Table 4.1 Guidelines for empirical therapy

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Footnote

[1] Classification and definition of group A streptococcal toxic shock syndrome (336)

Definite case = criteria IA + IIA + IIB; *probable case* = criteria IB + IIA + IIB

Criteria IA: Isolation of Group A streptococci (*Streptococcus pyogenes*) from a normally sterile site (e.g. blood, cerebrospinal, pleural, or peritoneal fluid, tissue biopsy, surgical wound).

Criteria IB: Isolation of Group A streptococci (*Streptococcus pyogenes*) from a nonsterile site (e.g. throat, sputum, vagina, superficial skin lesion).

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

Criteria IIB: ≥2 of the following signs:

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

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

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

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

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

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