GUIDE TO ANTIMICROBIAL THERAPY IN THE ADULT ICU

Malaysian Society of Intensive Care

Dose schedules are being continually revised and new side effects recognised. The Writing Committee has endeavoured to ensure drug dosages are current and accurate. However, the reader is strongly encouraged to always keep abreast with developments in drug information and clinical application.

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PREFACE

Sepsis remains a major contribution to mortality in healthcare settings all over the world. In Malaysia, sepsis is still the commonest cause of admission to Intensive Care Units. Managing sepsis is more challenging now especially in the era of emerging antimicrobial resistance.

This book is the fourth edition of its series. The objective of this book is to provide a comprehensive guide in antimicrobial therapy in accordance with the principles of antimicrobial stewardship and prescribing antimicrobials. These measures are significant in curbing the emergence of resistant organisms in healthcare facilities.

The chapters in this handbook were written after many hours of discussion and exchanging views based on the latest evidence available and our clinical practices. The text, tables and notations are designed and written explicitly to facilitate easy clinical reference and hospital bedside decision. Needless to say, we welcome our readers to read the introduction paragraphs of each chapter in order to better understand the correlation of disease and antibiotics usage.

It is our sincere hope that this handbook will be instrumental in aiding doctors to prescribe antimicrobials in critically ill patients.

Dr Azmin Huda binti Abdul Rahim
Chairperson and Editor, Writing Committee for
Guide to Antimicrobial Therapy in the Adult ICU 2023

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SUMMARY OF IMPORTANT CHANGES

A new chapter on antimicrobial resistance and antimicrobials for parapneumonic effusions and empyema have been added in this edition. There is also a chapter on central line associated bloodstream infection in place of catheter-related bloodstream infection.

A dedicated chapter on microbiological investigations has been removed. The microbiological investigation specimens and methods are now incorporated into each relevant chapter.

In line with new evidence and better understanding of pharmacokinetics and pharmacodynamics, a more detailed and self-explanatory appendices have been formulated:

- Dosage adjustments for high protein-bound antibiotics in patients with hypoalbuminaemia
- Expanded appendix on extended infusion of antibiotics, duration for loading dose and maintenance dose is provided
- Vancomycin TDM using $AUC_{0\text{-}24}$/MIC ratio
- Loading dose for echinocandins in obese patients
- A new appendix with list of antimicrobials in pregnancy
- Use of polymyxins

The use of inhaled polymyxin has been omitted due to weak evidence on its usefulness.

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ANTIMICROBIAL STEWARDSHIP IN ICU

The dilemma of current antimicrobial use in ICUs is the balance between providing adequate coverage against likely pathogens whilst minimising selection of antibiotic resistant organisms. The key aims of antimicrobial stewardship (AMS) are to ensure the right drug is given at the right time, at the right dose and for the right duration, aiming to eradicate infection whilst minimising adverse effects and costs.

A structured AMS program consisting of an interdisciplinary team, educational interventions, system innovations, process indicator evaluation and feedback to healthcare workers is essential for successful implementation. Appropriateness of a prescribed antimicrobial therapy can be assessed during AMS rounds or normal everyday rounds.

The selective pressure that results from inappropriate use of antimicrobials highly correlates with the emergence of resistance. Appropriate AMS consists of rapid identification and treatment of infections based on pharmacokinetic/pharmacodynamic properties, avoiding the use of needless broad-spectrum agents, shortening the duration of administration and minimising the number of patients receiving unnecessary antimicrobials. Alongside the appropriate use of antimicrobials, rapid source control is equally important.

Optimal dosing should be individualised to the patient's clinical characteristics, causative organism, site of infection and pharmacokinetics/pharmacodynamics of the antimicrobial agent.

Antimicrobial stewardship in the critically ill includes:

1. **Rapid identification of patients with infection**
   - A clinical diagnosis of infection should be made before administration of any antimicrobial.
   - Obtaining specimens for appropriate cultures before antimicrobial administration is essential to identify responsible pathogens and enable de-escalation therapy. However, the results are often unavailable for the first 24 hours.
   - The decision to start antimicrobials in a possibly infected patient needs to be balanced between the uncertainty of infection and risk of delaying treatment against the overuse of antibiotics.
   - Biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) are available for clinical use in acute infections, however their diagnostic accuracy is suboptimal and lacks sensitivity and specificity.
   - Molecular diagnostic testing may be used for timely and rapid identification of causative microorganism.

2. **Ensuring appropriate empirical antimicrobial therapy (AMT)**
   - Empirical AMT should be based on regularly updated local data on the incidence of causative organisms and their susceptibility to antimicrobial agents, for both community and hospital-acquired infections.
   - Recent antimicrobial exposure should be taken into consideration when initiating empirical AMT.

3. **Minimising time to initial antimicrobial dose**
   - The timing of initial therapy should be guided by the urgency of the situation.

- In critically ill patients with septic shock, febrile neutropenia or bacterial meningitis, empirical AMT should be initiated immediately after obtaining microbiological specimens or even before, if the procedure is delayed.
- In patients with possible sepsis without shock, appropriate specimens or investigations should be obtained prior to AMT.

4. Optimising antimicrobial dose and interval

Pharmacokinetic changes in the critically ill can be described as follows:

Antibiotic Characteristics	Pharmacokinetic Parameters	General Pharmacokinetics	Altered Pharmacokinetics in Critically Ill Patients
Hydrophilic antibiotics	Volume of distribution (V_d)	Low	Increased
	Clearance	Predominantly renal	Clearance higher/lower depending on renal function
	Distribution	Poor intracellular penetration	Interstitial penetration
	Examples	ß-lactams, aminoglycosides, glycopeptides and polymyxins	

Antibiotic Characteristics	Pharmacokinetic Parameters	General Pharmacokinetics	Altered Pharmacokinetics in Critically Ill Patients
Lipophilic antibiotics	Volume of distribution (V_d)	High	Unchanged
	Clearance	Predominantly hepatic	Clearance higher/lower depending on hepatic function
	Distribution	Good intracellular penetration	Unchanged
	Examples	Fluoroquinolones, macrolides and Tigecycline	

Strategies that may be considered for dose optimisation include:

- extended or continuous infusion of ß-lactams
- once-daily dosing of aminoglycosides
- appropriate dosing of antimicrobials with narrow therapeutic range e.g. Vancomycin
- dosing of certain antimicrobials in special populations e.g. obesity, pregnancy
- dose adjustments for patients with renal or liver dysfunction
- dose adjustments for patients with hypoalbuminaemia
- dose adjustments for patients on renal replacement therapy

Factors affecting dosing in the critically ill include:

- *Increase in volume of distribution (V_d) of hydrophilic antibiotics*
  V_d of hydrophilic antibiotics (e.g. aminoglycosides, ß-lactams, Vancomycin, polymyxins) is increased in

patients with sepsis and burns. The increase in V_d can lower the plasma concentration during initial therapy. Hence, administration of a loading dose is necessary to achieve appropriate concentration at the site of infection.

- *Hypoalbuminaemia*
  Hypoalbuminaemia is associated with a lower degree of protein binding in highly protein-bound antimicrobials (e.g. Ceftriaxone, Cloxacillin, Ertapenem, Vancomycin) leading to altered pharmacokinetics (PK). The increase in the free fraction (unbound) of the drug results in higher V_d and drug clearance. This may reduce antimicrobial exposure and compromise pharmacodynamic target *(Refer to **Appendix B** for dosage adjustment)*.

- *Augmented renal clearance*
  Augmented renal clearance (ARC) [CrCl ≥ 130ml/min/1.73m^2] is common in patients with sepsis, burns, polytrauma, traumatic brain injury and febrile neutropenia. Eight-hour urine sample for creatinine clearance may be collected to confirm ARC. Significant correlations between subtherapeutic concentrations of ß-lactams or Vancomycin and ARC were observed. Hence, the dose of antimicrobials may have to be increased and levels to be monitored.

- *Extracorporeal therapies*
  In patients with kidney failure, the time to achievement of steady-state is increased for antimicrobials cleared by the kidneys. Those on continuous renal replacement therapy (CRRT) frequently have an increased V_d. Hence, a loading dose is also necessary.

CRRT is effective at elimination of hydrophilic antimicrobials especially those with low protein binding. However, the amount of antimicrobials eliminated depends on the mode, dose of CRRT delivered, blood flow rate, filter material and surface area. Similarly, antimicrobial pharmacokinetics in sustained low-efficiency dialysis (SLED) should be based on blood and dialysate flow rates, duration and filter surface area.

Time-dependent antimicrobials are more affected in SLED than in intermittent HD potentially resulting in prolonged periods of concentration below minimum inhibitory concentration (MIC). Hence, supplemental doses during or after SLED or prolongation of infusion times may be necessary. Antibiotic dosing guidelines for use across all renal replacement therapy (RRT) modalities are not possible because of varied drug clearances across the different modalities and settings.

There is limited data on optimal dosing for antibiotics in the presence of extracorporeal membrane oxygenation (ECMO). Common mechanisms that influence pharmacokinetics during ECMO are sequestration in the circuit, increased V_d, decreased drug elimination and direct adsorption to the membrane. Hydrophilic antibiotics with a small V_d are prone to haemodilution and direct adsorption by the membrane. In contrast, lipophilic and highly protein-bound antimicrobials (e.g. Voriconazole) with a large V_d are sequestered in the circuit.

5. De-escalation of therapy

- Antimicrobial de-escalation refers to a strategy of replacing a broad-spectrum with a narrower-spectrum antimicrobial targeting the specific organism from the culture available or discontinuation of antimicrobials.

- When culture and sensitivity results become available, choose susceptible antimicrobial with the narrowest spectrum, least toxicity and most cost effective.
- Discontinue empirical antimicrobial therapy if susceptibility testing or subsequent clinical correlation does not support the presence of infection.

6. Appropriate treatment duration

- A 7-day duration is generally appropriate for most patients including septic shock with or without bacteraemia and those infected with multi-resistant organisms.
- However, duration of treatment also depends on the type and site of infection, ability to attain source control, general response to therapy and immune status.
- Procalcitonin-guided therapy has resulted in shorter duration of antimicrobials in units where antimicrobial duration exceeds 10 days.

7. Intravenous (IV) to oral (PO) antimicrobial conversion

- Evidences have demonstrated the efficacy, safety and economic impact of IV to PO antimicrobials conversion. IV to PO antimicrobials conversion also benefits the patient by eliminating adverse events associated with IV therapy, increasing patient comfort and mobility as well as enabling early hospital discharge.

Conditions that may be considered for PO conversion following adequate parenteral therapy:

- Osteomyelitis
- Septic arthritis

- Infected implant or prosthesis
- Necrotising soft tissue infection
- Complicated orbital cellulitis (abscess or other complication)
- Intra-abdominal infection without deep-seated collections

Conditions not recommended for IV to PO conversion:

- Endocarditis
- Central nervous system infections (e.g. meningitis, brain abscess, etc.)
- *Staphylococcus aureus* bacteraemia

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PRINCIPLES OF ANTIMICROBIAL THERAPY

Antimicrobial agents are commonly used for prophylaxis or treatment of infections.

Prophylactic Antimicrobial Therapy

Antimicrobial prophylaxis (AP) can be primary (prevention of an initial infection) or secondary (prevention of the recurrence of an infection). It is often used for surgical or nonsurgical indications. Examples of nonsurgical AP include prevention of infective endocarditis in valvular heart disease undergoing dental procedures and prevention of infection by encapsulated organisms in asplenic patients.

Preoperative antibiotic prophylaxis is defined as administering antibiotics prior to performing surgery to help decrease the risk of postoperative infections. Clean surgery usually does not require antibiotic prophylaxis unless an artificial implant or foreign body is implanted, in bone grafting procedures, and other surgeries with extensive dissections or expected high blood loss.

Intravenous prophylaxis should be given within 30 to 60 minutes before the surgical incision or torniquet inflation to maximise its effectiveness. However, Vancomycin requires administration within 120 minutes of incision due to its longer administration time. If a patient is already receiving an antimicrobial for another infection before surgery and that agent is appropriate for surgical prophylaxis, an extra dose of the antimicrobial may be administered within 60 minutes of the incision.

Intraoperative redosing (interval of the time from the first operative dose) should be administered in surgeries lasting more than 4 hours or in excessive blood loss more than 1.5L. Unless there is a known infection, prophylactic antimicrobials should be discontinued within 24 hours. Additional prophylactic antibiotics should not be administered after the surgical incision is closed in clean and clean-contaminated procedures. Although there could be procedure-specific exceptions, this recommendation applies to patients with or without a drain after the surgical site is closed.

Empirical Antimicrobial Therapy

Sepsis in the critically ill remains a diagnostic and management challenge. Besides adequate fluid resuscitation, vasopressor therapy and support of the failing organ systems, the use of appropriate antimicrobial therapy and source control are equally important for good clinical outcomes. The aim of antimicrobial therapy (AMT) is to achieve effective concentration at the target sites whilst minimising adverse events.

In general, management of patients with suspected infection consists of initiation of empirical AMT followed by targeted therapy once microbiological data becomes available. Empirical AMT should be administered without delay and guided by severity of illness, local epidemiology and resistant patterns, site of infection and likely causative organism. All appropriate microbiological specimens, including blood cultures, should be obtained before commencing therapy whenever possible.

Inappropriate use and/or delay in initiation of antimicrobials in the ICU is associated with poor outcomes. Inappropriate antimicrobial use can also lead to the emergence of resistant organisms, antimicrobial-related

adverse events and increase in healthcare costs. Antibiotic stewardship has been suggested to overcome these problems.

When initiating empirical antimicrobials in patients with sepsis, consider the following factors:

1. Likely causative organism

- Decide if community or nosocomial infection.
- Identify the most likely source of infection.
- Consider local epidemiological data and laboratory-oriented surveillance. Knowing the resistance profiles in the community, hospital or ICU helps in choosing antimicrobials appropriately.
- Evaluate risk factors for multidrug-resistant (MDR) organisms e.g. MDR Gram-negative bacilli, MRSA, VRE.

2. Patient factors

- *Exposure history*
  Take a travel history (e.g. malaria in endemic areas), occupational exposure e.g. rice farmers (Burkholderia pseudomallei), fishermen *(Vibrio vulnificus)*, intravenous drug users *(Staphylococcus aureus)*, activities in contaminated soil/water (leptospirosis).
- *Co-morbidities*
  Examples in diabetes mellitus (melioidosis), chronic lung diseases *(Pseudomonas aeruginosa)* and valvular heart diseases (endocarditis).

- *Severity of illness*
  Patients in septic shock require antimicrobial administration within an hour.
- *Prior antimicrobial use or prolonged hospitalisation*
  Both are risk factors for the presence of resistant organisms.
- *Immunosuppressive states*
  Patients with underlying malignancy, post-splenectomy, unvaccinated, malnourished, on steroids or immunosuppressive drugs may require broad-spectrum therapy including antifungal.
- *Presence of renal or hepatic dysfunction*
  Drug clearance may be affected. After the loading dose, adjust maintenance doses and intervals based on severity of organ dysfunction. The risk-benefit ratio of the antimicrobials must be determined on a case-to-case basis.
- *Obesity, pregnancy and lactation*
  Adjust drug doses in obesity. Ascertain the risk categories of antimicrobials in pregnancy.
- *Others*
  Consider alternatives in drug allergies.

3. Antimicrobial profile

- *Route of administration*
  The intravenous route should be used in severe infection as oral absorption is unpredictable even for drugs with good oral bioavailability. In addition to intravenous administration, intrathecal or inhalational route may be considered to improve target site concentrations.

- *Dose and interval*

  Pathophysiological changes in critically ill patients alter the pharmacokinetic (PK) and pharmacodynamic (PD) profile of the antimicrobials particularly volume of distribution (V_d) and clearance. ICU patients often have an increased V_d for hydrophilic antibiotics. Lower antibiotic concentrations can be potentiated by hypoalbuminaemia and augmented renal clearance for renally excreted drugs. Antibiotics can be categorised into three different classes depending on the pharmacokinetic/pharmacodynamic (PK/PD) indices associated with their optimal killing activity. Understanding exposure-effect relationships is required to optimise antibiotic dosing in the critically ill.

PD kill characteristics	**Optimal PK parameter**	**Goals of therapy/application**	**Examples**
Time-dependent	T>MIC Percentage of time that drug concentration remains above MIC during a dosing interval	Maximise duration of exposure → administer extended infusion **(Refer to Appendix C)**	Penicillins Cephalosporins Carbapenems
Concentration-dependent	C_{max}/MIC Ratio of maximum drug concentration to MIC	Maximise concentration of drug → use higher maintenance dose **(Refer to Appendix E)**	Aminoglycosides
Concentration-dependent with time dependence	$AUC_{0\text{-}24}$/MIC Ratio of area under the concentration-time curve (AUC) during a 24-hour period to MIC	Optimise amount of drug → administer loading dose	Glycopeptides Polymyxins

MIC: Minimum Inhibitory Concentration

- *Achievable antimicrobial concentrations at target tissue*
  Dose optimisation based on pharmacokinetic properties of antimicrobials should be undertaken to maximise the antimicrobial exposure at the target site as illustrated in the table above. Consider therapeutic drug monitoring (TDM) of antimicrobials to prevent the risk of treatment failure and minimise toxicity.

  Aminoglycosides and glycopeptides penetrate tissues poorly. Aminoglycosides should not be used as monotherapy whilst a higher plasma level of glycopeptides is recommended to ensure adequate tissue penetration.

  Both ß-lactams and quinolones have good tissue penetration. However, higher doses are still required to achieve adequate concentrations in infections of the central nervous system.

- *Post-antibiotic effect (PAE)*
  This is defined as persistent suppression of bacterial growth even after the serum antibiotic concentration falls below the MIC of the target organism. Aminoglycosides, fluoroquinolones and carbapenems have PAE against Gram-negative bacteria.

- *Adverse events*
  Risk-benefit of antimicrobials with potential serious adverse events should be considered on a case-to-case basis. If use is unavoidable, serum levels should be monitored for toxicity (e.g. aminoglycosides).

- *Ecological profile*
  Limit the use of antimicrobials with potential for selecting resistant organisms e.g. third generation cephalosporins result in selection pressure for ESBL producing Enterobacterales.

Empirical therapy should be re-evaluated after 48-72 hours or when culture results become available. Once a causative pathogen is identified, narrow the spectrum of AMT (de-escalation). Susceptibility tests should be interpreted carefully as in-vitro susceptibility does not equate to clinical effectiveness (e.g. ESCAPPM organisms: *Enterobacter spp, Serratia spp, Citrobacter freundii, Aeromonas spp, Proteus vulgaris, Providencia spp, Morganella morganii*).

If the patient is improving, and where relevant, definitive source control has been achieved, the recommended duration of AMT is 5-7 days. There is increased risk of resistance with prolonged use of antimicrobials. However, certain conditions may require prolonged therapy e.g. complicated *Staphylococcus aureus* infections, osteomyelitis, infective endocarditis, etc. Consider switching to the oral route whenever possible *(Refer to page 7 & 8 for IV to PO antimicrobial conversion)*.

