 years</li> <li>• Acute cholecystitis / pancreatitis</li> <li>• Obstructive jaundice</li> <li>• Common bile duct stones</li> <li>• Morbid obesity</li> <li>• Intra-operative cholangiogram</li> <li>• Bile spillage</li> <li>• Pregnancy</li> <li>• Immuno-suppression</li> <li>• Insertion of prosthetic devices</li> <li>• Laparoscopic converts to laparotomy</li> </ul>	<ul style="list-style-type: none"> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup> OR</li> <li>• I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg</li> </ul>
Endoscopic Retrograde Cholangio-Pancreatography (ERCP)	<ul style="list-style-type: none"> <li>• Biliary obstruction</li> </ul>	<ul style="list-style-type: none"> <li>• P.O. ciprofloxacin 500-750 mg 2 hours prior to procedure OR</li> <li>• I.V. tazocin 4.5 g 1 hour prior to procedure</li> </ul>
Appendectomy		<ul style="list-style-type: none"> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup> OR</li> <li>• I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg</li> </ul>
Colorectal	<ul style="list-style-type: none"> <li>• Most procedures require parenteral ± oral prophylaxis</li> </ul>	<p><i>Parenteral</i></p> <ul style="list-style-type: none"> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup> OR</li> <li>• I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg</li> </ul> <p><i>Oral</i></p> <ul style="list-style-type: none"> <li>• P.O. neomycin and erythromycin base 1 g each t.i.d. the day before operation</li> </ul>

Type of operation	Indications	Recommended drugs <sup>c</sup>
Abdominal/ Vaginal Hysterectomy		<ul style="list-style-type: none"> <li>I.V. cefazolin 1 g<sup>b</sup></li> <li>OR</li> </ul> When vaginal wound is present: <ul style="list-style-type: none"> <li>I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg</li> <li>OR</li> <li>I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup></li> </ul>
Cesarean Section [340]	<ul style="list-style-type: none"> <li>Emergency procedures (e.g. premature rupture of membrane)</li> </ul>	<p><u>Note:</u> For Cesarean Section, the initial dose of antimicrobial agents should be given immediately after clamping the umbilical cord.</p>
Abortion <sup>f</sup>		Antimicrobial prophylaxis should be based on individual clinical condition.
Urology	<ul style="list-style-type: none"> <li>Significant bacteriuria</li> <li>TURP, TURBT, TUR</li> <li>Stone operations,</li> <li>Nephrectomy</li> <li>Total cystectomy</li> </ul>	<ul style="list-style-type: none"> <li>Treat according to mid-stream urine culture result prior to elective procedures</li> </ul>
Hernia Repair <sup>d</sup>	<ul style="list-style-type: none"> <li>Non Mesh Hernia Repair</li> </ul>	Antimicrobial prophylaxis is not indicated
	<ul style="list-style-type: none"> <li>Adult Hernia Mesh Repair</li> </ul>	<ul style="list-style-type: none"> <li>I.V. cefazolin 1 g<sup>b</sup></li> <li>OR</li> <li>I.V. cefuroxime 1.5 g</li> </ul>
Mastectomy	<ul style="list-style-type: none"> <li>Without implant</li> </ul>	Antimicrobial prophylaxis is not indicated
	<ul style="list-style-type: none"> <li>With implant / foreign body</li> </ul>	<ul style="list-style-type: none"> <li>I.V. cefazolin 1 g<sup>b</sup></li> <li>OR</li> <li>I.V. cefuroxime 1.5 g</li> </ul>



**Table 6.4 Antimicrobial prophylaxis in contaminated-infected operations**

Type of operation	Indications	Recommended drugs <sup>g</sup>
Ruptured viscus	For treatment of established infection	<ul style="list-style-type: none"> <li>• I.V. cefuroxime 1.5 g + I.V. metronidazole 500 mg OR</li> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup></li> </ul> <p>(Therapy is often continued for about 5 days)</p>
Bite wound		I.V. or P.O. amoxicillin-clavulanate <sup>e</sup>
Traumatic wound		<ul style="list-style-type: none"> <li>• I.V. cefazolin 1-2 g<sup>b</sup> OR</li> <li>• I.V. cefuroxime 1.5 g OR</li> <li>• I.V. amoxicillin-clavulanate 1.2 g<sup>e</sup></li> </ul>

**Remarks for Tables 6.2-6.4:**

<sup>a</sup>For hospitals or units with a high incidence of postoperative wound infections by MRSA or MRSE, 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 [257, 258].

