Guide to Antimicrobial Therapy in the Adult ICU 2017

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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FOREWORD

Sepsis still remains the leading cause of admissions and deaths in the ICU. The administration of antibiotics is imperative in its treatment. Like many areas of medicine the knowledge of sepsis and antibiotic use has markedly increased especially the latter in areas of pharmacokinetics and pharmacodynamics. It becomes urgent to continually evaluate and apply this knowledge, hence the need to revise this antimicrobial guide after five years.

The threat that one day antibiotics may be obsolete is not a fallacy. Often we are oblivious to the fact that we, the prescribers, play a significant role in the propagation of resistant organisms through poor prescribing habits. Antibiotic stewardship calls for a multidisciplinary approach to the handling of antibiotics. A chapter has been dedicated to this.

The book remains true to its aims as a convenient up-to-date pocket guide for local doctors caring for the critically ill septic patient. However it must be emphasised that the recommendations do not over ride sound clinical judgement and local antibiotic-susceptibility data.

We would like to thank our reviewers for their expertise and invaluable recommendations. This book has been a culmination of many hours of evidence review and exchange of opinions. We hope it will be a useful compendium for daily practice.

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Guide to Antimicrobial Therapy in the Adult ICU 2017

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SUMMARY OF IMPORTANT CHANGES

A new chapter on antibiotic stewardship.

In line with more evidence and better understanding of pharmacokinetics and pharmacodynamics of antibiotics, some new dosing has been introduced:

- Loading doses recommended for certain antibiotics e.g. fluconazole, ceftriaxone.
- Polymyxin and high-dose sulbactam dosing has changed.
- Expanded appendix on dose adjustment for renal failure.
- Appendix on drugs affected by hypoalbuminaemia.
- Appendix on drug dosing in obesity.

The use of cefoperazone/sulbactam to deliver high dose sulbactam has been omitted, as it would exceed daily dose limits of cefoperazone. Cefoperazone increases the risk of coagulopathy.

Other new recommended dosing:

- IV cefepime 2g q8h
- IV ceftriaxone 1g q12h
- IV ceftazidime 2g q6h in melioidosis
- IV cloxacillin 2g q4h
- IV gentamicin 3mg/kg q24h in endocarditis
- IV imipenem 1g q8h for severe infections

Potential use of inhaled polymyxin and amikacin as adjunct to IV therapy in the treatment of ventilator-associated pneumonia caused by certain multi-drug resistant organisms.

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ANTIBIOTIC STEWARDSHIP IN ICU

The dilemma of current antibiotic use in ICUs is the balance between providing adequate coverage against likely pathogens and at the same time minimising selection of antibiotic resistant organisms. Antibiotic stewardship refers to activities that help optimise antibiotic therapy, ensuring the best clinical outcome for the patient while lowering the risk of development of antimicrobial resistance and minimising adverse effects and costs.

Appropriate measures in antibiotic stewardship in ICUs include:

1. Rapid identification of patients with infections

- An accurate diagnosis of bacterial infection should be made before administration of any antibiotics.
- Obtaining specimens for appropriate cultures before antibiotic administration is essential to confirm infection, identify responsible pathogens and enable de-escalation therapy. However, the results are often unavailable for the first 24 hours.
- The decision to start antibiotics in a possibly infected critically ill patient needs to be balanced between the uncertainty of infection and risk of delaying treatment against the overuse of antibiotics. Observational data suggested that delaying antibiotics in haemodynamically stable surgical patients with suspected intensive care unit-acquired infections could be an option when exercised with sound clinical judgement.
- Currently, there is no biomarker of infection that clinicians can rely exclusively on.
- Molecular diagnostic testing has the potential to be used for timely and rapid identification of causative micro-organism.

2. Ensure appropriate empiric antibiotic therapy

- Appropriate therapy is defined as the use of antibiotics at its correct dose, in which the organism is susceptible to, as determined by in vitro tests.
- Studies have shown that early use of appropriate antibiotic therapy improves outcome.
- Empirical therapy should be based on regularly updated local data on the incidence of causative organisms and their susceptibility to antimicrobial agents. This applies to both community and hospital-acquired infections.
- Another consideration in selection of antibiotics includes previous antibiotic use within the preceding 2 weeks. Whenever possible, do not use the same class of antibiotics.