If there is poor clinical response within 48-72 hours, consider:
- possibility of a secondary infection
- presence of resistant organisms
- inadequate source control e.g. abscesses not drained, infected prosthesis not removed
- inadequate penetration of antimicrobial to the site of infection

- inadequate spectrum of antimicrobial coverage
- inadequate dose or interval
- non-infectious causes e.g. deep vein thrombosis, acute myocardial or pulmonary infarctions, acute pancreatitis, hyperthyroidism, Addisonian crisis, malignancies and central nervous system haemorrhages

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ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) continues to be a global crisis. Carbapenem-resistant Enterobacterales (CRE), AmpC ß-lactamase-producing Enterobacterales (AmpC-E) and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*) are emerging resistant organisms in the ICU. Other multidrug-resistant (MDR) organisms include extended-spectrum ß-lactamase-producing Enterobacterales (ESBL-E), carbapenem-resistant *Acinetobacter baumannii* (CRAB), methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant enterococci (VRE). With limited treatment options, these MDR organisms are associated with high mortality and are now recognised as important healthcare-associated infections.

Infection control measures should be implemented in all patients with MDR organisms (e.g. ESBL-E, CRAB, MRSA, VRE, CRE, AmpC-E and DTR-*P. aeruginosa*). Hand hygiene is the single most important measure in preventing transmission of infection. The 5 moments of hand hygiene should be followed strictly. Other measures include contact precautions, isolation of patients and surveillance.

Contact precautions involve appropriate patient placement, use of personal protective equipment, limiting transport and movement of patients, use of disposable or dedicated patient-care equipment and prioritising cleaning and disinfection of patients' rooms.

Patients colonised or infected with MDR organisms should be isolated in a single room or cohorted with patients with the same resistant organism. Active surveillance for CRE infection or colonisation should be

performed in high-risk patients or in epidemiologically linked contacts, guided by resource availability and clinical impact of a CRE outbreak.

Carbapenem-resistant Enterobacterales (CRE)

CRE is defined as Enterobacterales that are resistant to at least one of the carbapenem antibiotics (i.e. MIC of ≥ 4 mg/L for Doripenem, Meropenem and Imipenem, and ≥ 2 mg/L for Ertapenem) or Enterobacterales that produce a carbapenemase.

CRE comprise a heterogenous group of pathogens with multiple potential mechanisms of resistance including:

1. Carbapenemase producing enzymes
2. Non-carbapenemase producing enzymes due to amplification of non-carbapenemase ß-lactamase genes with concurrent outer membrane porin disruption

The most common carbapenemase variants in Malaysia are *New Delhi metallo-ß-lactamase-1 (NDM-1)* and *oxacillinase-48 (OXA-48)*.

Risk factors for CRE colonisation are underlying comorbid conditions, prior antimicrobial exposure, indwelling catheters or device, prolonged ICU/hospital stay and co-colonisation with MDR organisms. The use of carbapenem is a risk factor for CRE acquisition, however the proportion reported for carbapenem use among colonised patients varies from 15% to 75%.

CRE can be colonised up to 12 months after initial acquisition. Although there is no consensus regarding discontinuation of contact precautions, most hospitals in Malaysia continue surveillance for a year. In hospitals with high incidence of CRE infections, active surveillance with pre-emptive contact isolation is recommended to control CRE by reducing transmission and colonisation pressure. Screening of CRE includes rectal or perianal swab molecular based method.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Carbapenem-resistant Enterobacterales (CRE) *New Delhi metallo-ß-lactamase-1 (NDM-1)* *OXA-48*	IV Polymyxin E (Colistin) 4.5 million units q12h *OR* IV Polymyxin B 15,000 units/kg q12h × 7 days	IV Ceftazidime/ Avibactam 2.5g q8h *PLUS* IV Aztreonam 2g q8h × 7 days	*NDM-1* is the most predominant variant in Malaysia. IV Aztreonam is not required for non-NDM infections (e.g. *OXA-48*). Ceftazidime/Avibactam plus Aztreonam is recommended as first line treatment in international guidelines, however it is currently not available in MOH formulary. Refer to **Appendix D** for loading dose of polymyxins. Polymyxin B is an active drug and is less nephrotoxic. However, in urinary tract infection, Polymyxin E (Colistin) is preferred.

AmpC ß-lactamase-producing Enterobacterales (AmpC-E)

AmpC-E is also emerging in ICU. Exposure to ß-lactams in these organisms can trigger a cascade of events leading to significant AmpC production and ß-lactam resistance, thus complicating treatment options.

Mechanisms of resistance can be divided into 3 categories:

- Inducible resistance via chromosomally encoded AmpC genes
- Non-inducible chromosome
- Plasmid-mediated

Therefore, when *Enterobacter cloacae*, *Klebsiella aerogenes* or *Citrobacter freundii* are isolated in clinical cultures, treatment with a 3rd generation cephalosporin e.g. Ceftriaxone or Ceftazidime should be avoided even if isolates test susceptible to these antibiotics. The emergence of resistance after exposure to an agent like Ceftriaxone may occur in approximately 8 - 40% of infections caused by these organisms.

Carbapenem provides reliable coverage against AmpC hyperproducers. 4th generation cephalosporin e.g. Cefepime is an alternative as it has an advantage of being a weak inducer of AmpC production and withstanding hydrolysis by AmpC ß-lactamases.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
AmpC ß-lactamase-producing Enterobacterales (AmpC-E) *Enterobacter cloacae* *Klebsiella aerogenes* *Citrobacter freundii* *Serratia spp* *Aeromonas spp* *Proteus vulgaris* *Providencia spp* *Morganella morganii*	IV Cefepime 2g q8h × 7 days	IV Meropenem 1g q8h × 7 days	Ertapenem can be considered in targeted therapy once patient is clinically stable and source control is adequate. Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing.

***Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*)**

DTR is defined as *Pseudomonas aeruginosa* exhibiting non-susceptibility to all of the following: Piperacillin/Tazobactam, Ceftazidime, Cefepime, Aztreonam, Meropenem, Imipenem/Cilastatin, Ciprofloxacin and Levofloxacin.

Mechanisms of resistance include:

- Decreased expression of outer membrane porins
- Hyperproduction of AmpC enzymes
- Upregulation of efflux pumps
- Mutations in penicillin-binding protein targets

In an observational study involving 200 patients with DTR-*P. aeruginosa*, favourable clinical outcome was observed in 81% of patients receiving Ceftolozane/Tazobactam.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
DTR-*P. aeruginosa*	IV Polymyxin E (Colistin) 4.5 million units q12h *OR* IV Polymyxin B 15,000 units/kg q12h × 7 days	IV Ceftolozane/ Tazobactam 1.5-3g q8h *OR* IV Ceftazidime/ Avibactam 2.5g q8h × 7 days	Higher dose of Ceftolozane/ Tazobactam is required in HAP/VAP. Refer to **Appendix D** for loading dose of polymyxins. Polymyxin B is an active drug and is less nephrotoxic. However, in urinary tract infection, Polymyxin E (Colistin) is preferred.

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SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Severe community-acquired pneumonia (sCAP) generally refers to pneumonia requiring respiratory (invasive/ non-invasive) or vasopressor support. In Malaysia, it is one of the three leading causes of ICU admission and has a hospital mortality rate of 35%. Risk factors for mortality related to sCAP include advanced age, co-morbidities and severity of illness on admission.

Common pathogens identified include *S. pneumoniae*, *H. influenzae*, *Legionella*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, Respiratory viruses *(COVID-19, Influenza A & B)*. In Southeast Asia, CAP caused by *Klebsiella pneumonia*, *Burkholderia pseudomallei* and *Mycobacterium tuberculosis* were identified at a higher proportion.

Combination therapy with ß-lactams and macrolides has been shown to achieve better outcomes, with most patients showing clinical improvement within 48-72 hours of initial antibiotic treatment. However, in those not responding to therapy, consider complications such as parapneumonic effusions, empyema, lung abscesses, or non-infective aetiologies (e.g. congestive heart failure, pulmonary embolism, neoplasm and pulmonary haemorrhage). Duration of antibiotics in empyema is prolonged, however, video-assisted thoracoscopic surgery debridement (VATS-D) has been shown to reduce duration of antibiotics and hospital stay.

In a recent single-centre RCT, early treatment with hydrocortisone was beneficial in patients with sCAP who lack contraindications to steroids, however, further studies are required before advocating its use.

Respiratory and other relevant specimens

Specimen	Notes
Sputum or tracheal aspirate for gram stain and culture and sensitivity	A good sputum or tracheal aspirate specimen should have < 10 epithelial cells for gram stain or culture and sensitivity.
Serum *Mycoplasma* serology and urine antigen test for Legionella	A *Mycoplasma* serology titre of ≥ 1:80 is considered significant.
Throat swab for *Influenza* with a rapid *Influenza* molecular assay (i.e. *Influenza* nucleic acid amplification test)*	Tracheal aspirate specimen for *Influenza* viral PCR should be sent in intubated patients for better yield.
Bronchoalveolar lavage (BAL)	A diagnostic BAL is not indicated except in non-resolving pneumonia.
Blood culture and sensitivity	The yield is generally low.

*Availability of the test should be confirmed with the laboratory within the institution.

Pleural fluid specimen

Pleural effusion and empyema are not uncommon complications in severe pneumonia. Pleural fluid can be classified into exudate or transudate based on Light's criteria. It is an exudate if at least one of the following exists:

- Pleural fluid:serum protein > 0.5 or absolute pleural fluid protein > 30 g/L
- Pleural fluid:serum LDH > 0.6
- Pleural fluid LDH level > two-thirds upper limit of normal serum value

Characteristics	Normal	Parapneumonic effusion		
		Uncomplicated	Complicated	Empyema
Appearance	Clear	Clear, slightly turbid	Cloudy	Pus
Biochemistry				
pH	7.60 - 7.64	> 7.30	< 7.20	N/A
Glucose (mmol/L)	Similar to plasma	> 3.3	< 2.2	N/A
Ratio of pleural fluid to serum glucose	1.0	> 0.5	< 0.5	N/A
Lactate dehydrogenase (IU/L)	< 50% of plasma	< 700	> 1000	N/A
Polymorphonuclear count (cells/mL)	< 1000 leucocytes/mm^3	< 15,000	> 125,000	N/A
Microbiological test result	-	Negative	May be positive	May be positive
Treatment	-	Antibiotics	Antibiotics and drainage	Antibiotics and drainage

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy in patients with sCAP			
Streptococcus pneumoniae *Haemophilus influenzae* *Klebsiella pneumoniae*	IV Amoxicillin/ Clavulanate 1.2g q8h × 5-7 days *PLUS*	IV Ceftriaxone 1g q12h *OR* IV Cefotaxime 2g q8h × 5-7 days *PLUS*	Indiscriminate use of 3rd generation cephalosporins can promote the emergence of ESBL producers. If pneumococcal pneumonia is confirmed, de-escalate to IV Benzylpenicillin 4 million units q6h if MIC ≤2mg/L. The emergence of drug resistant *S. pneumoniae* is on the rise. Consider Levofloxacin / Moxifloxacin if macrolides are contraindicated, e.g. increased transaminases.
Mycoplasma pneumoniae *Legionella pneumophilia* *Chlamydophila pneumoniae*	IV Azithromycin 500mg q24h × 3-5 days	IV Levofloxacin 750mg q24h *OR* IV Moxifloxacin 400mg q24h × 5 days	Duration of therapy for confirmed atypical pneumonia: • *Mycoplasma:* Azithromycin × 5 days Levofloxacin / Moxifloxacin × 5 days • *Legionella:* Immunocompetent × 7-10 days Immunocompromised: longer duration • *Chlamydophila:* Azithromycin × 5 days Levofloxacin / Moxifloxacin × 5-7 days

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy in patients with sCAP			
Staphylococcus aureus	IV Cloxacillin 2g q6h × 7 days		Suspect *S. aureus* in: • necrotising infiltrates • empyema • intravenous drug users • post influenza In *S. aureus* bacteraemia, echocardiography should be performed to rule out endocarditis.
Pseudomonas aeruginosa	IV Cefepime 2g q8h × 7 days	IV Piperacillin/ Tazobactam 4.5g q6h × 7 days	Risk factors for *Pseudomonas* infection: • Severe structural lung disease (e.g. bronchiectasis) • COPD • Steroid use • Immunosuppressed A longer duration of therapy is indicated in: • pneumonia with extrapulmonary manifestations (meningitis, endocarditis, lung abscess, empyema) • melioidosis

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy in patients with sCAP			
Pneumocystis jiroveci	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q6-8h × 21 days	IV Pentamidine 4mg/kg/day *OR* PO Primaquine 30mg q24h *PLUS* IV Clindamycin 600-900mg q8h × 21 days	Prednisolone should be given 15-30 mins before antimicrobials. PO Prednisolone dose: 40mg q12h × 5 days, then 40mg q24h × 5 days, then 20mg q24h × 11 days. Consider alternative therapy if intolerant to Trimethoprim/Sulfamethoxazole.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy in patients with sCAP			
Influenza A (e.g. H1N1) *Influenza B*	PO Oseltamivir 75mg q12h × 5 days	PO Favipiravir D1 1800mg q12h D2-D5 800mg q12h	Antibiotic coverage is recommended if bacterial co-infection is suspected especially in the elderly or immunocompromised.
SARS-CoV-2	No antiviral is recommended in severe COVID-19 pneumonia.		There is insufficient evidence to support concurrent antibiotic therapy in COVID-19 pneumonia. Steroid in severe COVID-19 pneumonia: • IV Dexamethasone 6mg q24h up to 10 days or earlier if clinically improving Immunomodulating agent in severe COVID-19 pneumonia: • PO Baricitinib 4mg q24h × 14 days or until hospital discharge, whichever comes first
Parainfluenza viruses *Adenovirus* *Coronavirus (MERS-CoV, SARS-CoV)*	No antiviral is recommended.		
Herpes simplex *Varicella zoster*	IV Acyclovir 10mg/kg q8h × 7 days		

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy in patients with parapneumonic effusions/empyema			
Streptococcus pneumoniae *Streptococcus milleri* *Cutibacterium spp* *Staphylococcus aureus*	IV Amoxicillin/ Clavulanate 1.2g q8h	IV Ceftriaxone 1g q12h *PLUS* IV Metronidazole 500mg q8h	In patients with penicillin hypersensitivity, use combination therapy with a respiratory fluoroquinolone (Levofloxacin, Moxifloxacin) plus Metronidazole. Duration of therapy: • Uncomplicated parapneumonic effusions × 1-2 weeks
Pseudomonas aeruginosa	IV Piperacillin/ Tazobactam 4.5g q6h	IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h	• Complicated parapneumonic effusions × 2-3 weeks (+ drainage) • Empyema × 4-6 weeks (+ drainage) Optimal duration of post-operative antibiotics following VATS-D is not known but generally may be given for approximately 3-7 days.

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ASPIRATION PNEUMONIA AND LUNG ABSCESS

Aspiration pneumonia refers to pneumonia resulting from entry of gastric or oropharyngeal contents into the lower airways whilst chemical pneumonitis is a non-infectious inflammatory reaction to irritative gastric contents.

Antimicrobials are not indicated in aspiration without evidence of infection. However, consider antibiotics in chemical pneumonitis if the pneumonitis fails to resolve within 48 hours, in patients with small bowel obstruction or on acid suppression therapy.

Lung abscess is defined as liquefactive necrosis of the lung parenchyma and formation of cavities caused by microbial infection. Primary lung abscess results from existing parenchymal process (e.g. aspiration pneumonia, necrotising pneumonia). Secondary lung abscess results from bronchial obstruction from foreign body or neoplasm, co-existing lung diseases (e.g. bronchiectasis, cystic fibrosis) or haematogenous dissemination (e.g. infective endocarditis, Lemierre's disease).

Lung abscesses arising as a complication of aspiration are typically polymicrobial which includes *Bacteroides, Prevotella*, *Peptostreptococcus*, *Fusobacterium* or *Streptococcus*. Less commonly, lung abscesses complicate acute monomicrobial infections with pyogenic bacteria (e.g. *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*).

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Community-acquired aspiration pneumonia/lung abscess			
Anaerobes *(Peptostreptococci, Fusobacterium spp, Prevotella melaninogenica, Bacteroides spp)* *Streptococcus pneumoniae* *Haemophilus influenzae* *Staphylococcus aureus* *Enterobacterales (Escherichia coli, Klebsiella pneumoniae)* *Moraxella catarrhalis*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h	IV Ceftriaxone 1g q12h *PLUS* IV Metronidazole 500mg q8h *OR* IV Clindamycin 600mg q8h	Clindamycin is used in patients with allergy to penicillin. Duration of therapy: • Aspiration pneumonia: 5-7 days • Lung abscess: minimum 4 weeks depending on causative organism, clinical response or resolution by CT scan Switch to oral antibiotics after 3 weeks of IV antibiotics.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Healthcare-associated aspiration pneumonia/lung abscess			
Enterobacterales *(Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa)* Anaerobes	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h	Duration of therapy: • Aspiration pneumonia: 7 days • Lung abscess: minimum 4 weeks depending on causative organism, clinical response or resolution by CT scan Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing.
Lung abscess secondary to tricuspid valve endocarditis			
Methicillin-susceptible *Staphylococcus aureus* Methicillin-resistant *Staphylococcus aureus*	Refer to chapter on Infective Endocarditis.		

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HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA

Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours after hospitalisation whilst ventilator-associated pneumonia (VAP) is pneumonia that occurs 48 hours following invasive mechanical ventilation.

Prior intravenous antibiotic use within 90 days and previous colonisation or infection with multidrug-resistant (MDR) organism are significant risk factors for MDR HAP/VAP. Additional risk factors for MDR VAP include septic shock at time of VAP, acute respiratory distress syndrome (ARDS) or acute renal replacement therapy (RRT) preceding VAP and ≥ 5 days of hospitalisation prior to onset of VAP.

The Malaysian Registry of Intensive care (MRIC) report (2020-2021) revealed that the common organisms isolated were *Acinetobacter spp*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

The duration of antibiotics in HAP/VAP should not exceed 7 days including those infected with MDR organisms. However, longer duration may be appropriate for patients with delayed clinical response.

In patients with suspected VAP, non-invasive sampling (e.g. endotracheal aspirate collection) is preferred to bronchoalveolar lavage (BAL). However, a positive respiratory specimen culture does not differentiate true pathogens from colonisers. Hence, results must be interpreted in context with patients' clinical condition to prevent unnecessary antimicrobial prescription.