<sup>b</sup>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 may cause hypotension, which could be especially dangerous during induction of anesthesia.

<sup>c</sup>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.

<sup>d</sup>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.

<sup>e</sup>Amoxicillin-clavulanate and ampicillin-sulbactam are similar in spectrum coverage and centers may choose to use ampicillin-sulbactam.

<sup>f</sup>The optimal antibiotic and dosing regimens for abortion are unclear. The antimicrobial prophylaxis for abortion stated in ROCG 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 twice daily 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.

<sup>g</sup>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 (generic)	Trade name / generic	Dosage form (unit cost, HK\$)	Usual adult regimen (daily dose, route, dosing interval) <sup>a</sup>
Amikacin [119]	Amikin	0.25 g vial (\$41.2) 0.5 g vial (\$60)	I.V. 15 mg/kg q24h (750 mg q24h) <sup>b</sup> or 7.5 mg/kg q12h
Amoxicillin	Generic	250 mg cap. (\$0.1) 125 mg/5 mL syr. (\$0.15/mL)	P.O. 500 mg t.i.d.
Amoxicillin-clavulanate	Augmentin	0.6 g vial (\$14.1) 1.2 g vial (\$7.8) 375 mg tab. (\$0.72) 1 g tab. (\$ 1) 156 mg/5 mL syr. (\$0.13/mL) 457 mg/5ml 'b.i.d. syr.' (\$0.34/mL)	I.V. 1.2 g q8h P.O. 375-750 mg t.i.d. P.O. 1 g b.i.d. P.O. 312 mg (10 mL) t.i.d. (syr.) P.O. 914 mg (10 mL) b.i.d. (syr.)
Ampicillin	Generic	500 mg vial (\$1.7) 250 mg cap. (\$0.24) 500 mg cap. (\$0.4) 125 mg/5 mL syr. (\$0.44/mL)	I.V. 1 g q6h P.O. 250–500 mg q.i.d.
Ampicillin-sulbactam	Unasyn	750 mg vial (\$11.8) 375 mg tab. (\$5.93) 250 mg/5mL syr. (\$1.53/mL)	I.V. 1.5–3 g q6h P.O. 375 mg t.i.d.
Azithromycin	Zithromax	500 mg vial (\$165) 250 mg tab. (\$2.92) 200 mg/5ml syr. (\$1.67/mL)	I.V. 500 mg q24h P.O. 500 mg on first day then 250 mg once daily
Cefazolin	Generic	1 g vial (\$3)	I.V. 1 g q8h
Cefepime	Maxipime	1 g vial (\$102) 2 g vial (\$204)	I.V. 1–2 g q12h

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<b>Agents (generic)</b>	<b>Trade name / generic</b>	<b>Dosage form (unit cost, HK\$)</b>	<b>Usual adult regimen (daily dose, route, dosing interval) <sup>a</sup></b>
Cefoperazone+ sulbactam	Sulperazon	1 g vial (\$33)	I.V. 1-2 g q12h
Ceftazidime	Fortum	1 g vial (\$25.7) 2 g vial (\$51.7)	I.V. 1 g q8h
Cefotaxime	Generic	1 g vial (\$11.5)	I.V. 1 g q6-8h (max 12 g/day)
Ceftriaxone	Rocephin / Generic^	0.25 g I.M. (\$80) 1 g vial ( \$14.50)^	I.M. 250 mg once I.M./I.V. 1-2 g/day q12-24h (max 4 g/day)
Cefuroxime	Generic	0.75 g vial (\$4.69)	I.V. 0.75-1.5 g q8h
Cefuroxime-axetil	Zinnat	125 mg tab. (\$3.8) 250 mg tab. (\$1) 125 mg/5 mL suspension (\$1.11/mL)	P.O. 250-500 mg b.i.d.
Cephalexin	Generic	250 cap. (\$0.32) 500 cap. (\$0.71)	P.O. 250-500 mg q.i.d.
Ciprofloxacin	Generic^ / Ciproxin	200 mg vial (\$69.45)^ 400 mg vial (\$635) 250 mg tab. (\$0.78))^	I.V. 200-400 mg q12h P.O. 500-750 mg b.i.d.
Clarithromycin	Klacid / Generic^	500 mg vial (\$78) 250 mg tab. (\$1.16)^ 500 mg tab. (\$2.32)^ 125 mg/5 mL syr. (\$0.42/mL)	I.V. 500 mg q12h P.O. 250-500 mg b.i.d.
Clindamycin	Generic^ / Dalacin C	150 mg/mL in 2 ml vials (\$10)^ 150 mg cap. (\$2.6)	I.V. 600 mg q8h (max 2.7 g/day) P.O. 150-300 mg q.i.d.
Cloxacillin	Generic	500 mg vial (\$4.4) 250 mg cap. (\$0.3) 500 mg cap. (\$0.38)	I.V. 0.5-1 g q6h (max 12 g/day) P.O. 500 mg q.i.d.
Colistin	Colomycin	1.MU vial (\$85)	I.V. 1-2 MU q8h