3. Minimise time to initial antibiotic dose

- The timing of initial therapy should be guided by the urgency of the situation.
- In critically ill patients with septic shock, patients with febrile neutropenia or bacterial meningitis, empiric therapy should be initiated immediately after obtaining microbiological specimens or even before, if the procedure is delayed.
- In more stable patients, antimicrobial therapy can be withheld until appropriate specimens or investigations have been obtained.

4. Optimise antibiotic dose and interval

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, beta-lactams, vancomycin, linezolid, polymyxins) is

increased in patients with sepsis and burns. These increases in V_d can cause lower than expected plasma concentrations during the first day of therapy. Larger V_d will require the administration of loading doses to saturate body tissues where the drug distributes to whilst still achieving appropriate concentrations at the site of infection.

- Hypoalbuminaemia
  Hypoalbuminaemia is likely to increase the V_d and clearance of highly protein-bound antibiotics (e.g. ceftriaxone, cloxacillin, ertapenem). In the presence of increased clearance, the increased V_d still causes a significant prolongation of half-life of the antibiotic, which is beneficial for sustaining concentrations throughout the dosing interval for highly susceptible pathogens. However, the decreased concentrations from the increased V_d may cause therapeutic failure against pathogens with higher MICs. In these situations, higher loading doses followed by an increase in frequency of administration or continuous infusion is required (Refer to **Appendix B**).

- Augmented renal clearance
  Augmented renal clearance (CrCl > 130ml/min/1.73m^2) is common in patients with sepsis, burns, polytrauma, traumatic brain injury and febrile neutropenia. Eight-hour creatinine clearance may be done to confirm this. Significant correlations between subtherapeutic concentrations of beta-lactams or vancomycin and augmented renal clearance were observed. Hence, the dose of antibiotics may have to be increased and levels to be monitored.

- Extracorporeal therapies

  In patients with renal failure, the time to achievement of steady-state is increased for antibiotics cleared by the kidneys. In addition, patients on continuous renal replacement therapy (CRRT) frequently have an increased V_d. Hence a loading dose is also necessary in these patients.

  CRRT is effective at elimination of hydrophilic antibiotics especially those with low protein binding. However, the amount of antibiotic eliminated depends on the mode, dose of CRRT delivered, blood flow rate, filter material and surface area. Like CRRT, antibiotic pharmacokinetics in sustained low-efficiency dialysis (SLED) should be interpreted with knowledge of blood and dialysate flow rates, treatment duration and filter surface area. Time-dependent antibiotics are more affected in SLED than in HD potentially resulting in prolonged periods of concentration below MIC. Hence, it may be necessary to administer supplemental doses during or after SLED or prolong the infusion times. However, antibiotic dosing guidelines for use across all RRT are not possible because of widely 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 therapy

- De-escalation refers to the modification of an empirical antibiotic regimen to an alternate regimen with a narrower spectrum of activity.
- Stop antibiotic therapy on day 3 if infection becomes unlikely based on negative cultures and clinical course.
- De-escalate the empirical antibiotic regimen once the aetiological pathogen is identified.
- Switch to monotherapy after 3 to 5 days, provided that the initial therapy was appropriate and the clinical response was good. However, be cautious if resistant organisms with high in-vitro MICs are isolated.
- Benefits from combination therapy have been inconsistent.

6. Shorten treatment duration

- Duration of antibiotic therapy can be shortened to 7 days for most patients including septic shock, based on therapeutic response and microbiological data. The exceptions are the immunosuppressed, those infected with multi-resistant organisms, those whose course deteriorates despite appropriate antibiotic or those whose initial therapy was inappropriate for the responsible organism.
- Studies have shown that procalcitonin-guided therapy resulted in shorter duration of antibiotics in units where antibiotic duration exceeds 10 days.

7. Implement a structured antibiotic stewardship program

- Successful implementation requires an interdisciplinary team, educational interventions, system innovations, process indicator evaluation and feedback to health-care workers.

- Refer to 'Protocol on Antimicrobial Stewardship Program in Healthcare Facilities' by Ministry of Health Malaysia, First Edition 2014.