Respiratory specimen

Respiratory Specimen	Notes
Tracheal aspirate culture and sensitivity	Semiquantitative cultures, good sputum or tracheal aspirate sample should have less than 10 epithelial cell per power field.
Bronchoalveolar lavage (BAL)	Quantitative cultures 10^4 or 10^5 colony forming units per mL (cfu/mL) to diagnose VAP.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Empirical therapy in patients with HAP or VAP without risk factors for MDR organisms			
Streptococcus pneumoniae *Haemophilus influenzae* *Staphylococcus aureus* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ceftriaxone 1g q12h × 7 days	IV Cefepime 2g q8h *OR* IV Piperacillin/ Tazobactam 4.5g q6h × 7 days	Consider alternative therapy in patients with shock or chronic lung disease due to increased risk of *P. aeruginosa* infection. Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy in patients with HAP or VAP with risk factors for MDR organisms			
Klebsiella pneumoniae *Pseudomonas aeruginosa*	IV Cefepime 2g q8h *OR* IV Piperacillin/ Tazobactam 4.5g q6h × 7 days	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h × 7 days	For risk factors for MDR HAP/VAP, refer to text. Consider alternative therapy in haemodynamically unstable patients.
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)	IV Ampicillin/ Sulbactam 9g q8h × 7 days	IV Polymyxin E (Colistin) 4.5 million units q12h *OR* IV Polymyxin B 15,000 units/kg q12h × 7 days	Refer to **Appendix D** for loading dose of polymyxins. Polymyxin B is an active drug and is less nephrotoxic.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Empirical therapy in patients with HAP or VAP with risk factors for MDR organisms			
Klebsiella pneumoniae *Escherichia coli (ESBL)*	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h × 7 days		
Carbapenem-resistant Enterobacterales (CRE)	IV Polymyxin E (Colistin) 4.5 million units q12h *OR* IV Polymyxin B 15,000 units/kg q12h × 7 days		Refer to **Appendix D** for loading dose of polymyxins. Polymyxin B is an active drug and is less nephrotoxic.
Methicillin-resistant *Staphylococcus aureus* (MRSA)	IV Vancomycin 15-20mg/kg q12h × 7 days	IV Linezolid 600mg q12h × 7 days	Refer to **Appendix E** for loading dose and monitoring of Vancomycin. Consider MRSA coverage if > 10-20% MRSA isolates in the unit.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy in patients with HAP or VAP			
Stenotrophomonas maltophilia	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q8h × 7 days	IV Levofloxacin 750mg q24h *OR* IV Moxifloxacin 400mg q24h × 7 days	Consider alternative therapy if intolerant to Trimethoprim/Sulfamethoxazole.
Burkholderia cepacia	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q8h × 7 days	IV Ceftazidime 2g q8h × 7 days	

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy in patients with HAP or VAP			
Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)	IV Polymyxin E (Colistin) 4.5 million units q12h *OR* IV Polymyxin B 15,000 units/kg q12h × 7 days	IV Ceftolozane/ Tazobactam 3g q8h × 7 days	Refer to **Appendix D** for loading dose of polymyxins. Polymyxin B is an active drug and is less nephrotoxic.
AmpC ß-lactamase-producing Enterobacterales (AmpC-E) *Enterobacter cloacae* *Klebsiella aerogenes* *Citrobacter freundii* *Serratia spp* *Aeromonas spp* *Proteus vulgaris* *Providencia spp* *Morganella morganii*	IV Cefepime 2g q8h × 7 days	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h × 7 days	Intrinsic resistance to Imipenem: • *Proteus spp* • *Providencia spp* • *Morganella morganii* Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy in patients with HAP or VAP			
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)	IV Polymyxin E (Colistin) 4.5 million units q12h *OR* IV Polymyxin B 15,000 units/kg q12h *PLUS* IV Ampicillin/ Sulbactam 9g q8h × 7 days		Refer to **Appendix D** for loading dose of polymyxins. Polymyxin B is an active drug and is less nephrotoxic. Ampicillin/Sulbactam is infused over 4 hours.
Carbapenem-resistant Enterobacterales (CRE)	IV Polymyxin E (Colistin) 4.5 million units q12h *OR* IV Polymyxin B 15,000 units/kg q12h × 7 days	IV Ceftazidime/ Avibactam 2.5g q8h *PLUS* IV Aztreonam 2g q8h × 7 days	Ceftazidime/Avibactam plus Aztreonam is recommended as first line treatment in international guidelines, however it is currently not available in MOH formulary.

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TUBERCULOSIS

Mycobacterium tuberculosis causes progressive bacterial replication and pulmonary necrosis. In 2020, the incidence of tuberculosis (TB) in Malaysia was 72.4 per 100,000 population with the mortality of 7.1 per 100,000 population. The incidence of extrapulmonary tuberculosis was reported as 15.5%.

The aim of TB treatment is to reduce severity of disease, stop transmission, prevent relapse and emergence of resistant strains. In pulmonary, abdominal, pleural, pericardial and lymph nodes TB, the duration of anti-TB treatment is 6 months. Bone or joint TB requires 6-9 months of treatment, whilst TB meningitis requires 12 months of treatment.

The current drug regimen involves four main drugs: Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. The treatment regimen includes an intensive phase of 8 weeks followed by continuation phase. Consult Respiratory or Infectious Disease specialist in the following conditions: relapse, treatment failure, liver failure or co-infection with HIV.

Respiratory specimen

Sputum / Tracheal Aspirate	Notes
Sputum / tracheal aspirate direct smear for acid fast bacilli	Minimum 2 samples.
Mycobacterial culture and sensitivity	The gold standard for TB diagnosis and detection of drug resistance.
Xpert Ultra	Has lower limit of detection for pulmonary TB (15.6 cfu/mL of sputum).

Pleural fluid specimen

Characteristics of tuberculous pleural effusion	Notes
Straw coloured pH 7.3-7.4 Glucose similar to plasma LDH > 500 IU/L Leucocytes 1000-6000 cells/mL (predominantly lymphocytes) Adenosine deaminase (ADA) > 40 IU/L	Turbid, low glucose, pH < 7.2 and elevated ADA indicate tuberculous empyema. Acid fast bacilli using Ziehl-Neelsen stain is only positive in 5%. Culture in solid media (e.g. Lowenstein-Jensen) is positive in 12-30%. Xpert MTB test on pleural fluid has 98% specificity but sensitivity of only 28.6%.

Organisms	Antimicrobials		Notes
	Intensive Phase	Continuation Phase	
Pathogen specific / Targeted therapy			
Mycobacterium tuberculosis	PO Isoniazid 5 (4-6) mg/kg/day *PLUS* PO Rifampicin 10 (8-12) mg/kg/day *PLUS* PO Ethambutol 15 (15-20) mg/kg/day *PLUS* PO Pyrazinamide 25 (20-30) mg/kg/day × 8 weeks (2 months)	PO Isoniazid 5 (4-6) mg/kg/day *PLUS* PO Rifampicin 10 (8-12) mg/kg/day	PO Pyridoxine 10-30mg q24h should be given to prevent isoniazid induced neuropathy. Those at high risk of neuropathy should be given 30mg of Pyridoxine per day which include pregnant patients, HIV, elderly patients, patients with diabetes mellitus, alcoholism, malnutrition and chronic kidney disease. For duration of continuation phase, refer to text.

Fixed-Dose Combination (FDC)	Content	Dose based on body weight
4-FDC e.g. AKuriT-4	Isoniazid 75mg, Rifampicin 150mg, Ethambutol 275mg, Pyrazinamide 400mg	30-37kg: 2 tablets q24h 38-54kg: 3 tablets q24h 55-70kg: 4 tablets q24h >70kg : 5 tablets q24h
3-FDC e.g. AKuriT-3	Isoniazid 75mg, Rifampicin 150mg, Ethambutol 275mg	
e.g. Rimcure 3FDC or AKuriT Z	Isoniazid 75mg, Rifampicin 150mg, Pyrazinamide 400mg	
2-FDC e.g. AKuriT-2	Isoniazid 75mg, Rifampicin 150mg	

Steroids in TB

Conditions	Steroid Dose
TB Meningitis	IV Dexamethasone 0.4mg/kg/day, taper over 6-8 weeks
TB Adrenalitis	IV Hydrocortisone 100mg q8h and taper
TB Pericarditis	PO Prednisolone 60mg q24h, taper over 6-12 weeks

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INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) can present with diverse clinical presentations making the diagnosis challenging. Risk factors include prosthetic valves or intracardiac devices, congenital heart disease, previous history of IE and intravenous drug users (IVDU). Modified Duke criteria may be used to aid the diagnosis of IE when echocardiography is unavailable or delayed.

Prior to initiation of antibiotics, three sets of blood cultures should be obtained from different venepuncture sites at 30-minute intervals, but administration of antibiotics should not be delayed in severely ill patients *(Refer to page 112 & 113 for details on blood specimen collection).* Culture negative endocarditis can occur in up to 31% of cases. This may be due to prior antimicrobial therapy, inadequate microbiological techniques or fastidious organisms. Transthoracic echocardiography (TTE) plays a key role in diagnosis of suspected IE and transoesophageal echocardiography (TOE) may be warranted if TTE is negative.

Treatment is guided by native or prosthetic valve and organism virulence with the goals of eradicating infection and treating complications. Surgery is indicated in patients with heart failure, uncontrolled infection (abscess, pseudoaneurysm, fistula, enlarging vegetation) and those at high risk of embolisation (aortic or mitral valve vegetations >10mm). Blood cultures should be repeated every 48-72 hours until results are negative. Duration of treatment begins from the day of first negative culture.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy			
Native valve Prosthetic valve (≥12 months post-surgery) *Staphylococcus spp* *Streptococcus spp* *Enterococcus spp*	IV Ampicillin 2g q4h *OR* IV Benzylpenicillin 3 million units q4h *PLUS* IV Gentamicin 3mg/kg q24h *PLUS OPTIONAL* IV Cloxacillin 2g q4h		Consider Cloxacillin in intravenous drug users. Penicillin allergy: IV Vancomycin 15-20mg/kg q12h *PLUS* IV Gentamicin 3mg/kg q24h Refer to **Appendix E** for monitoring of Gentamicin.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy			
Prosthetic valve (<12 months post-surgery) Methicillin-resistant *Staphylococcus aureus* *Enterococcus spp* Non-HACEK Gram-negative bacilli	IV Vancomycin 15-20mg/kg q12h *PLUS* IV Gentamicin 3mg/kg q24h *PLUS* PO Rifampicin 300-450mg q12h *PLUS OPTIONAL* IV Cefepime 2g q8h *OR* IV Piperacillin/ Tazobactam 4.5g q6h		Refer to **Appendix E** for loading dose and monitoring of Vancomycin and Gentamicin. To avoid development of resistance, Rifampicin is added only in prosthetic valve endocarditis and is started 3-5 days after Vancomycin and Gentamicin. The concomitant use of Vancomycin and Gentamicin is associated with increased risk of nephrotoxicity and ototoxicity, hence antimicrobial spectrum should be narrowed based on culture and sensitivity results. Antipseudomonal ß-lactam is indicated if local epidemiology suggests for non-HACEK Gram-negative bacilli infections. Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Streptococcus viridans *Streptococcus bovis* Highly penicillin susceptible: MIC ≤ 0.125 mg/L	**4 weeks regime (Native)** **6 weeks regime (Prosthetic)** IV Benzylpenicillin 3 million units q4h *OR* IV Ceftriaxone 1g q12h	**2 weeks regime (Native)** IV Benzylpenicillin 3 million units q4h *OR* IV Ceftriaxone 1g q12h *PLUS* IV Gentamicin 3mg/kg q24h	Preferred therapy is recommended for patients >65 years, impaired renal function, deafness and known cardiac or extra cardiac abscess and prosthetic valves. Alternative therapy is recommended in the absence of heart failure, extra-pulmonary metastatic infection, e.g. osteomyelitis, aortic or mitral valve involvement, meningitis, MRSA infection, prosthetic valves. Refer to **Appendix E** for monitoring of Gentamicin.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Streptococcus viridans *Streptococcus bovis* Relatively resistant to penicillin: 0.125 mg/L ≤ MIC < 2.0 mg/L	IV Benzylpenicillin 4 million units q4h × 4 weeks *PLUS*	IV Ceftriaxone 1g q12h × 4 weeks *PLUS*	Duration of therapy for prosthetic valve endocarditis is 6 weeks.
Group B, C and G Streptococcus	IV Gentamicin 3mg/kg q24h × 2 weeks	IV Gentamicin 3mg/kg q24h × 2 weeks	Refer to **Appendix E** for monitoring of Gentamicin.
Streptococcus viridans *Streptococcus bovis* Highly resistant to penicillin: MIC ≥ 2.0 mg/L	Treat as resistant enterococcal endocarditis - see below.		

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Staphylococcus aureus (Native valve)	**Methicillin-susceptible** IV Cloxacillin 2g q4h × 4-6 weeks	**Methicillin-resistant** IV Vancomycin 15-20mg/kg q12h × 4-6 weeks	In uncomplicated right sided MSSA endocarditis, duration of therapy may be shortened to 2 weeks with the following criteria: • Absence of left sided endocarditis • Absence of metastatic sites of infection or empyema • Vegetations < 10mm • Absence of severe immunosuppression (CD4 < 200 cells/mL) Refer to **Appendix E** for loading dose and monitoring of Vancomycin.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Staphylococcus aureus (Prosthetic valve)	**Methicillin-susceptible** IV Cloxacillin 2g q4h × ≥6 weeks *PLUS* IV Gentamicin 1mg/kg q8h × 2 weeks *PLUS* PO Rifampicin 300-450mg q12h × ≥6 weeks	**Methicillin-resistant** IV Vancomycin 15-20mg/kg q12h × ≥6 weeks *PLUS* IV Gentamicin 1mg/kg q8h × 2 weeks *PLUS* PO Rifampicin 300-450mg q12h × ≥6 weeks	To avoid development of resistance, Rifampicin is added only in prosthetic valve endocarditis and is started 3-5 days after Vancomycin and Gentamicin. Treatment ≥6 weeks is indicated in post-surgical cases where tissue cultures remain positive. Refer to **Appendix E** for loading dose and monitoring of Vancomycin and Gentamicin.

Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Pathogen specific therapy			
Enterococcus faecalis *Enterococcus faecium*	**Ampicillin-susceptible** IV Ampicillin 2g q4h *PLUS* IV Gentamicin 1mg/kg q8h	**Ampicillin-resistant** IV Vancomycin 15-20mg/kg q12h *PLUS* IV Gentamicin 1mg/kg q8h	Duration of therapy: • Native valve with symptoms <3 months: Ampicillin / Vancomycin × 4 weeks Gentamicin × 2 weeks • Native valve with symptoms > 3 months: Ampicillin / Vancomycin × 6 weeks Gentamicin × 6 weeks • Prosthetic valves: Ampicillin / Vancomycin × 6 weeks Gentamicin × 6 weeks If Gentamicin is contraindicated or there is high level aminoglycoside resistance (HLAR), consider combination of Ampicillin or Vancomycin with IV Ceftriaxone 2g q12h for 6 weeks. Once daily dosing of Gentamicin should not be used in enterococcus IE.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
HACEK *Haemophilus spp* *Aggregatibacter spp* *Cardiobacterium hominis* *Eikenella corrodens* *Kingella spp*	IV Ceftriaxone 1g q12h	IV Ampicillin/ Sulbactam 3g q6h	Duration of therapy: • Native valve : 4 weeks • Prosthetic valve : 6 weeks

Bibliography:

1. 2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J.* 2015;36(44):3075-3128
2. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications. *Circulation* 2015;132(15):1435-1486
3. Clinical Practice Guidelines for the prevention, diagnosis & management of infective endocarditis. National Heart Association of Malaysia, 2017
4. National Antibiotic Guideline 2019, Ministry of Health, Malaysia
5. The Sanford Guide to Antimicrobial Therapy 2023

ACUTE INFECTIOUS DIARRHOEA

Most cases of acute infectious diarrhoea in adults are self-limiting. Causes include viruses (e.g. *Norovirus, Rotavirus*), bacteria (e.g. *Salmonella*, *Shigella*, enterotoxigenic *Escherichia coli*) and protozoa (e.g. *Cryptosporidium*, *Giardia*, *Cyclospora*, *Entamoeba*).

Factors relevant to the cause of diarrhoea include stool characteristics, food ingestion history, water exposure (e.g. swimming pools, contaminated water), travel history and animal exposure. The severity and course of illness depend on the causative organism and host factors.

Antimicrobial therapy is not recommended in clinically stable patients without signs of hypovolaemia (mild to moderate disease). Consider empirical treatment in patients with significant hypovolaemia (severe disease), immunocompromised, immunocompetent host with high grade fever, severe symptoms and bloody diarrhoea.

Stool specimen

Stool	Notes
Stool for ova and parasites	Recommended in patients with persistent or bloody diarrhoea or during waterborne outbreaks.
Stool culture and sensitivity	At least 5mls of diarrhoeal stool collected in clean leak proof container. Sensitivity >95% for detection of enteric bacterial pathogen. Negative culture for *Salmonella, Shigella, Campylobacter* rules out infection as excretion of pathogen is continuous.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Empirical therapy: acute severe diarrhoea			
Salmonella typhi *Salmonella non-typhi* Enterotoxigenic *Escherichia coli* (ETEC)	IV Ceftriaxone 1g q12h × 3-5 days *PLUS OPTIONAL*	IV Ciprofloxacin 400mg q12h × 3 days	Duration of therapy in salmonellosis: • 7-14 days
Vibrio cholera	IV Azithromycin 1g single dose *OR* PO Doxycycline 300mg single dose		Azithromycin or Doxycycline is given if suspicious of *Vibrio cholera*.
Empirical therapy: bloody diarrhoea			
Shigella dysenteriae Shiga toxin-producing *Escherichia coli* (STEC)	IV Ceftriaxone 1g q12h × 3-5 days *PLUS OPTIONAL*	IV Ciprofloxacin 400mg q12h × 3 days	Duration of therapy in Shigella dysentery: • 7-10 days for immunocompromised patients Duration of therapy in Entamoeba histolytica dysentery: • 7-10 days
Entamoeba histolytica	IV Metronidazole 750mg q8h		

***Clostridioides difficile* infection (CDI)**

CDI is the presence of diarrhoea characterised by three or more watery stools per day in the setting of positive *C. difficile* toxin. It is the most common infectious cause of diarrhoea in the ICU that may result in fulminant colitis, toxic megacolon and death. Antibiotic use is the major risk factor for CDI. Offending antibiotics include Clindamycin, cephalosporins, quinolones and penicillin.

Diagnosis is made on detection of *C. difficile* toxin in stools. Colonoscopy findings of pseudomembranous colitis may aid diagnosis when laboratory confirmation is delayed or negative. Offending antibiotics should be discontinued whenever possible.

Recurrence occurs in up to 27% of cases and is defined as recurrence of symptoms with a positive stool test within 8 weeks after the completion of a course of therapy with resolution of symptoms. Patients are known to excrete *C. difficile* for weeks following recovery which may present as an infection control challenge. Risk factors include age of 65 years or older, immunocompromised and severe CDI. Fidaxomicin is currently advocated for the treatment of CDI as it reduces the incidence of recurrent CDI. However, it is currently not available in our setting.

Stool specimen

Stool	Notes
Stool for *Clostridioides difficile* toxin assay	Diagnostic testing for CDI should only be performed in symptomatic patients. Toxin assays available are enzyme immunoassay (EIA) for *C.difficile* toxin A and toxin B. Positive antigen detection without toxin detection represents colonisation and does not require treatment.

Organisms	Antimicrobials		Notes
	Non-severe/severe CDI	Fulminant CDI	
Clostridioides difficile	PO Vancomycin 125mg q6h × 10 days	PO Vancomycin 500mg q6h *PLUS* IV Metronidazole 500mg q8h × 10-14 days	Non-severe CDI: • White blood cell count (WBC) < 15 × 10^9/L • Serum creatinine < 132 µmol/L Severe CDI: • White blood cell count (WBC) ≥ 15 × 10^9/L • Serum creatinine > 132 µmol/L Fulminant CDI: • Shock with peritonitis, ileus or megacolon In ileus, consider adding rectal instillation of Vancomycin 500mg in 100mls normal saline q6h via enemas. Oral Vancomycin is currently not available. Injection Vancomycin is thus given via oral route.