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<b>Agents (generic)</b>	<b>Trade name / generic</b>	<b>Dosage form (unit cost, HK\$)</b>	<b>Usual adult regimen (daily dose, route, dosing interval) <sup>a</sup></b>
Daptomycin	Cubucin	500 mg vial (\$1250)	4 mg/kg (cSSSI) or 6 mg/kg ( <i>S. aureus</i> bloodstream infection) q24h I.V. 250-500 mg q24h
Doxycycline	Generic	100 mg tab. (\$0.9) I.V. form is no longer available in HK	P.O. 100 mg b.i.d.
Ertapenem	Invanz	1 g (\$228)	I.V. 1 g q24h
Erythromycin	Generic	500 mg vial (\$110) 250 mg tab, (\$0.54) 200 mg/5 mL syr. (\$4.95/mL)	I.V. 500 mg q6h P.O. 250–500 mg q.i.d.
Flucloxacillin	Generic	125 mg/5 ml solution (\$0.14/mL)	P.O. 250–500 mg q.i.d.
Fosfomycin	Fosfocine Monurol	4 g vial (\$500) 3 g sachet (Not in HA formulary)	I.V. 8-12 g/day (100-200 mg/kg/day) P.O. 3 g sachet x 1 dose for uncomplicated UTI
Gentamicin [119]	Generic	80 mg/2 mL (\$2.43)	I.V. 3.6 mg/kg/day q24h (180 mg q24h) <sup>b</sup> or 1.2 mg/kg/dose q8h
Imipenem	Tienam	500 mg vial (\$62)	I.V. 500 mg q6h
Levofloxacin	Generic	500 mg vial (\$125) 100 mg tab. (\$0.88) 250 mg (\$1.65)	I.V. 500 mg q24h P.O. 500 mg once daily
Linezolid	Zyvox	600 mg vial (\$430) 600 mg tab. (\$410) 20 mg/mL syr. (\$13.63/ml)	I.V./P.O. 600 mg q12h
Meropenem	Meronem	500 mg vial (\$82) 1g vial (\$128)	I.V. 1 g q8h
Metronidazole	Generic	500 vial (\$4.10) 200 mg tab. (\$0.13)	I.V. 500 mg q8h P.O. 400 mg t.i.d.

Agents (generic)	Trade name / generic	Dosage form (unit cost, HK\$)	Usual adult regimen (daily dose, route, dosing interval) <sup>a</sup>
Minocycline	Generic	100 mg vial (\$116) 100 mg cap. (\$3.5) 50 mg cap. (\$1.9)	P.O. 100 mg b.i.d.
Moxifloxacin	Avelox	400 mg vial (\$270) 400 mg tab. (\$23)	I.V. 400 mg q24h P.O. 400 mg q.i.d.
Netilmicin [119]	Netromycin	50 mg vial (\$19.8) 150 mg vial (\$37.5)	I.V. 4.4 mg/kg q24h (200 mg q24h) <sup>b</sup> or I.V. 2.2 mg/kg q12h
Penicillin G	Generic	1 MU vial (\$5.90)	I.V. 1–2 million unit q4–6h (max 24 million unit/day)
Piperacillin	Generic	4 g vial (\$26.9)	I.V. 4 g q6h
Piperacillin-tazobactam	Tazocin	4.5 g vial (\$74.2)	I.V. 4.5 g q6–8h
Teicoplanin	Targocid	200 mg vial (\$400)	I.V. 400 mg x 1 dose then 200 mg q24h
Ticarcillin-clavulanate	Timentin	3.2 g vial (\$54.5)	I.V. 3.2 g q4–6h
Tigecycline	Tygacil	50 mg vial (\$333)	I.V. 100 mg loading then 50 mg q12h
Tobramycin [119]	Generic	40 mg/mL 2 ml vial (\$48)	I.V. 3.6 mg/kg q24h (180 mg q24h) <sup>b</sup> or 1.2 mg/kg q8h
Vancomycin	Generic	500 mg vial (\$13.5)	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 <i>C. difficile</i> colitis)

<sup>a</sup> Typical dosages in 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.