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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), secondary (prevention of the recurrence of an infection) or for eradication of colonising organisms. It is often 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.

Perioperative antimicrobial prophylaxis is to prevent surgical site infections (SSI). Optimal agents for prophylaxis should be bactericidal, inexpensive and active against the typical pathogens that can cause SSI postoperatively. Intravenous prophylaxis should be given within 30 to 60 minutes before the surgical incision to maximise its effectiveness. Giving more than one dose postoperatively is generally not advised except in prolonged procedures where risk of bacteraemia is present and in significant blood loss. The practice of continuing prophylactic antibiotics is not recommended even if surgical drains are still insitu.

Empirical Antimicrobial Therapy

Sepsis in the critically ill remains a diagnostic and management challenge. Besides adequate fluid resuscitation, vasopressor therapy and the 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 is to achieve effective concentration at the target sites while minimising adverse events.

In general, management of patients with suspected infection consists of initiation of empirical therapy followed by targeted therapy once microbiological data become available. Empirical antibiotics should be administered without delay. The decision for empirical therapy should be guided by the knowledge of the most likely site of infection and likely causative organisms. All appropriate microbiological specimens, including blood cultures, should be obtained before commencing therapy whenever possible.

Inappropriate and/or delayed antimicrobial use in the ICU is associated with poor outcomes. Moreover this can 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 likely organisms, patient factors and antimicrobial profiles.

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. MRSA, VRE and MDR Gram-negative bacilli.
- Obtain source control as rapidly as is practical to ensure success of therapy.

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 sepsis and septic shock require emergent and broad-spectrum antimicrobial therapy. Every one hour delay of intravenous antimicrobials is associated with significant increased mortality.
- *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 steroid 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 to the severity of organ dysfunction. The risk-benefit ratio of the antimicrobials must be determined on a case-to-case basis.

- *Pregnancy and lactation*
  Ascertain the risk categories of antimicrobials in pregnancy.
- *Others*
  Adjust drug dosage in obesity and 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 routes 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 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 (Refer to **Appendix D**)	T>MIC Percentage of time where drug concentration remains above MIC during a dosing interval	Maximise duration of exposure → administer continuous infusion	Penicillins Cephalosporins Carbapenems
Concentration-dependent	C_{max}/MIC Ratio of peak concentration to MIC	Maximise concentration of drug → use higher maintenance dose	Aminoglycosides Polymyxin
Concentration-dependent with time dependence	AUC_{0-24}/MIC Ratio of area under concentration-time curve (AUC) during a 24-h period to MIC	Optimise amount of drug → administer loading dose	Fluoroquinolones Vancomycin

MIC: Minimum Inhibitory Concentration

- *Achievable antimicrobial concentrations at target tissue*
  Dose optimisation strategies should be taken to increase the antimicrobial activities at the target sites as illustrated in the table above.

  Aminoglycosides and glycopeptides penetrate tissues poorly. Aminoglycosides should not be used as monotherapy while a higher plasma level of glycopeptides is recommended to ensure adequate tissue penetration. Both ß-lactams and quinolones have good tissue penetration. Even then higher doses are required to achieve adequate concentrations in infections of the central nervous system. Consider therapeutic drug monitoring (TDM) of antibiotics to minimise toxicity and also to prevent the risk of treatment failure.

- *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 and fluoroquinolones have post-antibiotic effect 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 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 Enterobacteriaceae.

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 antimicrobial therapy (de-escalation). Sensitivity tests should be interpreted carefully. In vitro sensitivity does not equate with 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 antimicrobial therapy 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, and infective endocarditis. Consider switching to the oral route whenever possible.

If there is no 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 hemorrhages.

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MICROBIOLOGICAL INVESTIGATIONS

Identification of causative organisms is central to effective antimicrobial therapy. Whenever possible, appropriate cultures should always be obtained before commencing antimicrobials.

Below are some common microbiological investigations that are relevant to the intensive care practice.

Blood specimen

All septic patients (irrespective of source) should have blood cultures taken prior to commencement of antimicrobials. Blood cultures must be taken with proper skin antisepsis to prevent contamination with skin commensals (*Corynebacterium spp* and *Propionibacterium spp*). Coagulase-negative Staphylococcus (CoNS) isolated from peripheral blood alone is usually a contaminant. The recommended skin antiseptic is 2% chlorhexidine in 70% isopropyl alcohol. A venipuncture 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). Blood cultures from devices alone have increased risk of contamination.