Bibliography:

1. Acute infectious diarrhea in immunocompetent adults. *N Engl J Med* 2014;370:1532-40
2. 2017 IDSA Clinical Practice Guidelines for diagnosis and management of infectious diarrhea. *Clin Infect Dis* 2017;65(12):e45-e80
3. IDSA and SHEA: 2021 Focused update guidelines on management of *C. difficile* infection in adults. *Clin Infect Dis* 2021;73: e1029-e1044
4. ASCRS Clinical Practice Guidelines for management of *C. difficile* infection. *Dis. Colon Rectum* 2021;64:650-668

SEVERE ACUTE PANCREATITIS

Prophylactic use of antibiotics is not recommended in severe acute pancreatitis as it has not been shown to reduce morbidity or mortality. Similarly, use of antibiotics to prevent the development of infection in sterile pancreatic necrosis is not recommended.

Infected pancreatic necrosis with persistent organ failure carries a high mortality. However, diagnosing infection can be challenging due to the clinical picture that cannot distinguish other infections, persistent inflammation from acute pancreatitis or pancreatic necrosis. Antibiotics that penetrate pancreatic necrosis well are ß-lactams (Ceftazidime, Cefepime, Piperacillin/Tazobactam), carbapenems, quinolones and Metronidazole. Antifungal coverage should be considered if multiple risk factors for invasive candidiasis are present.

In patients not responding to antimicrobial therapy, percutaneous or endoscopic drainage should be considered in pancreatic necrosis, peripancreatic collections, pancreatic pseudocysts and pancreatic abscesses.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Enterobacterales *(Escherichia coli, Klebsiella spp, Proteus spp)* *Pseudomonas aeruginosa* *Enterococcus spp* *Bacteroides spp* *Candida albicans* *Candida* non-albicans	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h *PLUS* IV Metronidazole 500mg q8h	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h *PLUS OPTIONAL* IV Anidulafungin D1 200mg followed by 100mg q24h *OR* IV Caspofungin D1 70mg followed by 50mg q24h *OR* IV Micafungin 100mg q24h	Duration of therapy is guided by repeated clinical and serial radiological assessments. Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing.

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1. AGA Clinical Practice Update: Management of pancreatic necrosis. *Gastroenterology* 2020;158:67-75

BILIARY SEPSIS

Biliary sepsis is an infection of the biliary tree which requires prompt diagnosis and treatment. It includes acute cholecystitis and acute cholangitis. 80% of bile infections are polymicrobial and are often associated with bacteraemia. The goals of antimicrobials in biliary sepsis are to limit systemic response, prevent complications and intrahepatic abscess formation. Besides antimicrobial therapy, prompt drainage and relief of obstruction of biliary tract need to be considered.

Acute cholecystitis is primarily an inflammation of the gallbladder due to cystic duct obstruction or bile stasis. Antimicrobial therapy is instituted in the presence of leucocytosis or fever and radiological findings indicative of acalculous cholecystitis, gallbladder empyema, rupture or necrosis.

Acute cholangitis is a life-threatening infection of the biliary tract due to obstruction of the bile or hepatic ducts, accompanied by ascending infection. Other aetiologies include complication of percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP), stent obstruction, primary sclerosing cholangitis, hepatolithiasis, biliary anastomosis stenosis and complications of liver transplantation.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Enterobacterales *(Escherichia coli, Klebsiella spp, Enterobacter spp)* *Pseudomonas aeruginosa* *Enterococcus spp* *Streptococcus spp* Anaerobes *(Bacteroides fragilis, Clostridium perfringens)*	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h *PLUS* IV Metronidazole 500mg q8h × 7-10 days	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h × 7-10 days	Consider enterococcal cover in the immunocompromised (solid organ transplant or steroid therapy), patients with prior endoscopic sphincterotomy and previous antibiotic use. Shorter duration of therapy in: • post cholecystectomy for perforated, emphysematous or necrosis of gallbladder × 4-7 days • acute cholangitis with source of infection controlled × 4-7 days Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing.

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1. Tokyo Guidelines 2018: Diagnostic criteria and severity grading of acute cholangitis. J Hepatobiliary Pancreat Sci (2018) 25:17-30
2. National Antibiotic Guideline 2019, Ministry of Health, Malaysia
3. 2020 WSES Updated guidelines for the diagnosis and treatment of acute calculus cholecystitis. *World J of Emergency Surgery* 2020;15:61
4. The Importance of early management of severe biliary infection: current concepts. *Int Surg* 2021;105:667-678

LIVER ABSCESS

Liver abscess can be divided into pyogenic or amoebic. Pyogenic abscess is more common and is due to diseases of the biliary tract, infectious GI disorders spreading via portal vein, haematogenous spread via hepatic artery, direct extension from an intra-abdominal infection and trauma.

Invasive *Klebsiella pneumoniae* liver abscess syndrome (KLAS) is a community-acquired primary liver abscess that may have metastatic manifestation. Liver abscess due to *Burkholderia pseudomallei* should be considered in diabetic patients who present with shock, whilst *Staphylococcus* associated abscesses usually result from haematogenous spread of organisms involved with distant infection such as endocarditis.

Amoebic liver abscess is due to *Entamoeba histolytica* and may be seen in patients who are from or have visited endemic areas.

Pyogenic liver abscess will require 4-6 weeks of antimicrobial therapy. On the other hand, amoebic liver abscess requires 10 days of antimicrobial therapy followed by a luminal agent for eradication of gut colonisation. Drainage of abscesses need to be considered.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Enterobacterales *(Escherichia coli, Klebsiella pneumoniae)* *Streptococcus milleri* *Enterococcus spp* *Staphylococcus aureus* Anaerobes *(Bacteroides spp, Fusobacterium spp, Actinomyces spp, Clostridium perfringens)*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ceftriaxone 1g q12h *PLUS* IV Metronidazole 500mg q8h × 4-6 weeks	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h × 4-6 weeks	Consider alternative therapy if haemodynamically unstable. Consider carbapenem when melioidosis is suspected or recent history of antibiotic use. If *Entamoeba histolytica* is suspected, add IV Metronidazole 750mg q8h. Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing.

Bibliography:

1. Hepatic cysts and liver abscess. Surg Clin N Am 90 (2010) 679-697
2. National Antibiotic Guideline 2019, Ministry of Health, Malaysia
3. Amoebic liver abscess: a neglected tropical disease. *Lancet Infect Dis* 2020 Feb;20(2):160-162
4. Management practices and predictors of outcome of liver abscess in adults. *J Clin Exp Hepatol* 2021 May-Jun;11(3):312-320

INTRA-ABDOMINAL INFECTIONS

Intra-abdominal infections (IAIs) represent a heterogeneous group of infections of abdominal origin, ranging from simple acute appendicitis to more complex diffuse peritonitis. Uncomplicated IAIs are infections originating from an abdominal organ, without extending to the peritoneum (e.g. acute appendicitis). Complicated IAIs are infections extending into the peritoneum, giving rise to localised peritonitis with abscess formation or diffuse peritonitis.

IAIs may be categorised as community-acquired or hospital-acquired IAIs. In community-acquired IAIs, empirical antimicrobials with narrower spectrum of activity are adequate. Hospital-acquired IAIs often involve multidrug-resistant organisms.

Diffuse peritonitis is classified into:

- **Primary peritonitis or spontaneous bacterial peritonitis (SBP)**. It is due to bacterial translocation across an intact gut wall.
- **Secondary peritonitis**. It is caused by microbial contamination through a perforation, laceration or necrotic segment of the GI tract.
- **Tertiary peritonitis**. It represents an infection that is persistent or recurrent at least 48 hours after appropriate management of primary or secondary peritonitis.

The cornerstone of effective treatment of IAIs includes early recognition, adequate source control and appropriate antimicrobial therapy. Following adequate source control, antimicrobials may be stopped in uncomplicated IAIs.

In complicated IAIs, antimicrobials are usually continued after source control and duration of therapy is tailored according to patients' response. For patients in whom source control is suboptimal, antimicrobial duration is uncertain and duration of treatment may be prolonged.

Peritoneal fluid specimen

Analysis of peritoneal fluid obtained through paracentesis should be carried out to determine if there is presence of ascitic fluid infection in septic patients with ascites. Cultures from in-situ abdominal drains may be inaccurate due to risk of contamination.

The decision to begin early empirical antibiotic treatment of suspected ascitic fluid infection is based largely on the absolute neutrophil count rather than culture, which takes 24-48 hours to demonstrate growth.

Characteristics of ascitic fluid infections

	Polymorphs count (cells/ mm^3)	**Bacterial culture**	**Glucose (mmol/L)**	**Protein (g/dL)**	**LDH (IU/L)**	**Treatment**	**Notes**
Spontaneous bacterial peritonitis (SBP)	≥ 250	Positive (usually 1 type of organism) Poor yield for Gram-stain	> 2.7	< 1.0	< 225	Antibiotics	Inoculate peritoneal fluid into blood culture bottles at bedside to improve sensitivity.

	Polymorphs count (cells/ mm^3)	Bacterial culture	Glucose (mmol/L)	Protein (g/dL)	LDH (IU/L)	Treatment	Notes
Culture negative neutrocytic ascites	≥ 250	Negative	N/A	N/A	N/A	Treat as SBP	Causes include: • prior antibiotics • peritoneal carcinomatosis • pancreatitis • tuberculous peritonitis
Monomicrobial non-neutrocytic bacterascites	< 250	Positive (1 type of organism)	N/A	N/A	N/A	Treat as SBP in presence of sepsis	May be early stage of SBP. In asymptomatic patients, repeat paracentesis.
Polymicrobial bacterascites	< 250	Positive (polymicrobial)	N/A	N/A	N/A	Antibiotics if develop peritonitis	Usually due to inadvertent puncture of the intestines during paracentesis.
Secondary bacterial peritonitis	≥ 250 (> 10,000 WBC/ml)	Positive (polymicrobial)	< 2.7	> 1.0	> 225	Antibiotics and source control	
Tuberculous peritonitis	150 – 4000 WBC/ml (> 70% lymphocytes)	-	Lower than serum	> 2.5 (SAAG < 1.1)	> 90	-	Acid-fast bacilli - Ziehl-Neelsen stain is positive in only 3% of cases.

LDH lactate dehydrogenase, *SAAG* serum ascites albumin gradient, *SBP* spontaneous bacterial peritonitis.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Spontaneous bacterial peritonitis			
Escherichia coli *Klebsiella pneumoniae* *Streptococcus milleri*	IV Cefotaxime 2g q8h *OR* IV Ceftriaxone 1g q12h × 5-7 days	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h × 5-7 days *PLUS OPTIONAL*	Consider alternative therapy in patients with nosocomial infection. Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing.
Enterococcus spp		IV Vancomycin 15-20mg/kg q12h × 7 days	Refer to **Appendix E** for loading dose and monitoring of Vancomycin.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Community-acquired IAIs			
Escherichia coli *Klebsiella pneumoniae* *Streptococcus milleri* *Bacteroides spp*	IV Ceftriaxone 1g q12h *OR* IV Cefoperazone 2g q12h *PLUS* IV Metronidazole 500mg q8h *OR* IV Amoxicillin/ Clavulanate 1.2g q8h × 3-5 days	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h	Consider alternative therapy with longer duration of therapy in patients at high risk of mortality: • Inability to achieve adequate source control • Immunocompromised • Severe peritoneal contamination Duration of therapy depends on source control and patient's response. De-escalate once culture results are available.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Hospital-acquired IAIs			
Enterobacterales *(Escherichia coli, Klebsiella pneumoniae, Enterobacter spp, Proteus spp)* *Pseudomonas aeruginosa* *Bacteroides spp*	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8-12h *PLUS* IV Metronidazole 500mg q8h *PLUS OPTIONAL*	IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h *PLUS OPTIONAL*	Consider alternative therapy in: • haemodynamically unstable patients • patients with recent exposure to antibiotics (especially ß-lactams or fluoroquinolones) within 90 days Consider AMT for *Enterococcus spp* in: • recurrent IAIs • patients with prior antimicrobial therapy • immunocompromised • valvular heart disease • prosthetic heart valves or intravascular devices
Enterococcus spp Methicillin-resistant *Staphylococcus aureus*	IV Vancomycin 15-20mg/kg q12h	IV Vancomycin 15-20mg/kg q12h	Refer to **Appendix E** for loading dose and monitoring of Vancomycin. Duration of therapy depends on source control and patient's response. De-escalate once culture results are available.
	PLUS OPTIONAL		

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Hospital-acquired IAIs			
Candida albicans *Candida* non-albicans	IV Fluconazole 400mg q24h	IV Anidulafungin D1 200mg followed by 100mg q24h *OR* IV Caspofungin D1 70mg followed by 50mg q24h *OR* IV Micafungin 100mg q24h	Consider antifungal therapy in patients with: • recurrent gastro-duodenal perforations • anastomotic leaks • necrotising pancreatitis • no clinical improvement despite on antibiotics Fluconazole should be first-line antifungal in: • haemodynamically stable patients • patients colonised with azole susceptible *Candida* • patients with no prior exposure to azoles Consider echinocandins in: • haemodynamically unstable patients • patients with previous exposure to azoles

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2. National Antibiotic Guideline 2019, Ministry of Health, Malaysia
3. WSES/GAIS/SIS-E/WSIS/AAST Global clinical pathways for patients with intra-abdominal infections. *World J Emerg Surg* 2021;16:49
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CENTRAL NERVOUS SYSTEM INFECTIONS

Acute central nervous system (CNS) infections have high morbidity and mortality with risk of long-term complications. Approach to the patient with suspected acute CNS infection should be early recognition, performance of rapid diagnostic tests, prompt antimicrobial therapy and adjunctive therapy when appropriate.

Acute bacterial meningitis can present with classical symptoms of fever, headache, neck stiffness, followed by altered mental status. However, a vast majority of patients do not present with the full spectrum of signs and symptoms. In patients with suspected bacterial meningitis, it is strongly recommended to perform lumbar puncture to obtain cerebrospinal fluid (CSF) for analysis and blood cultures. The choice of empirical antibiotic is influenced by the patient's age, immune status and predisposing conditions. The antibiotic should have bactericidal action against the infecting pathogen, able to penetrate the CNS and attain adequate concentration in the CSF as the immune activity in the CSF is poor.

Corticosteroids have been shown to significantly reduce hearing loss and neurologic sequelae but did not reduce overall mortality. It is recommended to administer dexamethasone before or with the first dose of empirical antibiotic in all adults with acute bacterial meningitis. Dexamethasone should be discontinued if the causative organism is not *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Mycobacterium tuberculosis*.

Viral encephalitis has a similar presentation as bacterial meningitis. However, encephalitis has more prominent neurological symptoms of altered sensorium, focal signs and seizures. Until CSF analysis suggests otherwise

or a definitive organism is identified, empirical therapy usually includes Acyclovir even though it is only specific to herpes virus (*Herpes simplex* and *Varicella zoster*) infection.

Healthcare-associated ventriculitis and meningitis are usually associated with lines and devices, such as external ventricular drains (EVD) and lumbar drains, or surgical procedures such as craniotomy/-plasty and ventriculoperitoneal (VP) shunt insertions. The most likely microorganisms involved are multi-resistant Gram-negative bacilli and staphylococci.

Lumbar puncture and blood culture should be done prior to antibiotic administration. Lumbar puncture is crucial to diagnose the aetiology of meningoencephalitis and should be performed after a neurological examination without delaying the administration of antimicrobials. A CT scan is indicated to rule out raised intracranial pressure prior to lumbar puncture. CSF should be analysed within an hour of collection. If there is a delay, it should be stored between 4-8°C. Routine biochemistry, cell count, gram stain, culture and sensitivity testing should be performed on all samples. Direct antigen testing or polymerase chain reaction (PCR) for specific organisms has a role in culture negative patients with high suspicion of bacterial CNS infection.

PCR assay has become the standard for detecting viruses associated with aseptic meningitis or encephalitis. In some cases, serological testing may be more appropriate for suspected arbovirus infection (West Nile, St. Louis encephalitis, Eastern equine encephalitis, Japanese encephalitis viruses) since immunocompetent patients may not have these viruses in their CSF at time of presentation.

Cerebrospinal fluid specimen

CSF analysis	**Minimum volume (mL)** (may vary from lab to lab)
Microscopy and stain (Gram stain, India ink and Ziehl-Neelsen)	1
Biochemistry	1
Culture and sensitivity (aerobic and anaerobic)	2
Latex agglutination test: *Streptococcus pneumoniae*, group B streptococcus, *Haemophilus influenzae* type B, *Neisseria meningitidis* group A, B, C, Y and W135, *Escherichia coli* K1, *Listeria monocytogenes*	1
Viral: PCR and/or serology *Herpes simplex* type 1 & 2, *Varicella zoster* virus, Japanese B encephalitis virus, Cytomegalovirus, *Epstein-Barr* virus, Nipah virus, human herpesvirus 6, enterovirus, human parechovirus	3
Parasite PCR *Toxoplasma gondii*	3
Mycobacterium tuberculosis PCR and culture	3
Fungal antigen and culture *Aspergillus fumigatus, Cryptococcus neoformans*	1

Characteristics of CSF in CNS infections

	Normal	Bacterial meningitis	Viral meningitis / encephalitis	Tuberculous meningitis	Fungal meningitis	Meningitis or ventriculitis in the presence of drains or shunts
Pressure (cmH_2O)	10-20	> 30	N or ↑	↑	↑	-
Appearance	Clear	Turbid	Clear	Fibrin web	Clear or turbid	Clear or turbid
Protein (g/L)	0.18-0.45	> 1.0	N or ↑	1.0-5.0	0.2-5.0	N or ↑
Glucose (mmol/L)	2.5-3.5	< 2.2	N or ↓	↓	↓	↓
CSF:serum glucose ratio	0.6	< 0.4	> 0.6	< 0.5	< 0.5	< 0.5
Cell count/mm^3 (predominant cell type)	0-5 lymphocytes (70%) and monocytes (30%)	> 1000 polymorphs	5-1000 lymphocytes and monocytes	< 500 lymphocytes	10-500 lymphocytes	> 15 polymorphs WBC:RBC ratio is less than 1:100 (normal 1:500)
Notes		Partial treatment with antibiotics may alter CSF parameters. Patients with neutropenia may not have characteristic polymorph responses.	Neutrophils may predominate early in the illness.			Cell count index > 1 (ratio WBC:RBC in CSF to blood). Positive CSF culture may represent contaminant and clinical correlation is needed.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Community-acquired meningoencephalitis			
Streptococcus pneumoniae *Neisseria meningitidis* *Haemophilus influenzae* Aerobic Gram-negative bacilli Herpes simplex virus Varicella zoster virus Enteroviruses Japanese B encephalitis virus Adenovirus Cytomegalovirus Epstein-Barr virus	IV Ceftriaxone 2g q12h *OR* IV Cefotaxime 2g q6h *PLUS* IV Acyclovir 10mg/kg q8h × 14 days		Add IV Vancomycin in cephalosporin-resistant *S. pneumoniae* (MIC ≥ 2 mg/L). Administer IV Dexamethasone 10mg q6h × 4 days, 20 minutes before or with the first dose of antibiotic. Omit if antibiotics have been started. Discontinue if the causative organism is not *H. influenzae* or *S. pneumoniae*.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Community-acquired meningoencephalitis			
Listeria monocytogenes (uncommon in Malaysia)	*PLUS OPTIONAL* IV Ampicillin 2g q4h		Treat for Listeria meningitis if CSF gram stain reveals Gram-positive bacilli or when confirmed. Risk factors for *L. monocytogenes:* • Age > 60 years • Pregnant • Immunocompromised
Mycobacterium tuberculosis	Refer to chapter on Tuberculosis.		Duration of therapy: • *N. meningitidis* × 7 days • *H. influenzae* × 7-10 days • *S. pneumoniae* × 10-14 days • Aerobic Gram-negative bacilli × 21 days • *L. monocytogenes* × 21 days (longer if immunocompromised)