<sup>b</sup> 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.

**Table 7.2 Cost comparison of selected I.V. antibiotics**

<b>Antibiotics</b>	<b>Usual dosage</b>	<b>Cost (HK\$/day)</b>
<b>Aminoglycosides</b>		
I.V. Gentamicin* (3.5 mg/kg/day)	180 mg q24h	7
I.V. Netilmicin* (4.4 mg/kg/day)	200 mg q24h	75
I.V. Tobramycin* (3.5 mg/kg/day)	180 mg q24h	144
I.V. Amikacin* (15 mg/kg/day)	750 mg q24h	101
<b>Penicillins</b>		
I.V. Ampicillin	0.5-1 g q6h	7-14
I.V. Cloxacillin	0.5-1 g q6h	18-35
I.V. Amoxillin-clavulanate	1.2 g q8h	23
I.V. Ampicillin-sulbactam	1.5 g q8h	71
I.V. Ticarcillin-clavulanate	3.2 g q6h	218
I.V. Piperacillin	4 g q8h	81
I.V. Piperacillin-tazobactam	4.5 g q8h (4.5 g q6h)	223 (297)
<b>Cephalosporins</b>		
I.V. Cefuroxime	750 mg q8h	14
I.V. Cefazolin	1 g q8h	9
I.V. Ceftriaxone	1 g q12h	29
I.V. Cefotaxime	1 g q8h	35
I.V. Cefoperazone-sulbactam (Sulperazon)	1 g q12h (1 g q8h)	66 (99)
I.V. Cefepime	1 g q12h	204
I.V. Ceftazidime	1 g q8h	77
<b>Carbapenems</b>		
I.V. Meropenem	0.5 g q8h (1 g q8h)	246 (384)
I.V. Imipenem-cilastatin	500 mg q6h	248
I.V. Ertapenem	1 g q24h	228



Antibiotics	Usual dosage	Cost (HK\$/day)
<b>Fluoroquinolones</b>		
I.V. Moxifloxacin	400 mg q24h	270
P.O. Moxifloxacin	400 mg once daily	23
I.V. Levofloxacin	500 mg q24h	125
P.O. Levofloxacin	500 mg once daily	3
I.V. Ciprofloxacin	400 mg q12h	278
P.O. Ciprofloxacin	500 mg once daily	3
<b>Macrolides</b>		
I.V. Clarithromycin	500 mg q12h	156
I.V. Azithromycin	500 mg once daily	165
<b>Others</b>		
I.V. Metronidazole	500 mg q8h	12
I.V. Vancomycin	1 g q12h	54
I.V. Linezolid	600 mg q12h	860
(P.O. Linezolid)	(600 mg b.i.d.)	(820)

Note: Approximate cost updated as of October 2011 in HA.

\*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.i.d.	15
P.O. Itraconazole (solution)	200 mg b.i.d.	252
I.V. Itraconazole	200 mg q12h	1157
P.O. Fluconazole	100-400 mg daily	3.75-15
P.O. Fluconazole (suspension)	100-400 mg daily	73.75-295
I.V. Fluconazole	200 mg q12h	162
P.O. Posaconazole (suspension)	Prophylaxis: 200 mg q8h	558
P.O. Voriconazole	200 mg b.i.d.	757
I.V. Voriconazole	200 mg q12h	1620
I.V. Anidulafungin	Candidemia: Loading 200 mg (Day 1) Maintenance 100 mg q24h	1500-3000
	Esophageal candidiasis: Loading 100 mg (Day 1) Maintenance 50 mg q24h	750-1500
I.V. Micafungin	Prophylaxis in HSCT: 50 mg q24h	530
	Candidemia, acute disseminated candidiasis, candida peritonitis and abscesses: 100 mg q24h	1060
	Esophageal candidiasis: 150 mg q24h	1590
I.V. Caspofungin	Invasive aspergillosis: Loading 70 mg (Day 1) Maintenance 50 mg q24h	1521-1980
I.V. Amphotericin B (1 mg/kg/day) *	50 mg q24h	195
I.V. Liposomal amphotericin B (3 mg/kg/day) *	150 mg q24h	4995

Note: Approximate cost updated as of October 2011 in HA.

\*Dosage for a typical 50 kg person

**Table 7.4 Dosage of antimicrobial agents for CNS infections**

Antibiotics*	Recommended doses	Cost (HK\$/day)
I.V. Cefotaxime	2 g q4h	138
I.V. Ceftriaxone	2 g q12h	58
I.V. Cefepime	2 g q8h	612
I.V. Meropenem	2 g q8h	768
I.V. Ampicillin	2g q4h	41
I.V. Penicillin G	3–4 MU q4h	106-142
I.V. Metronidazole	500 mg q6h	16
I.V. Vancomycin	1 g q12h	54
P.O. Rifampin**	600 mg once daily	1

Note: \* Dosage for a typical body weight  $\geq 70$  kg and normal renal function.

\*\* 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 CAPD peritonitis**

<b>Antibiotics</b>	<b>Intermittent dosing (once daily) *</b> (Add drug into 1 bag/day unless otherwise specified) [341]
<b>Aminoglycosides</b>	
Amikacin	2 mg/kg
Gentamicin	0.6 mg/kg
Netilmicin	0.6 mg/kg
Tobramycin	0.6 mg/kg
<b>Cephalosporins</b>	
Cefazolin	15 mg/kg
Cefepime	1 g
Ceftazidime	1-1.5 g
<b>Others</b>	
Ampicillin-sulbactam	2 g q12h
Imipenem	1 g q12h

\* 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 can very reliably rule out IgE-mediated penicillin allergy. These tests however might not be available in all hospitals.
7. Patients with IgE-mediated beta-lactam allergy can be successful desensitized 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 desensitization can be performed (Table 8.1) with informed consent just prior to drug administration.
4. 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<sup>th</sup> 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, desensitization 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 beta-lactam ring is rapidly broken down in vivo.
2. To deal with patients with a remote history of cephalosporin allergy, see section A.
3. 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).
4. Since cephalosporin allergy is due to side-chain reactivity, skin testing with the native drug can reliably predict the likelihood of IgE-mediated reactions.
5. 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 this 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 beta-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).
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, quinolones, lincomycins and aminoglycosides do not cross-react with beta-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 beta-lactam desensitization protocol\***

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 beta-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 1:1000 on stand-by at bedside.
5. Once successfully desensitized, begin treatment immediately.
6. To maintain desensitized state, patient must not interrupt treatment for more than 2 days. Otherwise, patient would need to be desensitized again.

\* Reference: [342]



Table 8.2. Cross-reacting side chains between beta-lactam antibiotics.

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

Numbers denote position of side chains: **3**, similarity 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.