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Healthcare-associated ventriculitis and meningitis			
Staphylococcus aureus Coagulase-negative staphylococcus (CoNS) *Propionibacterium acnes*	IV Cloxacillin 2g q4h	IV Vancomycin 15-20mg/kg q12h	Refer to **Appendix E** for loading dose and monitoring of Vancomycin. Consider alternative therapy in: • haemodynamically unstable patients • patients with recent exposure to antibiotics (especially ß-lactams or fluoroquinolones) within 90 days
	PLUS	*PLUS*	Duration of therapy: • CoNS or *P. acnes* (no or minimal CSF pleocytosis, normal CSF glucose and few clinical symptoms) × 10 days • CoNS or *P. acnes* (significant CSF pleocytosis, low CSF glucose and systemic symptoms) × 10-14 days • *S. aureus* or Gram-negative bacilli × 10-14 days If CSF cultures are repeatedly positive despite on appropriate antimicrobial, continue therapy for 10-14 days after last positive culture.
Aerobic Gram-negative bacilli *Pseudomonas aeruginosa*	IV Cefepime 2g q8h	IV Meropenem 2g q8h	

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Healthcare-associated ventriculitis and meningitis			
Acinetobacter spp	*PLUS OPTIONAL* IV Polymyxin E (Colistin) 4.5 million units q12h *OR* IV Polymyxin B 15,000 units/kg q12h		Refer to **Appendix D** for loading dose of polymyxins. Polymyxin B is an active drug and is less nephrotoxic. Intrathecal or intraventricular antibiotics are usually limited to refractory cases, MDR organisms or when shunt removal is impossible. Remove infected shunts. The timing of new shunt placement varies between pathogens: • CoNS or *P. acnes* (no or minimal CSF pleocytosis, normal CSF glucose and few clinical symptoms) ~ 3 days after removal • CoNS or *P. acnes* (significant CSF pleocytosis, low CSF glucose and systemic symptoms) ~ 7-10 days from negative CSF culture • *S. aureus* or Gram-negative bacilli ~ 10 days from negative CSF culture

Brain abscess

Brain abscesses are uncommon but can occur via contiguous foci of infection (mastoiditis, otitis media, sinusitis), haematogenous spread from distal foci (endocarditis, lung abscess, skin or dental infections, cyanotic heart disease) or after neurosurgical procedures. The source is unknown in 15% of cases, especially in immunocompromised hosts. It is usually difficult to diagnose brain abscess on clinical grounds alone and neuroimaging is necessary.

Empirical antimicrobial therapy should be based on the mechanism of infection, host immune status and the ability of the antimicrobial to penetrate the abscess. Attempts should be made to obtain abscess aspirate (via stereotactic CT or surgery) or microbiological culture to allow directed therapy. Surgical drainage may be necessary especially in lesions larger than 2.5 cm. Neuroimaging should be repeated within 2 weeks or earlier to monitor treatment response.

Dexamethasone may be considered in selected cases to reduce mass effect (increased ICP) or neurological decline associated with the brain abscess.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Immunocompetent host			
Streptococcus spp *Bacteroides spp* Enterobacterales *(Escherichia coli,* *Klebsiella* *pneumoniae,* *Enterobacter spp,* *Proteus spp)* *Pseudomonas* *aeruginosa*	IV Ceftriaxone 2g q12h *OR* IV Cefotaxime 2g q6h *PLUS* IV Metronidazole 500mg q8h *PLUS OPTIONAL*	IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h *OR* IV Meropenem 2g q8h *PLUS OPTIONAL*	Metronidazole is added for *Bacteroides spp* in abscesses of dental, middle ear or sinus origin and in penetrating injury of paranasal sinus. Consider empirical *S. aureus* coverage in haematogenous spread, post neurosurgery, recent endoscopic sinus surgery, chronic sinusitis, recent nasal packing and penetrating injury of paranasal sinus. Duration of therapy: • cerebritis or post drainage × 4-6 weeks • encapsulated abscess with tissue necrosis, multiloculated abscess × minimum 6 weeks • immunocompromised × minimum 6 weeks Refer to **Appendix E** for loading dose and monitoring of Vancomycin.
Staphylococcus *aureus*	IV Cloxacillin 2g q4h	IV Vancomycin 15-20mg/kg q12h	

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Immunocompromised host: solid organ or bone marrow transplant recipients			
Aspergillus spp *Candida spp* Mucorales *Cryptococcus neoformans* *Mycobacterium spp*	Alternative antimicrobials as per immunocompetent hosts *PLUS* IV Voriconazole D1 6mg/kg q12h followed by 4mg/kg q12h *OR* IV Amphotericin B 0.7-1.0mg/kg q24h *PLUS OPTIONAL*		Aspergillus brain abscess usually occurs in the setting of disseminated aspergillosis. Consider combination antifungal in Aspergillus CNS infection.
Listeria monocytogenes	IV Ampicillin 2g q4h		Suspect Listeria brain abscess in presence of prodrome of meningoencephalitis and brain stem location of abscess.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Immunocompromised host: solid organ or bone marrow transplant recipients			
Nocardia spp	*PLUS OPTIONAL* IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q6h		Suspect Nocardia brain abscess in presence of lung abscess.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Immunocompromised host: HIV infected			
Toxoplasma gondii *Cryptococcus neoformans* *Listeria monocytogenes* *Mycobacterium spp*	Alternative antimicrobials as per immunocompetent hosts *PLUS* IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q6h	Alternative antimicrobials as per immunocompetent hosts *PLUS* PO Pyrimethamine D1 200mg followed by 50mg q24h (BW < 60kg) 75mg q24h (BW ≥ 60kg) *PLUS* IV Clindamycin 600mg q6h *PLUS* PO Folinic acid 10-25mg q24h	Suspect toxoplasma brain abscess in advanced AIDS, positive serum toxoplasma IgG, lack of prophylaxis and multiple ring-enhancing basal ganglia lesions. In a single enhancing brain lesion and with an undetectable anti-toxoplasma IgG, brain biopsy is recommended to rule out CNS lymphoma. Suspect Listeria brain abscess in presence of prodrome of meningoencephalitis and brain stem location of abscess. Consider alternative therapy if intolerant to Trimethoprim/Sulfamethoxazole.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Pathogen specific therapy			
Listeria monocytogenes	IV Ampicillin 2g q4h	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q6h	Duration of therapy: • minimum 6 weeks
Candida albicans	IV Amphotericin B 0.7-1.0mg/kg q24h		Duration of therapy: • until resolution of CNS signs and symptoms, CSF and radiological abnormalities Therapy may be stepped down to IV/PO Fluconazole 400-800mg per day in patients who have responded to initial treatment.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Pathogen specific therapy			
Toxoplasma gondii	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q6h	PO Pyrimethamine D1 200mg followed by 50mg q24h (BW < 60kg) 75mg q24h (BW ≥ 60kg) *PLUS* IV Clindamycin 600mg q6h *PLUS* PO Folinic acid 10-25mg q24h	Consider alternative therapy if intolerant to Trimethoprim / Sulfamethoxazole. Duration of therapy: • **Acute infection** × minimum 6 weeks (longer duration if clinical or radiologic disease is extensive) • **Maintenance therapy (required in HIV patients)** PO Trimethoprim / Sulfamethoxazole (80mg/400mg) 2 tabs q12h until asymptomatic of signs and symptoms of CNS toxoplasmosis and CD4 count > 200 cells/mm^3 if HIV RNA is suppressed > 6 months with anti-retroviral therapy

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Pathogen specific therapy			
Cryptococcus neoformans	**Induction therapy** IV Amphotericin B 0.7-1.0mg/kg q24h *PLUS* PO Flucytosine 25mg/kg q6h × minimum 2 weeks		Adjust Flucytosine dose in patients with renal dysfunction. Flucytosine has hepatotoxicity and myelotoxicity. In patients unable to tolerate Flucytosine, use Amphotericin B monotherapy and increase the duration of induction therapy to 4 weeks. After induction therapy, continue with • **consolidation therapy** IV Fluconazole 400mg q24h × minimum 8 weeks, followed by • **maintenance therapy** PO Fluconazole 200mg q24h × minimum 1 year

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Pathogen specific therapy			
Aspergillus spp	IV Voriconazole D1 6mg/kg q12h followed by 4mg/kg q12h	IV Amphotericin B 0.7-1.0mg/kg q24h	Consider alternative therapy if Voriconazole is unavailable. After clinical improvement following parenteral antifungal, continue therapy with PO Voriconazole 200mg q12h. Duration of therapy: • until infection is resolved
Nocardia spp	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q6h	IV Linezolid 600mg q12h *PLUS* IV Meropenem 2g q8h	Species identification of Nocardia is important, as antimicrobial susceptibility varies. Therapy may continue with oral Minocycline or Amoxicillin/Clavulanate or Linezolid after 3-6 weeks of parenteral therapy. Duration of oral therapy: • immunocompetent : minimum 3 months • immunocompromised : minimum 12 months

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Pathogen specific therapy			
Mucorales	IV Amphotericin B 0.7-1.0mg/kg q24h		Therapy may be stepped down to oral Posaconazole in patients who have shown clinical improvements. Duration of therapy: • minimum 6-8 weeks until clinical and radiographic response
Mycobacterium tuberculosis	Refer to chapter on Tuberculosis.		

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URINARY TRACT INFECTION

Urinary tract infection (UTI) refers to significant bacteriuria in a patient with signs or symptoms attributable to urinary tract and no alternate source.

Asymptomatic bacteriuria is significant bacteriuria (≥1 bacterial species with $\geq 10^5$ colony forming units per mL [cfu/mL] in the urine) in a patient without signs or symptoms of UTI. It should not be treated with antimicrobials except in pregnancy and in patients undergoing invasive urological procedures, e.g. transurethral resection of the prostate (TURP), ureteroscopy and lithotripsy.

Sterile pyuria is the persistent finding of white cells in the urine in the absence of bacteria. It is common in catheterised patients, has no predictive value and does not warrant treatment.

Catheter-associated urinary tract infection (CAUTI) is the presence of symptoms or signs consistent with UTI with no other identified source of infection with ≥1 bacterial species with $\geq 10^3$ cfu/mL in a catheterised patient or in a patient whose catheter has been removed within the past 48 hours. CAUTI should be treated with antimicrobials and the catheter removed or changed.

Complicated UTI refers to cystitis or pyelonephritis in a patient with underlying anatomical or functional abnormalities (nephrolithiasis, strictures, stents, urinary diversions, neurogenic bladder) or in immunocompromised and males.

Acute pyelonephritis should be presumed in a patient with flank pain or tenderness (with or without fever) plus urinalysis showing bacteriuria or pyuria (or both). The cornerstones of management are antimicrobial therapy and source control. Imaging (ultrasound or CT) to identify obstruction, abscess or necrotising infection (emphysematous pyelonephritis) is recommended. Treatment of hydronephrosis involves percutaneous or endourological drainage, whilst abscesses warrant drainage if large enough or if patient remains unstable. Emphysematous pyelonephritis usually requires partial or total nephrectomy.

Corticomedullary and perinephric abscesses are commonly due to ascending infections by organisms in the urine. Renal abscesses >5 cm should be considered for image-guided aspiration or surgical drainage. Duration of therapy is determined by extent of infection and clinical response. *Staphylococcus aureus* is the most likely causative organism in renal cortical abscesses due to haematogenous spread. They are often multiple and not drainable.

Urine specimen

Urine collection must be taken under aseptic technique to minimise the degree of bacterial contamination. The sample should be sent within an hour of collection since bacteria will continue to proliferate in the warm medium of freshly voided urine, leading to increased bacterial counts. Urine samples not sent immediately should be stored at 4°C, however this may affect leucocyte counts.

If the patient needs catheterisation, discard the first few mls of urine and collect the rest in the sterile container. If the patient is already catheterised, clamp the catheter and clean the sampling port with 70% alcohol and

collect a 10mL sample of urine. Do not take urine samples from the drainage bag due to high risk of bacterial overgrowth leading to false positive results. In and out catheterisation for urine samples in an uncatheterised patient can be done. In patients on long-term catheters, replace the catheter before collecting specimens.

Most cases of urinary tract infection (UTI) can be diagnosed using the criteria below:

	Symptom	**Bacteriuria (cfu/mL)**	**Pyuria (WBC/mm^3)**	**No. of species**	**Nitrite**	**Comments**
With catheter	Present	≥ 10^3	Pyuria is common in patients with catheters and has no predictive value.	≤ 2	undetected	Treat as UTI. Remove catheter if possible.
	Absent	Routine urine culture in asymptomatic catheterised patient is not recommended. Asymptomatic significant bacteriuria: • a single specimen ≥ 10^5 cfu/mL • specimen collected by in and out catheter ≥ 10^2 cfu/mL				Treat asymptomatic significant bacteriuria in • pregnancy • patients undergoing invasive urological procedures (e.g. TURP, ureteroscopy, lithotripsy)

	Symptom	Bacteriuria (cfu/mL)	Pyuria (WBC/mm^3)	No. of species	Nitrite	Comments
without catheter	Present	≥ 10^3 in pregnant women and acute uncomplicated cystitis in women ≥ 10^4 in acute uncomplicated pyelonephritis in women ≥ 10^4 in complicated UTI in men ≥ 10^5 in complicated UTI in women	≥ 10	≤ 2	detected (only positive in nitrite producing bacteria e.g. *E. coli*, *Serratia spp*, *Klebsiella spp* and *Proteus spp*)	Treat as UTI. For definition of uncomplicated and complicated UTI refer to text.
	Absent	Asymptomatic significant bacteriuria if 2 consecutive (> 24 hours apart) mid-stream urine specimens grow ≥ 10^5 cfu/mL of the same bacterial species in women and ≥ 10^3 cfu/mL in men.				Treat asymptomatic significant bacteriuria in • pregnancy • patients undergoing invasive urological procedures (e.g. TURP, ureteroscopy, lithotripsy)

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Uncomplicated UTI or Acute Uncomplicated Pyelonephritis			
Escherichia coli *Klebsiella spp* *Proteus mirabilis*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Cefuroxime 1.5g q8h	IV Ceftriaxone 1g q12h	Duration of therapy for: • uncomplicated UTI × 5-7 days • acute uncomplicated pyelonephritis × 10-14 days • CAUTI with prompt resolution of symptoms × 7 days • CAUTI with delayed response × 10-14 days • asymptomatic bacteriuria in pregnancy × 5-7 days

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Complicated UTI or Acute Complicated Pyelonephritis			
Escherichia coli *Klebsiella spp* *Proteus mirabilis* *Pseudomonas aeruginosa* *Citrobacter spp* Enterobacterales (ESBL)	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Cefuroxime 1.5g q8h *OR* IV Ceftriaxone 1g q12h	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q12h *OR* IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h *PLUS OPTIONAL*	Consider alternative therapy in patients with: • prior antibiotic exposure within 90 days • previous colonisation with MDR organisms • septic shock Duration of therapy: • 14 days Amoxicillin/Clavulanate is preferred in enterococcal infections. Enterococcal infections are more likely in post abdominal surgery, liver transplantation, prosthetic heart valves and vascular grafts. Switch to oral therapy when feasible to complete course.
Enterococcus spp		IV Vancomycin 15-20mg/kg q12h	Refer to **Appendix E** for loading dose and monitoring of Vancomycin.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Complicated UTI or Acute Complicated Pyelonephritis			
Candida albicans *Candida spp*	IV Fluconazole 400mg q24h	IV Micafungin 100mg q24h *OR* IV Anidulafungin D1 200mg followed by 100mg q24h *OR* IV Caspofungin D1 70mg followed by 50mg q24h *OR* IV Amphotericin B 0.3-0.6mg/kg q24h	Candiduria is often asymptomatic and is a common coloniser. Consider treatment only in patients with neutropenia or undergoing urological procedures. Remove indwelling catheter if possible. Use alternative therapy if: • recent azole exposure in the last 3 months • known to be colonised by azole-resistant *Candida spp* • intolerant to Fluconazole Duration of therapy: • 14 days Echinocandins do not achieve adequate urine concentrations in UTI, however clinical reports indicate successful treatment in eradicating candiduria.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Renal and Perinephric Abscess			
Enterobacterales *(Escherichia coli, Klebsiella spp, Enterobacter spp, Proteus spp, Serratia spp)* Methicillin-susceptible *Staphylococcus aureus* (MSSA)	Treat as acute complicated pyelonephritis.		Duration of therapy is determined by extent of infection and clinical response.
Methicillin-resistant *Staphylococcus aureus* (MRSA)		IV Vancomycin 15-20mg/kg q12h *OR* IV Linezolid 600mg q12h	Refer to **Appendix E** for loading dose and monitoring of Vancomycin. Risk factors for MRSA: • Long-term haemodialysis • Immunocompromised • Urological procedures

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SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections (SSTIs) encompass a variety of pathological conditions ranging from simple superficial infections to severe necrotising infections such as necrotising fasciitis, gas gangrene and toxic shock syndrome. Imaging may assist in uncertainty of diagnosis and in delineating the extent of SSTIs.

Necrotising fasciitis is a life-threatening, invasive, soft tissue infection involving the superficial dermis, subcutaneous tissue and the deeper fascia and muscle. It can involve the extremities, parapharyngeal space, abdominal wall or perineum (Fournier's gangrene). Surgical intervention is the primary therapeutic modality and most patients may require recurrent debridement.

There are 3 types of necrotising fasciitis. Type 1 is polymicrobial and is usually seen in patients with peripheral vascular disease, alcoholics, diabetes, chronic kidney disease and after surgical procedures. Type 2 is monomicrobial caused by *Streptococcus pyogenes* or *Staphylococcus aureus*, whilst type 3 infection is clostridial myonecrosis, also known as gas gangrene. It often occurs in penetrating wounds or crush injuries associated with local devascularisation and can rapidly progress to death.

Wound swabs

Wound infections should be diagnosed clinically. Chronic wounds have colonised microorganisms but this does not necessarily mean that the wound is infected. Wounds should only be cultured when signs and symptoms of a deep infection are present.