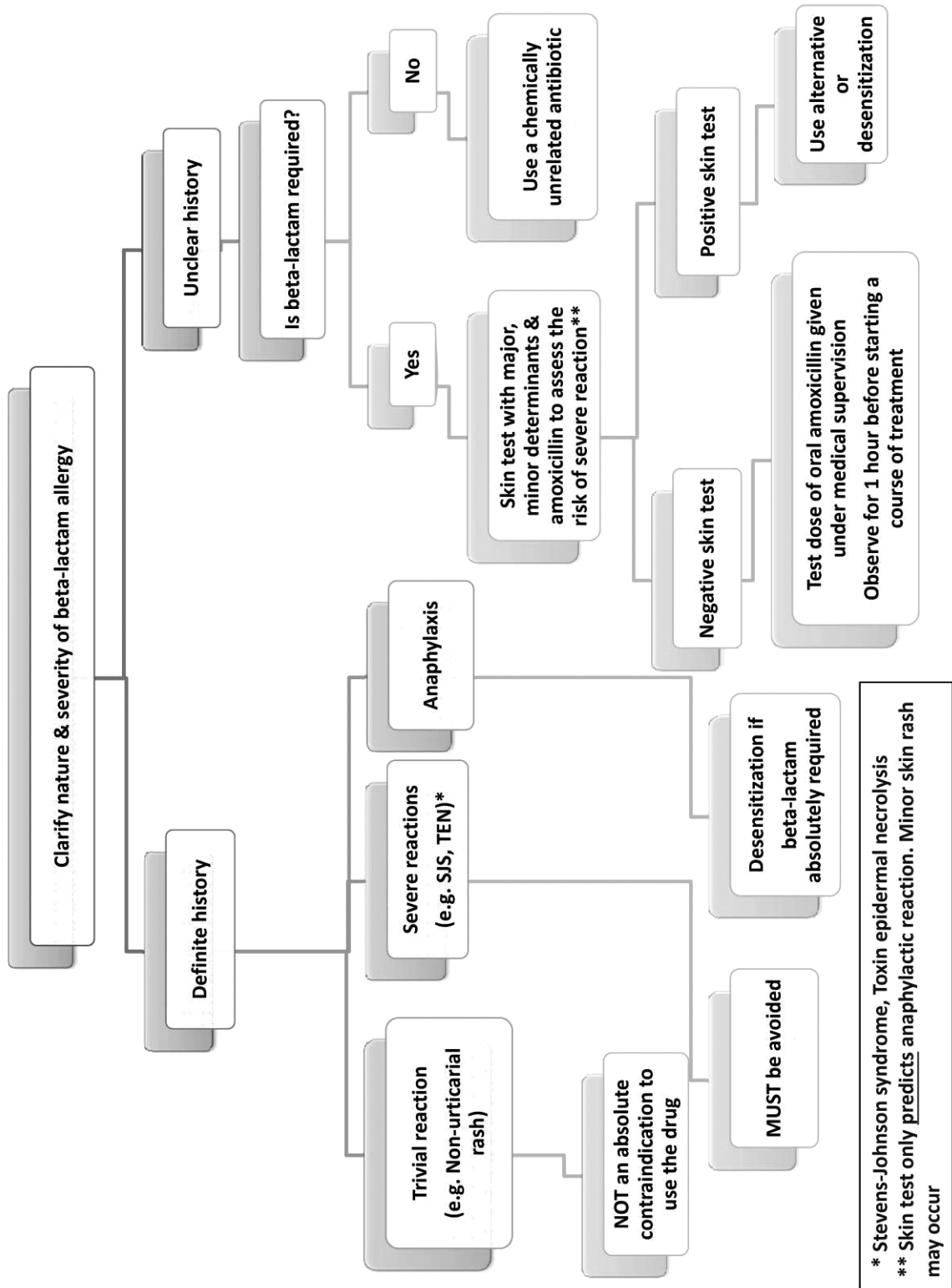
Each number in the matrix indicates side-chain similarity between two drugs. Cross-allergenicity is expected between each similar pair. For example, a patient allergic to amoxicillin would very likely manifest an allergic reaction to ampicillin, cefadroxil, cefaclor, cephaloxin, and cephradine. However, 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: [343]

**Table 8.3 Risk of cross-reactivity between different beta-lactams**

Allergic to	Drug of concern	Risk of cross-reactivity
Cephalosporin	Penicillin	8.3% - 25.5% in two series [344, 345]  *Cephalosporin with structures similar or identical to penicillin have 3-fold increase in risk
	Carbapenem	Imipenem 2% and meropenem 1% in one series
Penicillin	Cephalosporins	10.9% with most involving cephalothin and cefamandazole [346]
	Carbapenems	Meropenem 0.9%, imipenem 0.9% [347-349]
	All first generation cephalosporins	Odds ratio: first generation cephalosporins 4.2, Second generation cephalosporins 1.1 and third generation cephalosporins 0.8 [350]
	Cephalexin	31% in one series with 16 patients [351]
Amoxicillin	Cefadroxil	38% (cefadroxil has identical side chain to amoxicillin) [352]
	Cefamandole	0% for 21 patients (different side chain to amoxicillin) [352]

Figure 8.1 Flow chart on assessment of beta-lactam allergy



## Figure 8.2 Beta-lactam skin testing

### Stock test solutions:

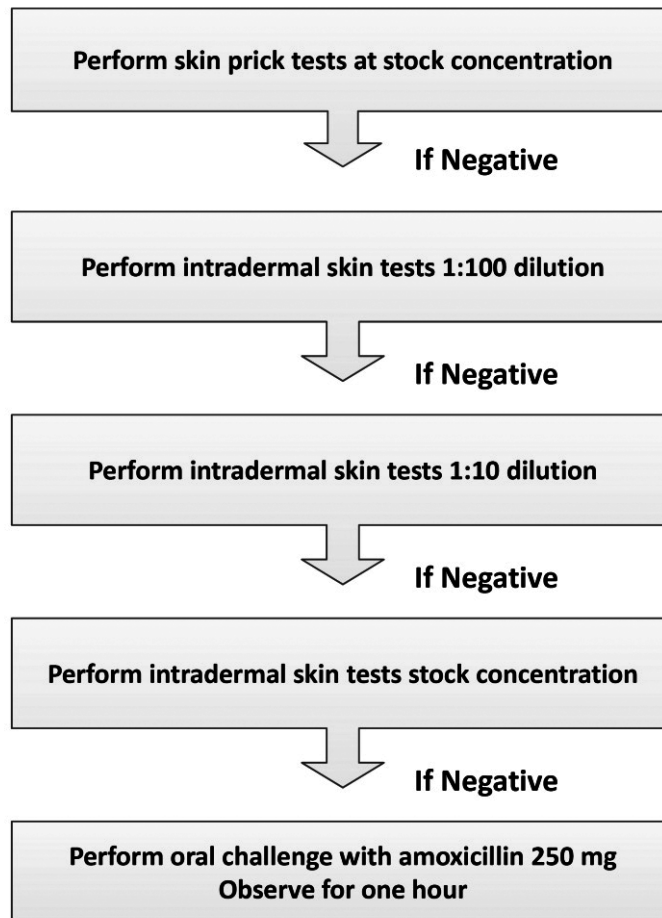
1. Benzylpenicilloyl poly-L-lisine\* 0.04 mg/ml
2. Minor determinant mix\*\* 0.5 mg/ml
3. Amoxicillin 20 mg/ml\*\*\*
4. Ampicillin 20 mg/ml
5. Cephalosporins 20 mg/ml

Note that all stock concentrations are in milligram per milliliter.

### Precautions

This should only be conducted by persons with the proper training. Have epinephrine 1:1000 on stand-by when performing skin tests.

### Procedures



\* DAP penicillin kit (Diater Laboratories)

\*\* MDM vial (sodium benzylpenicillin, benzylpenicilloic acid, sodium benzylpenicilloate), DAP penicillin kit (Diater Laboratories)

\*\*\* DAP amoxicillin kit (Diater Laboratories)

## 8.2 Tips on laboratory diagnostic tests

### 8.2.1 Urinary Legionella antigen test (UAT)

- The majority of Legionnaire's disease (LD) is caused by *Legionella pneumophila* serogroup 1 [353]. The test kit most commonly used in HA hospitals detects ***L. pneumophila* serogroup 1 ONLY** (Table 8.4).
- Most of the HA hospitals offering this test can guarantee a turnaround time of 1 day [354].
- Although more than 80% of patients with LD excrete antigens in urine during day 1 to 3 of symptoms [353], 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 [355].
- The UAT of majority of LD patients will turn negative within 60 days [353]. However, the longest documented duration of antigen excretion was 326 days [356]. Therefore a positive UAT can indicate either current or past infection.
- 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 [357]. Other causes of false positivity include rheumatoid-like factors, freeze-thawing of urine, and excessive urinary sediments [356].
- The sensitivity of UAT is variable, ranging from 70% to 80% [356]. 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%) [358]. 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 BCYE ± 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 TAT (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

- 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 [359, 360].
- In-vitro studies have noted a linear relationship between the bacterial inoculum size and TTP of blood culture [361]. 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).
- The differential time to positivity (DTP) is a reliable and simple technique to diagnose catheter-associated blood stream infection (CABSI) without the need for removal of the catheter [362]. 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 [361, 363]. (Information of TTP can usually be obtained from the microbiology laboratory) (Table 8.6).
- In a meta-analysis, the sensitivity and specificity of DTP in diagnosing CABSI is 89% and 87% respectively [362].

**Table 8.5 TTP of blood culture of different organisms**

Organism	Time to positivity	Reference
<i>Staphylococcus aureus</i> MSSA MRSA	19.9 ± 19.4 h 15h (14.1 ± 9.8) h 17h (28.6 ± 26.1) h	[364, 365]
Coagulase-negative staphylococcus	CFU <10 : >20 h CFU >100 : ≤16 h	[362]
<i>S. pneumoniae</i>	14 h	[366, 367]
<i>E. coli</i> ESBL-pos <i>E. coli</i>	9.7 – 11.2 h 8.3 h	[368] [360]
<i>Klebsiella pneumoniae</i>	<7 h	[369]
<i>Acinetobacter baumannii</i> Drug-sensitive strain Drug-resistant strain	10.4 ± 7.9 h 14.5 ± 9.5 h 8.6 ± 3.2 h	[370]
<i>Candida</i>	24.9 – 25.9 h	[371]