Wound / Site	Notes
Wound swab / tissue biopsy / needle aspiration culture and sensitivity	Swab culture and sensitivity is practical, non-invasive and cost effective. Viable wound tissue must be swabbed rather than necrotic tissue or pus. At least 1 cm^2 area of viable tissue is required. To obtain wound swabs, clean the wound with sterile saline to increase the adherence of bacteria. Rotate the swab whilst moving it across the entire wound in zigzag manner. Alternatively, Levine's technique can be used where one rotates the swab over 1 cm^2 of the cleansed wound exerting enough pressure to express exudates from within the tissue.
Pus culture and sensitivity	Should be obtained if debridement or incision and drainage (I&D) is performed and/or if there is a discrete collection of pus or drainage.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Non-purulent cellulitis (no purulent material or wound present)			
ß-hemolytic streptococcus *(Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae)* *Staphylococcus aureus*	IV Cloxacillin 2g q4-6h × 5-7 days	IV Amoxicillin/ Clavulanate 1.2g q8h × 5-7 days	IV Cloxacillin is preferred as empirical therapy to cover for possible *S. aureus* infection. It should be given 2g q4h in bacteraemia. If Streptococci is cultured, switch to IV Benzylpenicillin 4 million units q6h.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Purulent skin/soft tissue infections (abscesses, furuncles, carbuncles)			
Staphylococcus aureus Anaerobes *Peptostreptococci* *Fusobacterium spp* *Prevotella spp* *Bacteroides spp* Gram-negative bacilli *Klebsiella pneumoniae* *Escherichia coli*	IV Cloxacillin 2g q4-6h *OR* IV Cefazolin 2g q8h × 5-7 days	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h × 5-7 days	Incision and drainage need to be done promptly. Longer duration of therapy may be required in the setting of severe infection or slow response to therapy. Use alternative therapy in: • infections from parapharyngeal space or perineum • IV injection sites abscesses • diabetics or immunosuppressed

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Necrotising fasciitis, Fournier's gangrene, Ludwig's angina, Clostridial myonecrosis (gas gangrene)			
Head and Neck *Streptococcus spp* Anaerobes *Peptostreptococci* *Fusobacterium spp* *Prevotella spp* *Bacteroides spp*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h × 5-7 days *PLUS* IV Clindamycin 900mg q8h	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h × 5-7 days *PLUS* IV Clindamycin 900mg q8h	Consider alternative therapy in: • haemodynamically unstable patients despite surgery and antibiotics • patients with recent exposure to antibiotics • diabetics, elderly or immunosuppressed Longer duration of preferred therapy may be required in the setting of severe infection or slow response to therapy. If *Clostridium spp* or ß-hemolytic streptococcus is confirmed, switch to IV Benzylpenicillin 4 million units q4h. Clindamycin is added for toxin suppression in toxic shock syndrome. It should be discontinued once patient is clinically and haemodynamically stable for at least 48-72 hours.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Necrotising fasciitis, Fournier's gangrene, Ludwig's angina, Clostridial myonecrosis (gas gangrene)			
Abdominal / Perineum Anaerobes *Bacteroides spp* *Clostridium spp* *Peptostreptococci* Gram-negative bacilli *Klebsiella pneumoniae* *Escherichia coli* **Chest and extremities** Gram-positive cocci *ß-hemolytic streptococcus* *Staphylococcus aureus* Anaerobes *Bacteroides spp* *Clostridium spp* *Peptostreptococci* Gram-negative bacilli *Klebsiella pneumoniae* *Escherichia coli*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h × 5-7 days *PLUS* IV Clindamycin 900mg q8h	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h × 5-7 days *PLUS* IV Clindamycin 900mg q8h	Consider alternative therapy in: • haemodynamically unstable patients despite surgery and antibiotics • patients with recent exposure to antibiotics • diabetics, elderly or immunosuppressed Longer duration of preferred therapy may be required in the setting of severe infection or slow response to therapy. Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing. Clindamycin is added for toxin suppression in toxic shock syndrome. It should be discontinued once patient is clinically and haemodynamically stable for at least 48-72 hours.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Necrotising fasciitis (water-related injuries)			
Aeromonas hydrophila *Vibrio vulnificus*	IV Ceftriaxone 1g q12h *OR* IV Ciprofloxacin 400mg q8h *PLUS* PO Doxycyline 100mg q12h × 7-10 days	IV Cefepime 2g q8h *OR* IV Imipenem 500mg q6h *OR* IV Meropenem 1g q8h *PLUS* PO Doxycyline 100mg q12h × 7-10 days	*Aeromonas spp* and Vibrio spp need to be considered in water-related injuries. At risk are the immunocompromised, diabetics and those with liver cirrhosis. Consider alternative therapy in: • haemodynamically unstable patients despite surgery and antibiotics guided by local susceptibility pattern • patients with recent exposure to antibiotics

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Diabetic foot infections Mild : > 2 signs of local infection (induration, erythema, tenderness, warmth, pus) Moderate : Mild infection + abscess, osteomyelitis, septic arthritis, > 2cm erythema or lymphangitis Severe : Moderate infection + systemic signs of infection (fever, tachycardia, leucocytosis, hypotension, sepsis)			
Moderate / Severe ß-hemolytic streptococcus *Staphylococcus aureus* Gram-negative bacilli *Klebsiella pneumoniae* *Escherichia coli* Anaerobes	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h PLUS IV Metronidazole 500mg q8h	Mild infections can be treated with oral antibiotics. Consider alternative therapy in: • haemodynamically unstable patients despite surgery and antibiotics • patients with risk factors for *Pseudomonas* infection (macerated ulcers, significant water exposure, previous isolation of Pseudomonas) Duration of therapy will depend on source control and presence of osteomyelitis. With good source control 5-7 days should be adequate. MRSA infection is rare: • Cover only if risk factors (history of MRSA infection or colonisation) are present

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CENTRAL LINE ASSOCIATED BLOODSTREAM INFECTION

A central line associated bloodstream infection (CLABSI) is a laboratory-confirmed bloodstream infection not related to an infection at another site that develops within 48 hours of central line insertion. Diagnosing CLABSI requires both a positive blood culture and a collaborative clinical and microbiological review of the patient.

Catheter-related bloodstream infection (CRBSI) refers to bloodstream infection attributed to any intravascular catheter (central venous catheter, peripheral catheter or intra-arterial catheter).

CRBSI is diagnosed when the same organism is grown from paired blood samples (peripheral vein and catheter lumen) with either quantitative cultures (i.e. a 3-fold greater colony count from the catheter than peripheral sample) or differential time to positivity (i.e. growth from the catheter detected at least 2 hours earlier than peripheral sample).

This section only deals with CLABSI associated with short-term central venous catheter (CVC). CLABSI is suspected when there is fever, chills ± hypotension and bacteraemia with no other possible site of infection, and removal of catheter is warranted.

The initial choice of empiric antibiotic therapy for the treatment of CLABSI depends on the severity of illness, risk factors for infection and likely pathogens. In the Malaysian Registry of Intensive Care report 2021, Gram-negative organisms predominate. Thus, antibiotic coverage against Gram-negative bacteria is recommended in the empirical treatment of CLABSI.

Duration of therapy depends on the microbial species as well as the presence or absence of local or distant complications. The duration of therapy is generally 7 days in the absence of distant complications.

CLABSI is considered complicated when there is persistent bacteraemia or fungaemia despite CVC removal and appropriate therapy, or presence of suppurative thrombophlebitis, metastatic foci of infection (e.g. infective endocarditis, septic arthritis, osteomyelitis, epidural abscess, septic emboli).

Blood specimen

Blood cultures are used to aid in the diagnosis of patients with suspected sepsis. Ideally, it should be taken prior to commencement of antibiotics. Care must be taken to avoid contamination with normal skin flora such as *Corynebacterium spp* and *Propionibacterium spp*. Other organisms that are usually found to be contaminants include Coagulase-negative staphylococcus (CoNS), *Bacillus sp*, *Micrococcus sp*. In some circumstances, however, these bacteria may be clinically significant, thus, clinical correlation is required to establish significance.

A venepuncture is the preferred site and collection from an intravascular device is to be avoided unless for the purpose of diagnosing catheter-related bloodstream infection (CRBSI). A minimum of 20 mls of blood should be drawn; 10 mls each for aerobic and anaerobic bottle. Increasing the volume to 40-60 mls from different venepuncture sites (obtaining 2-3 pairs of blood cultures) has been shown to increase the yield further.

The recommended skin antisepsis is 2% chlorhexidine in 70% isopropyl alcohol, using a circular scrubbing motion spiralling out from the planned venepuncture site. Use a fresh swab for each scrub. Use 2 to 3 scrubs

and do this for a total of 1-2 minutes. Skin disinfectants should be allowed to dry for 30-60 seconds prior to venepuncture. Scrub the vial stoppers with 70% isopropyl alcohol before inoculating the blood specimen into culture bottles. The anaerobic bottle should be inoculated first to prevent entry of air. Invert the bottles gently several times to prevent clotting.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy			
Gram-negative bacilli *Klebsiella spp* *Pseudomonas aeruginosa* *Escherichia coli*	IV Cefepime 2g q8h *OR* IV Piperacillin/ Tazobactam 4.5g q6h *PLUS OPTIONAL*	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h *PLUS OPTIONAL*	Consider alternative therapy in: • patients with neutropenia • sepsis with haemodynamic instability • patients colonised with MDR organisms Consider MRSA coverage in patients: • with prior MRSA colonisation • on long-term haemodialysis
Coagulase-negative staphylococcus *Staphylococcus aureus* (Methicillin-susceptible or methicillin-resistant) *Enterococcus faecalis* *Enterococcus faecium*	IV Cloxacillin 2g q4h	IV Vancomycin 15-20mg/kg q12h	Refer to **Appendix E** for loading dose and monitoring of Vancomycin.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Coagulase-negative staphylococcus (except *Staphylococcus lugdunensis)* Methicillin-susceptible Methicillin-resistant	 IV Cloxacillin 2g q4h IV Vancomycin 15-20mg/kg q12h		Single positive culture of CoNS should not be treated unless: • confirmed by follow-up culture • patient is immunocompromised • patient has implanted device (e.g. prosthetic valves) Duration of therapy: • 7 days (uncomplicated) • 4-6 weeks (complicated)
Staphylococcus aureus *Staphylococcus lugdunensis* Methicillin-susceptible Methicillin-resistant	 IV Cloxacillin 2g q4h IV Vancomycin 15-20mg/kg q12h	 IV Daptomycin 6-10mg/kg q24h	Perform echocardiography to rule out endocarditis. Repeat blood cultures every 48-72 hours until cultures are negative. Duration of therapy (D1 is the first day on which blood cultures are negative): • 14 days (minimum) • 4-6 weeks in haematogenous complications • 6-8 weeks in osteomyelitis

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Enterococcus faecalis *Enterococcus faecium*			Perform echocardiography to rule out endocarditis if there is: • persistent bacteraemia after 3 days of appropriate antibiotics • presence of a prosthetic valve or vascular device Duration of therapy: • 7-14 days • 4-6 weeks in the presence of endocarditis or metastatic infection
Ampicillin-susceptible	IV Ampicillin 2g q4h		
Ampicillin-resistant, Vancomycin-susceptible	IV Vancomycin 15-20mg/kg q12h		
Ampicillin-resistant, Vancomycin-resistant	IV Linezolid 600mg q12h	IV Daptomycin 6-10mg/kg q24h	
Escherichia coli *Klebsiella spp*			Duration of therapy: • 7 days
ESBL negative	IV Ceftriaxone 1g q12h		
ESBL positive	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h		

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Pseudomonas aeruginosa	IV Cefepime 2g q8h *OR* IV Piperacillin/ Tazobactam 4.5g q6h	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h	Cefepime is associated with higher risk of neurotoxicity in elderly patients, renal impairment and inappropriate dosing. Duration of therapy: • 7 days
Acinetobacter baumannii	IV Ampicillin/ Sulbactam 9g q8h	IV Polymyxin E (Colistin) 4.5 million units q12h *OR* IV Polymyxin B 15,000 units/kg q12h *PLUS* IV Ampicillin/ Sulbactam 9g q8h	Use alternative therapy in carbapenem-resistant *Acinetobacter baumannii* (CRAB). Refer to **Appendix D** for loading dose of polymyxins. Polymyxin B is an active drug and is less nephrotoxic. Duration of therapy: • 7 days

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Enterobacter spp *Serratia spp* *Citrobacter spp* *Proteus spp*	IV Meropenem 1g q8h *OR* IV Imipenem 500mg q6h	IV Cefepime 2g q8h	*Proteus spp* is intrinsically resistant to Imipenem. De-escalate to Cefepime if susceptible. Duration of therapy: • 7 days
Stenotrophomonas maltophilia	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q8h	IV Levofloxacin 750mg q24h	Consider alternative therapy if intolerant to Trimethoprim/Sulfamethoxazole. Duration of therapy: • 7 days
Burkholderia cepacia	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q8h	IV Ceftazidime 2g q8h	Consider alternative therapy if intolerant to Trimethoprim/Sulfamethoxazole. Duration of therapy: • 7 days

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Candida albicans *Candida* non-albicans	IV Fluconazole D1 800mg followed by 400mg q24h IV Anidulafungin D1 200mg followed by 100mg q24h *OR* IV Caspofungin D1 70mg followed by 50mg q24h *OR* IV Micafungin 100mg q24h	IV Amphotericin B 0.7-1.0mg/kg q24h	Echocardiography and abdominal ultrasound should be performed to exclude endocarditis or disseminated candidiasis, and fundoscopy to exclude endophthalmitis or chorioretinitis. Repeat blood cultures every 48-72 hours until cultures are negative. Duration of therapy (D1 is the first day on which blood cultures are negative): • 14 days (no metastatic complications) In metastatic complications, the duration of therapy should be based on the site, clinical improvement and resolution of lesions on imaging.

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INVASIVE CANDIDIASIS

Invasive candidiasis (IC) comprises three clinical conditions: isolated candidaemia, deep-seated candidiasis or deep-seated candidiasis with candidaemia. Critically ill patients are particularly susceptible to IC and mortality is up to 55% if treatment is delayed or inappropriate.

Intra-abdominal candidiasis (IAC) accounts for most deep-seated cases, usually without candidaemia. Gastrointestinal perforation, anastomotic leaks, necrotising pancreatitis and abdominal organ transplants increase the risk in surgical patients. Deep-seated candidiasis with candidaemia is more commonly seen in immunosuppressed and neutropenic patients. Other risk factors for IC include parenteral nutrition and haemodialysis. There is no single factor that determines infection risk but rather a combination of risk factors that may suggest initiation of antifungal therapy.

Although *Candida albicans* is the most common organism, there is a growing proportion of non-albicans species. Other invasive fungal infections e.g. *Aspergillosis*, *Mucormycosis* are rare except in immunocompromised patients.

Critically ill patients are commonly colonised with *Candida* especially following antibiotic exposure. *Candida* colonisation is considered a pre-requisite in the development of IC and those with higher Candida colonisation index (CCI) are at a greater risk. Although CCI may be used to guide therapy, other risk factors should also be considered.

Conventional blood culture method remains the gold standard despite having limited sensitivity (75% in candidaemia and 5-20% in IAC) and prolonged time to culture positivity. Non-culture-based diagnostic tests such as serological (mannan/antimannan, 1,3-ß-glucan), molecular (candida-specific PCR) and T2 magnetic resonance *Candida* assay (T2Candida) techniques may be useful adjuncts to early diagnosis but are costly and not routinely available. These limitations present a challenge in providing timely treatment of IC whilst also avoiding overtreatment.

There are 4 types of antifungal therapy:

1	Prophylactic	Initiated in asymptomatic patients with high risk for fungal infection. In ICUs with IC rates of > 5%, prophylactic treatment should be started for recurrent GI surgery and leaks or undergoing transplantation.
2	Empirical	Initiated in patients with unexplained sepsis with risk factors for invasive candidiasis.
3	Pre-emptive	Initiated in patients with unexplained sepsis with risk factors and radiological or non-culture evidence for invasive candidiasis.
4	Targeted	Initiated when culture and sensitivity results are available.

In cases of persistent fever or candidaemia during appropriate treatment, rule out ongoing foci of infection e.g. endocarditis, infected intravascular catheters or abscesses within solid organs.

Likely Organisms	Antimicrobials		Notes
	Haemodynamically stable AND Without risk factors for resistant *Candida spp*	**Haemodynamically unstable OR With risk factors for resistant *Candida spp***	
Empirical therapy			
Candida spp	IV Fluconazole D1 800mg followed by 400mg q24h	IV Anidulafungin D1 200mg followed by 100mg q24h *OR* IV Caspofungin D1 70mg followed by 50mg q24h *OR* IV Micafungin 100mg q24h *OR* IV Amphotericin B 0.7-1.0mg/kg q24h	Risk factors for azole-resistant *Candida*: • Previous azole exposure within last 3 months • Previous abdominal surgery • Solid organ tumours • Haematopoietic transplant • Chemotherapy with extensive mucositis There is no documented superiority of one echinocandin over another.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Candida albicans	IV Fluconazole D1 800mg followed by 400mg q24h	IV Anidulafungin D1 200mg followed by 100mg q24h *OR* IV Caspofungin D1 70mg followed by 50mg q24h *OR* IV Micafungin 100mg q24h *OR* IV Amphotericin B 0.7-1.0mg/kg q24h	Repeat blood cultures every 48-72 hours until cultures are negative. Duration of therapy without metastatic complications is 14 days from first negative blood culture. In metastatic complications, duration of therapy is based on site, clinical improvement and resolution of lesions on imaging. Perform echocardiography to rule out endocarditis in candidaemia. Ophthalmic examination is recommended for all patients with candidaemia within 1 week of diagnosis to rule out endophthalmitis. Anidulafungin is preferred in liver impairment due to its extrahepatic metabolism.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific therapy			
Candida parapsilosis *Candida tropicalis* *Candida lusitaniae*	IV Fluconazole D1 800mg followed by 400mg q24h	IV Amphotericin B 0.7-1.0mg/kg q24h	*Candida lusitaniae* may be resistant to Amphotericin B.
Candida glabrata *Candida krusei* *Candida auris*	IV Anidulafungin D1 200mg followed by 100mg q24h OR IV Caspofungin D1 70mg followed by 50mg q24h OR IV Micafungin 100mg q24h	IV Amphotericin B 0.7-1.0mg/kg q24h	

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2. Invasive candidiasis in critical care: challenges and future directions, Intensive Care Med (2020) 46:2001-2014
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MELIOIDOSIS

Melioidosis, caused by *Burkholderia pseudomallei*, has diverse clinical presentations that include pneumonia, localised cutaneous lesion, bacteraemia without evident focus, septic arthritis, osteomyelitis, and sepsis with multiple organ abscesses. Risk factors include diabetes mellitus, hazardous alcohol use, chronic kidney disease, chronic lung disease, immunosuppression from disease or therapy, and occupational or recreational exposure to surface water and mud (e.g. rice farmers, construction site workers), with only 20% of cases having no identifiable risk factor.

Burkholderia pseudomallei are intrinsically resistant to multiple antimicrobials and prolonged therapy is required for cure. Treatment consists of an intravenous intensive phase of at least 2 weeks followed by an oral eradication phase of at least 3 months depending on the site of infection.

Culture is the mainstay of diagnosis, and blood cultures are positive in >50% of patients. Serologic testing alone is not a reliable method of diagnosis and culture confirmation should always be vigorously sought in patients with suspected melioidosis. CT or ultrasound of abdomen and pelvis is required in culture-positive melioidosis to detect abscesses. Deep-seated abscesses may need to be drained and infected joints may need surgical intervention.

<table>
<tr><th rowspan="2">Organisms</th><th colspan="2">Antimicrobials</th><th rowspan="2">Notes</th></tr>
<tr><th>Preferred</th><th>Alternative</th></tr>
<tr><td colspan="4">Phase 1: Initial intensive phase</td></tr>
<tr><td rowspan="2">Burkholderia pseudomallei</td><td>IV Meropenem
1g q8h
(2g q8h for CNS infection)

OR

IV Imipenem
500mg q6h</td><td>IV Ceftazidime
2g q6h</td><td rowspan="2">Carbapenem is preferred in severe disease as the benefits include:
• higher rate of bacterial killing in vitro due to enhanced cell wall penetration
• better post-antibiotic effect
• decreased endotoxin release

De-escalate to Ceftazidime following clinical improvement.

Evidence for the use of G-CSF is weak.

Trimethoprim/Sulfamethoxazole is added for tissue penetration and can potentially limit the emergence of resistance.

Add PO Folic Acid 5mg q24h if on Trimethoprim/Sulfamethoxazole.</td></tr>
<tr><td colspan="2">PLUS OPTIONAL
(in cutaneous melioidosis, osteomyelitis, septic arthritis, CNS infection, deep-seated collections)

IV/PO Trimethoprim/Sulfamethoxazole
< 40kg : 160/800mg q12h
40-60kg: 240/1200mg q12h
> 60kg : 320/1600mg q12h</td></tr>
</table>

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Phase 2: Eradication phase			
Burkholderia pseudomallei	PO Trimethoprim/ Sulfamethoxazole < 40kg : 160/800mg q12h 40-60kg: 240/1200mg q12h > 60kg : 320/1600mg q12h	PO Amoxicillin/ Clavulanate < 60kg: 1250mg q8h > 60kg: 1875mg q8h *OR* PO Doxycyline 100mg q12h	Consider alternative therapy if intolerant to Trimethoprim/Sulfamethoxazole. Add PO Folic Acid 5mg q24h if on Trimethoprim/ Sulfamethoxazole.

2020 Revised Darwin Melioidosis Treatment Duration

Antibiotic Duration Determining Focus	Minimum intensive phase duration (weeks)	Eradication phase duration (months)[d]
Skin abscess	2	3
Bacteraemia with no focus	2	3
Unilateral unilobar pneumonia without lymphadenopathy[a], ICU admission and bacteraemia	2	3
Multilobar unilateral or bilateral pneumonia without lymphadenopathy[a], ICU admission and bacteraemia *OR* Unilateral unilobar pneumonia without lymphadenopathy[a], ICU admission, but with bacteraemia	3	3
Pneumonia with either lymphadenopathy[a] or ICU admission *OR* Multilobar unilateral or bilateral pneumonia with bacteraemia	4	3
Deep-seated collection[b], septic arthritis	4[c]	3
Osteomyelitis	6	6
Central nervous system infection	8	6
Arterial infection (mycotic aneurysm)	8[c]	6 (May be lifelong)

[a] Hilar or mediastinal lymph node enlargement >10mm diameter.
[b] Abscess anywhere other than skin, lungs, bone, CNS or vasculature.
[c] Intensive phase duration is timed from date of most recent drainage or resection where culture of drainage specimen or resected material grew *Burkholderia pseudomallei* or where no specimen was sent for culture. Clock is not reset if specimen is culture-negative.
[d] If concurrent oral therapy is not indicated in intensive phase, oral eradication therapy to commence at the start of the final week of planned intensive intravenous therapy, with timing of eradication duration commencing from the day after last intravenous therapy.

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LEPTOSPIROSIS

Leptospirosis is a zoonotic infection caused by pathogenic spirochetes of the genus *Leptospira*. It is acquired from contact through skin, mucosa or conjunctiva with water or soil contaminated with urine of rodents, carrier or diseased animals in the environment.

It may have a biphasic course, ranging from mild illness (acute phase in the first week) to severe disease (immune phase). The immune-mediated complications seen in severe disease include aseptic meningitis and Weil's disease (jaundice, kidney failure, haemorrhage).

Presumptive diagnosis is made with a positive rapid screening test such as IgM ELISA. However, its specificity is affected by previous exposure (may remain detectable for several years) and other diseases. Diagnosis is confirmed with Microscopic Agglutination Test (MAT), demonstrating either a single serum specimen titre of ≥ 1:400 or a fourfold or greater rise in titres for paired serum samples obtained 2 weeks apart.

Treatment should be initiated if the clinical picture is consistent regardless of a negative rapid test. Antimicrobial therapy shortens duration of illness and reduces shedding of organism in the urine.

Organisms	Antimicrobials		Notes
	Severe disease	Mild disease	
Leptospira spp	IV Benzylpenicillin 1.5 million units q6h *OR* IV Ceftriaxone 1g q12h × 7 days	PO Azithromycin 500 mg q24h x 3 days *OR* PO Doxycyline 100mg q12h × 5-7 days *OR* PO Amoxicillin 500mg q8h × 7 days	Insufficient evidence to support the routine use of corticosteroids in pulmonary haemorrhage.

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3. The Sanford Guide to Antimicrobial Therapy 2023
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SEVERE MALARIA

Malaria is caused by infection with protozoan parasites of the genus *Plasmodium*. The 4 *Plasmodium* species that are transmitted from humans to humans are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, whereas *P. knowlesi* is a simian malaria parasite. Patients diagnosed with or suspected to have severe malaria should be started on parenteral anti-malarial therapy immediately as the risk of death due to severe malaria is greatest in the first 24 hours after clinical presentation.

Microscopic examination of thick and thin blood films [Blood Film for Malaria Parasite (BFMP)] remains the gold standard for confirmation of malaria. It should be repeated if initial film is negative and symptoms persist.

Complications include coma (cerebral malaria), convulsions, hypoglycaemia, acute kidney injury, severe anaemia, acute pulmonary oedema and shock. Patients with severe malaria are at risk of concurrent bacterial infection. Blood cultures should be obtained and empirical antimicrobial therapy initiated in unexplained clinical deterioration.

Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Plasmodium falciparum *Plasmodium knowlesi* *Plasmodium vivax* *Plasmodium ovale* *Plasmodium malariae*	IV Artesunate 2.4mg/kg at 0 hour, 12 hours and 24 hours (minimum 3 doses), then q24h × 7 days *PLUS* PO Doxycyline 100mg q12h × 7 days	IV Quinine Dihydrochloride 20mg/kg in 250mls D5% over 4 hours, and then 10mg/kg q8h *PLUS* PO Doxycyline 100mg q12h × 7 days	If Artesunate is not readily available, start Quinine first to avoid delay. Blood sugars and QT intervals need to be monitored regularly whilst on Quinine. Switch to oral Artemisinin Combination Therapy [ACT] (Artemether/Lumefantrine 20/120mg) if patient is able to tolerate orally and after 24 hours of IV Artesunate (total 3 doses). In pregnancy, use: • IV Artesunate + PO Clindamycin 300-600mg q8h × 7 days (Doxycycline is contraindicated in pregnancy) In *P. falciparum* infection, add PO Primaquine 0.75mg/kg (max 45mg) on day 1 in addition to Artesunate / Quinine, except in pregnancy. In *P. vivax* infection, add PO Primaquine 0.5mg/kg (max 30mg) q24h for 14 days to prevent relapse by eliminating hypnozoites in the liver. Screen for G6PD deficiency before starting Primaquine.

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3. The Sanford Guide to Antimicrobial Therapy 2023

APPENDIX A
DOSAGE ADJUSTMENT FOR RENAL IMPAIRMENT

Below is one of the formulas used to calculate the creatinine clearance (CrCl) based on Cockcroft-Gault Equation:

Males: $\text{CrCl (mls/min)} = \frac{(140 - \text{Age}) \times \text{IBW (kg)} \times 1.23}{\text{Sr. creat } (\mu\text{mol/L})}$ Females: $\text{CrCl (mls/min)} = \frac{(140 - \text{Age}) \times \text{IBW (kg)} \times 1.04}{\text{Sr. creat } (\mu\text{mol/L})}$

IBW = ideal body weight. In obese patients, use adjusted body weight (AdjBW). If BMI < 18.5 kg/m^2, use actual body weight.
Refer to Appendix F for IBW and AdjBW calculation.

Alternative calculation: GFR by CKD-EPI (Chronic Kidney Disease Epidemiology Collaborative) equation with the removal of body surface area normalization.

	Adjusted Maintenance Dose for Renal Impairment and Renal Replacement Therapy			
Antimicrobial / Normal Dose	**CrCl 31-50 ml/min**	**CrCl 10-30 ml/min**	**CrCl < 10 ml/min**	**Renal Replacement Therapy**
Acyclovir 10mg/kg q8h (infuse over 1 hour)	10mg/kg q12h	10mg/kg q24h	5mg/kg q24h	HD: 5mg/kg q24h CVVH: 10mg/kg q24h CVVHD/CVVHDF: 10mg/kg q12h
Amikacin	Refer to **Appendix E**			
Amoxicillin/Clavulanate 1.2g q8h	Unchanged	1.2g q12h	1.2g q12h	HD: 1.2g q12h CVVH/CVVHD/CVVHDF: 1.2g q8-12h

	Adjusted Maintenance Dose for Renal Impairment and Renal Replacement Therapy			
Antimicrobial / Normal Dose	**CrCl 31-50 ml/min**	**CrCl 10-30 ml/min**	**CrCl < 10 ml/min**	**Renal Replacement Therapy**
Ampicillin 2g q4-6h *Higher dose in bacteraemia, endocarditis, meningitis, obesity*	2g q6-8h	2g q8-12h	2g q12-24h	HD: 2g q12h CVVH: 2g q12h CVVHD: 2g q8h CVVHDF: 2g q6-8h
Ampicillin/Sulbactam *Acinetobacter.* 3g q6h (infuse over 30-60 minutes)	Unchanged	3g q12h	3g q24h	HD: 3g q24h CVVH: 3g q12h CVVHD/CVVHDF: 3g q6-8h
Carbapenem-resistant *Acinetobacter.* 9g q8h (infuse over 4 hours)	6g q8h	6g q12h	6g q12h	HD: 6g q12h CVVH/CVVHD/CVVHDF: 9g q8h
Benzylpenicillin 2-4MU q4-6h	1.5-3MU q4-6h		1-2MU q4-6h	HD: 1-2MU q4-6h CVVH: 2MU q4-6h CVVHD: 2-3MU q4-6h CVVHDF: 2-4MU q4-6h

Antimicrobial / Normal Dose	Adjusted Maintenance Dose for Renal Impairment and Renal Replacement Therapy			
	CrCl 31-50 ml/min	**CrCl 10-30 ml/min**	**CrCl < 10 ml/min**	**Renal Replacement Therapy**
Cefazolin 2g q8h	2g q8h	2g q12h	1g q24h	HD: 1g q24h + 1g AD* CVVH/CVVHD/CVVHDF: 2g q12h
Cefepime LD: 2g (infuse over 30 minutes) MD: 1-2g q8-12h (infuse over 4 hours) *Higher dose in bacteraemia, endocarditis, meningitis, severe pneumonia*	1-2g q12h	1-2g q24h	1g q24h	HD: 1g q24h + 1g AD* CVVH/CVVHD/CVVHDF: 1-2g q8-12h
Ceftazidime LD: 2g (infuse over 30 minutes) MD: 1-2g q8h (infuse over 4 hours) *Melioidosis / higher MIC*: MD: 2g q6h (infuse over 4 hours)	1-2g q12h 2g q8h	1-2g q24h 2g q12h	500mg-1g q24h 2g q24h	HD: 1g q24h + 1g AD* CVVH/CVVHD/CVVHDF: 1-2g q12h HD: 2g q24h + 2g AD* CVVH/CVVHD/CVVHDF: 1-2g q8-12h
Cefuroxime 1.5g q8h	Unchanged	1.5g q12h	1.5g q24h	HD: 1.5g q24h CVVH/CVVHD/CVVHDF: 1.5g q8-12h

	Adjusted Maintenance Dose for Renal Impairment and Renal Replacement Therapy			
Antimicrobial / Normal Dose	**CrCl 31-50 ml/min**	**CrCl 10-30 ml/min**	**CrCl < 10 ml/min**	**Renal Replacement Therapy**
Ciprofloxacin 400mg q8-12h	Unchanged	400mg q12-24h	400mg q24h	HD: 400mg q24h CVVH/CVVHD/CVVHDF: 400mg q8-12h
Daptomycin 6-10mg/kg q24h	Unchanged	6-10mg/kg q48h	6-10mg/kg q48h	HD: 6-10mg/kg q48h CVVH/CVVHD/CVVHDF: 6mg/kg q24-48h
Ertapenem 1g q24h	1g q24h	500mg q24h	500mg q24h	HD: 500mg q24h CVVH/CVVHD/CVVHDF: 1g q24h
PO Ethambutol 15-20mg/kg q24h	Unchanged	15-20mg/kg q48h		HD: 15-20mg/kg q48h CVVH/CVVHD/CVVHDF: 15-20mg/kg q24h
IV/PO Fluconazole Day 1: 800mg Day 2 onwards: 400mg q24h	200-400mg q24h			HD: 200-400mg q24h CVVH/CVVHD/CVVHDF: 400mg q12h
Gentamicin	Refer to **Appendix E**			
Imipenem LD: 1g (infuse over 30 minutes) MD: 500mg q6h (infuse over 4 hours)	500mg q8h	500mg q12h	250mg q12h	HD: 250mg q12h CVVH/CVVHD/CVVHDF: 500mg q8h

	Adjusted Maintenance Dose for Renal Impairment and Renal Replacement Therapy			
Antimicrobial / Normal Dose	**CrCl 31-50 ml/min**	**CrCl 10-30 ml/min**	**CrCl < 10 ml/min**	**Renal Replacement Therapy**
IV/PO Levofloxacin 750mg q24h	750mg q48h	500mg q48h	500mg q48h	HD: 500mg q48h CVVH/CVVHD/CVVHDF: 500mg q24h
Meropenem LD: 1g (infuse over 30 minutes) MD: 1g q8h (infuse over 4 hours)	1g q12h	500mg q12h	500mg q24h	HD: 500mg q24h + 250mg AD* CVVH/CVVHD/CVVHDF: 1g q12h
CNS infection / MDR organisms: LD: 2g (infuse over 30 minutes) MD: 2g q8h (infuse over 4 hours)	2g q12h	1g q12h	1g q24h	HD: 1g q24h + 500mg AD* CVVH/CVVHD/CVVHDF: 2g q12h
PO Oseltamivir 75mg q12h	75mg q24h	75mg q24h	No data	HD: 75mg q24h CVVH/CVVHD/CVVHDF: 75mg q12h
Piperacillin/Tazobactam LD: 4.5g (infuse over 30 minutes) MD: 4.5g q6h (infuse over 4 hours)	4.5g q6h	4.5g q8h	2.25g q6h	HD: 2.25g q6h CVVH: 2.25g q6h CVVHD/CVVHDF: 4.5g q6-8h
PO Pyrazinamide 20-30mg/kg q24h	Unchanged	20-30mg/kg q48h		HD: 20-30mg/kg q48h CVVH/CVVHD/CVVHDF: 20-30mg/kg q24h

	Adjusted Maintenance Dose for Renal Impairment and Renal Replacement Therapy			
Antimicrobial / Normal Dose	**CrCl 31-50 ml/min**	**CrCl 10-30 ml/min**	**CrCl < 10 ml/min**	**Renal Replacement Therapy**
Streptomycin 12-15mg/kg q24h (Max dose 1g; 500-750mg in elderly patients and body weight <50kg)	Unchanged	12-15mg/kg q48h		HD/CVVH/CVVHD/CVVHDF: 12-15mg/kg q48h
Trimethoprim/Sulfamethoxazole 5mg/kg (TMP component) q6-8h *Higher dose for PCP*	5mg/kg q8-12h	5mg/kg q12-24h	5-10mg/kg q24h	HD: 5-10mg/kg q24h CVVH: 5mg/kg q12h CVVHD/CVVHDF: 5mg/kg q8-12h
Vancomycin	Refer to **Appendix E**			
Voriconazole Day 1: 6mg/kg q12h Day 2 onwards: 4mg/kg q12h	Use oral formulation as carrier vehicle, sulfobutylether-beta-cyclodextrin (SBECD), in IV formulation accumulates in patients with CrCl < 50ml/min BW >40kg: 400mg q12h PO on Day 1, then 200mg q12h BW <40kg: 200mg q12h PO on Day 1, then 100mg q12h			HD/CVVH/CVVHD/CVVHDF: As per oral dosing in CrCl < 50ml/min

AD after dialysis, *BW* body weight, *CrCl* creatinine clearance, *CVVH* continuous venovenous haemofiltration, *CVVHD* continuous venovenous haemodialysis, *CVVHDF* continuous venovenous haemodiafiltration, *HD* haemodialysis, *IBW* ideal body weight, *LD* loading dose, *MD* maintenance dose, *PCP* pneumocystis pneumonia, *SLED* sustained low efficiency dialysis.

All antimicrobials will require stat doses except the following that will require loading doses for extended infusion: Cefepime, Ceftazidime, Imipenem, Meropenem, Piperacillin/Tazobactam

All antimicrobials are administered intravenously unless stated otherwise.

* If HD is not significantly delayed, serve the dose after HD and omit supplemental dose.
* If HD is significantly delayed, consider serving dose as scheduled and give supplemental dose after dialysis as per recommendation.

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APPENDIX B
DOSAGE ADJUSTMENT FOR HYPOALBUMINAEMIA

Hypoalbuminaemia (serum albumin ≤25g/L) is associated with a lower degree of protein binding in highly protein-bound antimicrobials (e.g. Ceftriaxone, Cloxacillin, Ertapenem, Vancomycin) leading to altered PK. The increase in the free fraction (unbound) of the drug results in higher volume of distribution and drug clearance. This may reduce antimicrobial exposure and compromise pharmacodynamic target. However, Ertapenem is not recommended for use in critically ill patients with hypoalbuminaemia.

Antibiotic	Standard ICU Dosing	Recommended Loading Dose	Recommended Maintenance Dose	Notes
Ceftriaxone	1g q12h	2g 1g	*Normal renal function (CrCl ≥ 40ml/min):* • 1g q8h (start MD 8 hours after LD) *Renal impairment (CrCl < 40ml/min):* • 1g q12h (start MD 12 hours after LD) *ARC (CrCl ≥ 130ml/min/1.73m²):* • 2g q12h (start MD 12 hours after LD) ***OR*** • Continuous infusion: 2-4g over 24 hours (MD immediately after LD)	For susceptible isolates with MIC < 1mg/L. LD and MD (intermittent infusion) to be infused over 30 minutes. In ARC: • Intermittent high dose *OR* • Continuous infusion
Cloxacillin	2g q4h	2g	Continuous infusion: • 2g (infuse over 4 hours) q4h (12g/day)	LD to be infused over 30 minutes. MD immediately after LD.

Antibiotic	Standard ICU Dosing	Recommended Loading Dose	Recommended Maintenance Dose	Notes
Vancomycin	15-20mg/kg q12h	20-30mg/kg	1.5g q12h (start MD 12 hours after LD)	Infusion rate should not exceed 10mg/min to avoid infusion related adverse event. Trough target: 15-20mg/L $AUC_{0\text{-}24}$/MIC target: 400-600

ARC augmented renal clearance, $AUC_{0\text{-}24}$/*MIC* ratio of area under the concentration-time curve during a 24-hour period to minimum inhibitory concentration, *CrCl* creatinine clearance, *LD* loading dose, *MD* maintenance dose. *MIC* minimum inhibitory concentration.