**Table 8.6 Diagnosing CABSIs by DTP**

<ol style="list-style-type: none"> <li>1. Blood culture performed with aerobic and anaerobic blood culture bottle from central venous catheter and peripheral site respectively.</li> <li>2. Approximately <b>equal volume</b> of peripheral blood and catheter blood (from ALL lumens) should be drawn <b>simultaneously</b> under aseptic technique.</li> <li>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.</li> <li>4. The time for blood culture broth to turn positive is recorded. (The TTP can be obtained from microbiology laboratory.)</li> <li>5. If catheter blood TTP is <b>&gt;2 hours early</b> than peripheral blood TTP, then the patient is likely to have CABSIs.</li> <li>6. The DTP is valid only if: <ul style="list-style-type: none"> <li>- The <b>volume</b> of peripheral blood injected into the blood culture bottles is approximately <b>equal</b> to the catheter blood</li> <li>- Blood culture are taken <b>simultaneously</b></li> <li>- Blood culture are incubated into the blood culture system <b>at the same time</b></li> </ul> </li> </ol>
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### **8.2.3 Prosthetic joint infection**

- Multiple intra-operative 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 [372].
- 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 [373].
- BACTEC blood culture bottles could be used for the diagnosis of prosthetic joint infection. Intraoperative specimens (synovial fluid or homogenized infected tissue) could be injected into BACTEC blood culture bottles and incubated in an automated monitoring machine [374-376]. BACTEC was found to have high sensitivity and specificity in diagnosing prosthetic joint infections, compared to conventional laboratory culture methods [376]. BACTEC was also found to have the shortest TTP comparing with different laboratory enrichment methods [376].

### **8.2.4 Culture of sterile body fluid**

- Use of BACTEC blood culture bottles can increase the sensitivity for recovery of microorganisms from sterile body fluids [377-380]. It can also reduce the time to detection and increase the yield of isolation of fastidious organisms [378-380].
- CAPD 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 [379, 381]. 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 [382].
- The use of BACTEC and BacT/ALERT blood culture bottles could increase the yield of microorganisms from pleural fluid [379, 381].



## Abbreviations

3GC	Third generation cephalosporins
AACP	American Association of Colleges of Pharmacy
ACP-ASIM	American College of Physicians- American Society of Internal Medicine
AECB	Acute exacerbation of chronic bronchitis
APUA	Alliance for the Prudent Use of Antibiotics
ASP	Antimicrobial stewardship programme
b.i.d.	Twice a day
BLBLI	Beta-lactam/beta-lactamase inhibitor
CA-MRSA	Community-associated methicillin-resistant <i>Staphylococcus aureus</i>
CAP	Community-acquired pneumonia
cap.	Capsule
CDC	Centers for Disease Control and Prevention
CLIS	Clinical and Laboratory Standards Institute
COPD	Chronic obstructive pulmonary disease
CRHD	Chronic rheumatic heart disease
CRKP	Ceftazidime-resistant <i>Klebsiella pneumoniae</i>
CT	Computerised tomography
D5	5% dextrose solution
DDD	Defined daily dose
DRSP	Drug-resistant <i>Streptococcus pneumoniae</i>
ESBL	Extended-spectrum beta-lactamase
ET	Empirical therapy
FDA	Food and Drug Administration
FNA	Fine needle aspiration

HA-MRSA	Healthcare-associated methicillin-resistant <i>Staphylococcus aureus</i>
HACEK	<i>Haemophilus parainfluenzae</i> , <i>H. aphropilus</i> , <i>Actinobacillus</i> , <i>Cardiobacterium</i> , <i>Eikenella</i> , <i>Kingella</i>
IBW	Ideal body weight
IDSA	Infectious Diseases Society of America
IE	Infective endocarditis
I.M.	Intramuscular
I.V.	Intravenous
IVDA	Intravenous drug abuser
KPT	Known-pathogen therapy
MIC	Minimal inhibitory concentration
MRPA	Multidrug-resistant <i>Pseudomonas aeruginosa</i>
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
NCCLS	National Committee for Laboratory Standards
NIH	National Institutes of Health
ODA	Once daily aminoglycosides
P.O.	Per oral
PPU	Perforated peptic ulcer
PVL	Panton-Valentine leukocidin
q.i.d.	Four times daily
syr.	Syrup
tab.	Tablet
TBW	Total body weight
TDM	Therapeutic drug monitoring
t.i.d.	Three times daily
US	Ultrasound

VRE Vancomycin-resistant enterococcus  
WHO World Health Organization

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