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APPENDIX C
PROLONGED INFUSION OF ß-LACTAMS

ß-lactam antibiotics exhibit time-dependent activity where the length of time for which the free drug concentration remains above the minimum inhibitory concentration (MIC) of a pathogen correlates with its bacterial killing activity. Therapeutic drug monitoring (TDM)-guided dosing is recommended in critically ill patients due to uncertainties in pharmacodynamic targets.

In non-TDM guided facilities, extended infusion for 40-50% of the dosing interval can be one of the ways to achieve PK/PD target for ß-lactam antibiotics whilst continuous infusion for 100% of the dosing interval may be needed for serious infections and infections caused by pathogens with elevated MICs. Drug stability (may differ between different manufacturers) is important in deciding between extended and continuous infusion. Due to concerns of drug stability and feasibility in continuous infusion, extended infusion can be utilised to maximise PK/PD of ß-lactam antibiotics.

Antibiotic	Loading Dose (Over 30 minutes)	Maintenance Dose (Over 4 hours immediately after a loading dose)
Cefepime	2g	1g or 2g in 50mls NS
Ceftazidime	2g	1g or 2g in 50mls NS
Imipenem	1g	500mg in 100mls NS 1g in 200mls NS (maximum concentration 5mg/ml)
Meropenem	1g or 2g	500mg or 1g in 50mls NS 2g in 100mls NS (maximum concentration 20mg/ml)
Piperacillin/Tazobactam	4.5g	4.5g or 2.25g in 50mls NS

NS normal saline.

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APPENDIX D
POLYMYXINS DOSING GUIDE

Polymyxins are polypeptide antibiotics used to treat MDR organisms such as carbapenem-resistant Acinetobacter baumannii (CRAB), carbapenem-resistant Enterobacterales (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Conversely, some organisms are intrinsically or naturally resistant to polymyxins *(Serratia spp, Proteus spp, Providencia spp, Morganella spp, Burkholderia cepacia)*.

Polymyxins are hydrophilic drugs that have concentration-dependent with time-dependent kill characteristics. There are 2 types of polymyxins commonly used in the healthcare setting, namely Polymyxin E (Colistin) and Polymyxin B. Both polymyxins have the same spectrum of activity but their difference is mainly attributed to the fact that Polymyxin B is administered in its active form whilst Polymyxin E (Colistin) is administered as an inactive prodrug. Besides that, Polymyxin E (Colistin) requires dose adjustment for renal impairment whilst Polymyxin B does not.

Polymyxin E (Colistin) Dosing Guide

Loading Dose:

Ideal Body Weight (kg)*	**Loading Dose in million units (MU)** (Dilute in 100mls NS, infuse over 30-60 minutes)
≥ 75	9MU
61 - 74	8MU
51 - 60	7MU
≤ 50	6MU

*Refer to **Appendix F** for IBW calculation.

Maintenance Dose:

CrCl (ml/min)	**Maintenance Dose in million units (MU)** (Dilute in 50-100mls NS, infuse over 30-60 minutes)	**Starting Time of MD after LD (hours)**
>50	4.5MU q12h	12
31 - 50	3MU q12h	12
10 - 30	2.5MU q12h	12
<10	2MU q12h	12
HD	2MU q12h + 1.5MU AD	8
SLED 4 hours	2MU q12h + 1.5MU after SLED	8
SLED 6 hours	2MU q12h + 2.5MU after SLED	8
CVVH/CVVHD/CVVHDF	4MU q8h*	8

AD after dialysis, *CrCl* creatinine clearance, *CVVH* continuous venovenous haemofiltration, *CVVHD* continuous venovenous haemodialysis, *CVVHDF* continuous venovenous haemodiafiltration, *HD* haemodialysis, *LD* loading dose, *MD* maintenance dose, *NS* normal saline, *SLED* sustained low efficiency dialysis.

*Cease this dosing regimen when CVVH/CVVHD/CVVHDF is stopped to prevent toxicity.

Polymyxin B Dosing Guide

Loading Dose:

Dose	Dilution		Administration
25,000 units/kg*	Central line	Dilute in 100mls D5%	Infuse over 1-2 hours
Maximum dose: 2,000,000 units (2MU)	Peripheral line	Dilute in 500mls D5%	

Maintenance Dose:

Dose	Dilution		Administration
15,000 units/kg* q12h	Central line	Dilute in 50mls D5%	Infuse over 60-90 minutes
Maximum dose: 2,000,000 units (2MU) per day	Peripheral line	Dilute in 250mls D5%	

*Use actual body weight (ABW).

Dose Adjustment for Renal Impairment:

No dose adjustment required as Polymyxin B is predominantly cleared by non-renal mechanism.

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APPENDIX E
THERAPEUTIC DRUG DOSING AND MONITORING

Aminoglycosides

Aminoglycosides exhibit concentration-dependent killing activity where higher dosage will increase the rate and the extent of bacterial kill. The pharmacodynamic goal is to maximise drug concentration at the site of infection. Optimal bactericidal activity for aminoglycosides is achieved when the concentration is around 8-10 times the MIC.

Aminoglycosides Dosing Guide:

<table>
<tr><th rowspan="2">CrCl
(ml/min)</th><th colspan="2">SINGLE DAILY DOSING</th><th colspan="2">SYNERGY DOSING FOR GENTAMICIN
(e.g. in Bacterial Endocarditis)</th></tr>
<tr><th>Gentamicin</th><th>Amikacin</th><th>CrCl
(ml/min)</th><th>Dose and Interval</th></tr>
<tr><td>≥ 80</td><td>5mg/kg q24h</td><td>15mg/kg q24h</td><td rowspan="2">≥ 60</td><td rowspan="2">1mg/kg q8h or 3mg/kg q24h</td></tr>
<tr><td>60 - 79</td><td>4mg/kg q24h</td><td>12mg/kg q24h</td></tr>
<tr><td>40 - 59</td><td>3.5mg/kg q24h</td><td>7.5mg/kg q24h</td><td>40 - 59</td><td>1mg/kg q12h or 2mg/kg q24h</td></tr>
<tr><td>30 - 39</td><td>2.5mg/kg q24h</td><td>4mg/kg q24h</td><td rowspan="2">20 - 39</td><td rowspan="2">1mg/kg q24h</td></tr>
<tr><td>20 - 29</td><td>4mg/kg q48h</td><td>7.5mg/kg q48h</td></tr>
<tr><td>< 20</td><td>3mg/kg q48h</td><td>4mg/kg q48h</td><td>< 20</td><td>1mg/kg q24h then
redose based on TDM</td></tr>
</table>

CrCl (ml/min)	SINGLE DAILY DOSING		SYNERGY DOSING FOR GENTAMICIN (e.g. in Bacterial Endocarditis)	
	Gentamicin	Amikacin	CrCl (ml/min)	Dose and Interval
HD	2mg/kg then redose based on TDM	8mg/kg then redose based on TDM	HD	1mg/kg q24h then redose based on TDM
CVVH/ CVVHD/ CVVHDF	LD 3mg/kg then 2mg/kg q24-48h	LD 10mg/kg then 7.5mg/kg q24-48h	CVVH/CVVHD/ CVVHDF	LD 3mg/kg then 1mg/kg q24h
ECMO	Insufficient data to recommend optimal dosing. TDM-guided dosing			

Notes:

- **Weight used:**

Normal weight / malnourished	ABW (Refer to **Appendix F** for calculation)
ABW > 20% IBW	AdjBW (Refer to **Appendix F** for calculation)

• **Sampling:**

Normal Renal Function	• Single daily dosing: At 2nd dose (post 2 hours and post 6 hours) • Conventional dosing (e.g. 8-hourly dosing): ~ Pre (trough): 30 minutes before the next dose ~ Post (peak) : 30 minutes after completion of 30-minute infusion (after the next dose) • Repeat assay: At least once weekly
Renal Impairment	• Initial trough monitoring (24-hour post 1st dose) • Post level is needed after second dose to determine the subsequent dose • Repeat assay: More frequent in changing renal function / other nephrotoxic drugs

ABW actual body weight, *AdjBW* adjusted body weight, *CrCl* creatinine clearance, *CVVH* continuous venovenous haemofiltration, *CVVHD* continuous venovenous haemodialysis, *CVVHDF* continuous venovenous haemodiafiltration, *ECMO* extracorporeal membrane oxygenation, *HD* haemodialysis, *IBW* ideal body weight, *LD* loading dose, *TDM* therapeutic drug monitoring.

Vancomycin

Vancomycin exhibits exposure-dependent (AUC-dependent) killing. Generally, AUC_{0-24}/MIC ratio of ≥400 is recommended. However, higher exposures are advocated when treating critically ill patients with septic shock. Trough concentrations are used as alternate indicators of AUC values. For a pathogen with MIC of 1mg/L, the minimum trough concentration of 15-20mg/L is recommended to achieve an AUC_{0-24}/MIC of ≥400.

Vancomycin Dosing Guide (use actual body weight)**:**

Vancomycin	Dose	Assay
Normal Renal Function		
	LD: 20-25mg/kg (not to exceed 2g/dose) **MD:**15-20mg/kg q12h (start 12 hours after LD)	**Initial assay:** • Pre : 30 minutes before the 4th dose • Post: 1 hour after completion of 4th dose **Repeat assay:** • Once weekly in haemodynamically stable patients • Earlier in patients who are haemodynamically unstable
Renal Impairment		
CrCl 30-50 ml/min	**LD:** 20-25mg/kg (not to exceed 2g/dose) **MD:**15-20mg/kg q24h (start 24 hours after LD)	**Initial assay:** • 24 hours after first MD **Repeat assay:** • Subsequent assays depend on patient's CrCl and initial assay reading
CrCl < 30 ml/min	**LD:** 20-25mg/kg (not to exceed 2g/dose), then redose based on TDM	**Initial assay:** • 24 hours after the loading dose

Vancomycin	Dose	Assay
Renal Replacement Therapy		
HD	**LD:** 20-25mg/kg, (not to exceed 2g/dose), then redose based on TDM Most patients will require 5-10mg/kg IV post dialysis for supplemental dose (~ 500-1000mg supplemental dose).	**Initial assay:** • If LD before HD, initial level 24 hours after supplemental dose • If LD after HD, initial level 24 hours after LD **Repeat assay:** • At least once a week Pre-level (trough) to be taken 30 minutes before the second MD.
CVVH/CVVHD/ CVVHDF	**LD:** 20-25mg/kg (not to exceed 2g/dose) **MD:**(start 12 hours after LD): • 500mg q12h (susceptible; MIC ≤0.5mg/L), *OR* • 500mg q8h (MIC ≤1mg/L; Effluent rate <30ml/kg/hr), *OR* • 1g q12h (MIC ≤1mg/L; Effluent rate >30ml/kg/hr)	

CrCl creatinine clearance, *CVVH* continuous venovenous haemofiltration, *CVVHD* continuous venovenous haemodialysis, *CVVHDF* continuous venovenous haemodiafiltration, *HD* haemodialysis, *LD* loading dose, *MD* maintenance dose, *MIC* minimum inhibitory concentration, *TDM* therapeutic drug monitoring.

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APPENDIX F
ANTIMICROBIAL DOSING IN OBESITY (BMI ≥30 kg/m^2)

Obese patients have a significant increase in fat mass with a smaller increase in lean tissue. This makes it difficult to determine a dosing weight for an obese patient. A number of different body weights (BW) are used (actual, ideal or adjusted BW). Some antibiotics have sufficient data to allow recommendations to be made, whereas others may necessitate the use of doses either at the upper end of the recommended range or modifications based on PK/PD principles. V_d is important to determine the loading dose whilst clearance is important to determine the maintenance dose.

In obese patients:

- Oral bioavailability does not change
- For hydrophilic antibiotics (e.g. ß-lactams, glycopeptides) there is no change in V_d since they have limited distribution in body fat, hence loading dose is unaffected
- For lipophilic antibiotics (e.g. fluroquinolones, macrolides) there are large increases in V_d, hence larger loading doses are required
- The renal and hepatic clearance of many drugs are increased, hence maintenance dose is based on adjusted BW

Abbreviation	Term	How to estimate (in kg)	
ABW	Actual body weight	-	
IBW	Ideal body weight	Male	50 + [0.91 × (height in cm - 152.4)]
		Female	45.5 + [0.91 × (height in cm - 152.4)]
AdjBW	Adjusted body weight	IBW + [0.4 × (ABW - IBW)]	

For example, a 160kg man whose height is 170cm (BMI = 55.4 kg/m^2). ABW = 160kg, IBW = 66kg and AdjBW = 103.6kg.

No.	Antimicrobial	Weight used for dosing			Remarks
		ABW	IBW	AdjBW	
1	Acyclovir			√	-
2	Amikacin			√	Initial dose is based on AdjBW with TDM to guide subsequent doses.
3	Amphotericin B • Conventional • Liposomal	 √ √		 √	In Liposomal Amphotericin B, use: • AdjBW for empirical therapy • ABW for confirmed fungal infections
4	Ampicillin				Insufficient data for obesity. Consider upper limit of normal dosing in severe infections: • 2g IV q4h

No.	Antimicrobial	Weight used for dosing			Remarks
		ABW	IBW	AdjBW	
5	Anidulafungin				ABW <140kg (use standard dose): • LD: 200mg IV • MD: 100mg IV q24h ABW ≥140kg (25% increase in LD and MD): • LD: 250mg IV • MD: 125mg IV q24h
6	Benzylpenicillin				Consider upper limit of normal dosing in severe infections: • 3-4MU IV q4-6h
7	Cefazolin				Consider upper limit of normal dosing in severe infections: • 2g IV q6h
8	Ceftriaxone				Consider 2g IV q24h or 2g IV q12h in severe infections. Refer to **Appendix B** for patients with hypoalbuminaemia.
9	Ciprofloxacin				Consider upper limit of normal dosing in severe infections: 400mg IV q8h or 750mg PO q12h
10	Clindamycin				600mg IV/PO q6h or 900mg IV/PO q8h.
11	Daptomycin			√	Monitor creatinine kinase due to higher incidence of myopathy.
12	Ertapenem				Use standard dose: • 1g IV q24h
13	Ethambutol		√		Maximum daily dose 1.6g PO.

No.	Antimicrobial	Weight used for dosing			Remarks
		ABW	IBW	AdjBW	
14	Fluconazole	√			LD: 12mg/kg IV (max 1.6g) MD: 6mg/kg IV q24h (max 1.6g) Close monitoring of liver function when high doses are used.
15	Flucytosine		√	√	Use IBW in non-life-threatening infections. Use AdjBW in severe infections.
16	Ganciclovir			√	-
17	Gentamicin			√	Initial dose is based on AdjBW with TDM to guide subsequent doses.
18	Isoniazid		√		Maximum daily dose 300mg PO.
19	Linezolid				Use standard dose: • 600mg IV/PO q12h
20	Meropenem				Use standard dose with extended infusion: • LD: 1g IV (infuse over 30 minutes) • MD: 1-2g IV q8h (infuse over 4 hours)
21	Metronidazole				Use standard dose: • 500mg IV q8h
22	Micafungin				BMI >45kg/m^2: 150mg IV q24h Weight >115kg: 200mg IV q24h

No.	Antimicrobial	Weight used for dosing			Remarks
		ABW	IBW	AdjBW	
23	Piperacillin/Tazobactam				Use standard dose with extended infusion: • LD: 4.5g IV (infuse over 30 minutes) • MD: 4.5g IV q6-8h (infuse over 4 hours)
24	Polymyxin B			√	Maximum daily dose 2MU IV.
25	Polymyxin E (Colistin)		√		-
26	Pyrazinamide		√		Maximum daily dose 2g PO.
27	Rifampicin		√		Maximum daily dose 1.2g PO.
28	Streptomycin		√		Maximum daily dose 1g IV/IM. (500-750mg/day if age >60 years)
29	Trimethoprim/ Sulfamethoxazole			√	-
30	Vancomycin	√			LD: 20-25mg/kg IV (not to exceed 2g/dose) MD: Initial dose of 1.5g IV q8h and adjust subsequent doses based on TDM
31	Voriconazole			√	-

ABW actual body weight, *AdjBW* adjusted body weight, *BMI* body mass index, *IBW* ideal body weight, *LD* loading dose, *MD* maintenance dose, *TDM* therapeutic drug monitoring.

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APPENDIX G
ANTIMICROBIAL USE IN PREGNANCY AND LACTATION

No.	Antimicrobial	Pregnancy Category / Risk	Lactation Consideration
1	Acyclovir	B	Present in human milk; Compatible
2	Amikacin	D	Insufficient data; Caution
3	Amoxicillin/Clavulanate	B	Present in human milk; Compatible
4	Amphotericin B	B	Insufficient data; Caution
5	Ampicillin	B	Present in human milk; Compatible
6	Ampicillin/Sulbactam	B	Present in human milk; Compatible
7	Anidulafungin	No human data; Animal data suggest low risk	Present in human milk; Compatible
8	Artesunate	Limited data for 1st trimester	Present in human milk; Caution
9	Azithromycin	Compatible	Present in human milk; Caution
10	Benzylpenicillin	B	Present in human milk; Caution
11	Caspofungin	No human data; Animal data suggest low risk	Insufficient data; Caution
12	Cefepime	Compatible	Present in human milk; Caution
13	Cefotaxime	B	Present in human milk; Caution

No.	Antimicrobial	Pregnancy Category / Risk	Lactation Consideration
14	Ceftazidime	B	Present in human milk; Caution
15	Ceftriaxone	Compatible	Present in human milk; Caution
16	Cefuroxime	Compatible	Present in human milk; Caution
17	Ciprofloxacin	C	Present in human milk; Not recommended
18	Clindamycin	B	Present in human milk; Not recommended
19	Cloxacillin	Compatible	Present in human milk; Caution
20	Doxycycline	Contraindicated in 2nd and 3rd trimesters	Present in human milk; Compatible for short course
21	Ertapenem	No human data; Probably compatible	Present in human milk; Caution
22	Ethambutol	B	Present in human milk; Compatible
23	Fluconazole	Human data suggest risk	Present in human milk; Compatible
24	Gentamicin	D	Present in human milk; Compatible
25	Imipenem/Cilastatin	Limited human data; Animal data suggest low risk	Insufficient data; Caution
26	Isoniazid	C	Present in human milk; Compatible

No.	Antimicrobial	Pregnancy Category / Risk	Lactation Consideration
27	Levofloxacin	Human data suggest low risk	Present in human milk; Not recommended
28	Linezolid	Compatible; Maternal benefit >> Embryo/Fetal risk	Present in human milk; Caution
29	Meropenem	Limited human data; Animal data suggest low risk	Present in human milk; Caution
30	Metronidazole	Human data suggest low risk	Present in human milk; Not recommended
31	Micafungin	No human data; Animal data suggest moderate risk	Insufficient data; Caution
32	Piperacillin/Tazobactam	Compatible	Compatible
33	Pyrazinamide	Compatible; Maternal benefit >> Embryo/Fetal risk	Present in human milk; Caution
34	Rifampicin	Compatible	Compatible
35	Streptomycin	Human data suggest low risk	Compatible
36	Trimethoprim/Sulfamethoxazole	May cause fetal harm	Present in human milk; Not recommended
37	Vancomycin	Compatible	Present in human milk; Caution
38	Voriconazole	Can cause fetal harm	Insufficient data

FDA Pregnancy Risk Categories

Category A	Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk.
Category B	May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk.
Category C	Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done.
Category D	Use in LIFE-THREATENING emergencies when no safer drug available. Positive evidence of human fetal risk.

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