The volume of blood determines the yield of positive result in blood culture. A minimum of 20mls of blood should be drawn; 10mls for each aerobic and anaerobic bottle. Increasing the volume to 40-60mls from different venipuncture sites (obtaining 2-3 pairs of blood cultures) has been shown to increase the yield further. In suspected endocarditis, 3 pairs of blood cultures taken in at least 30-minute intervals are required to confirm constant bacteraemia but administration of antimicrobials should not be delayed in severely ill patients. If CRBSI is suspected simultaneous blood sampling from the peripheral blood and catheter hub need to be taken.

Blood cultures are routinely incubated for 5 days. Longer incubation times if HACEK organisms, *Legionella, Brucella, Bartonella* or *Nocardia spp* are suspected. Incubation up to 4-6 weeks is needed for *Mycobacterium tuberculosis*.

When disseminated tuberculosis (TB) or fungaemia is suspected, BACTEC® Myco/F Lytic culture bottles should be used to improve yield of these suspected organisms.

Blood can be taken for serological testing to diagnose atypical pneumonias, leptospirosis, melioidosis, toxoplasmosis, rickettsial and typhoid infections.

Blood tests for viral infections include serology for herpes simplex type 1 and 2, cytomegalovirus (CMV), dengue, measles, viral hepatitis and respiratory viruses. Consider Human Immunodeficiency Virus (HIV) serology in patients at risk. Viral cultures are not routinely performed.

The diagnosis of malaria requires 3 sets of thick and thin blood smear preparations taken over a 48-hour period (at 6, 12 and 48 hour). In smear negative patients in whom malaria is still strongly suspected, blood for malaria polymerase chain reaction (PCR) can be sent.

Respiratory specimen

A good specimen of sputum or tracheal aspirate for Gram-stain and cultures should have less than 10 epithelial cells per low power field reflecting a lower respiratory tract sample. Special stains can be requested to diagnose

Pneumocystis jiroveci or *Mycobacterium tuberculosis*. Molecular testing by PCR for MTB DNA and rifampicin resistance can also be performed (Xpert *Mycobaterium tuberculosis*/Rifampicin).

Most laboratories report the results of sputum and tracheal aspirate cultures semi-quantitatively; either as light, moderate or heavy growth. A positive culture does not differentiate true pathogens from colonisers. Results must be interpreted in the context of the clinical condition to prevent unnecessary antimicrobial use. It is adequate to use tracheal aspirate semi-quantitative cultures to guide ventilator-associated pneumonia (VAP) therapy. If quantitative test is available, the threshold for diagnosing VAP with tracheal aspirate is 10^5 or 10^6 colony forming units (cfu)/ml.

Indications for bronchoalveolar lavage (BAL) or protected specimen brushing (PSB) include non-resolving pneumonia and for diagnosis of diffuse lung infiltrates in the immunocompromised host. BAL or PSB need to be analysed quantitatively based on the number of colony forming units (cfu). The threshold for diagnosing VAP with BAL is 10^4 or 10^5 cfu/ml and with PSB is 10^3 cfu/ml. False negatives can occur if sample is taken during antibiotic therapy.

Nasopharyngeal swabs and the above respiratory specimens can be sent using appropriate viral transport media for viral serology and PCR tests. Viral cultures are not routinely performed. The viruses commonly investigated are influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, CMV and measles. Viral detection does not exclude concurrent bacterial infection.

Of note, some respiratory infections can be diagnosed with urinary specimens e.g. Legionella Serotype 1 (legionella urinary antigen test) and pneumococcal infections (pneumococcal urinary antigen test).

Pleural fluid specimen

In diseased conditions, pleural fluid can be classified into exudate or transudate. According to Light's criteria, pleural effusion is likely to be an exudate if at least one of the following exists:

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

A parapneumonic effusion is an exudative pleural effusion formed secondary to pneumonia (bacterial or viral) or lung abscess, with a predominance of neutrophils.

Characteristics of parapneumonic effusions

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

Characteristics of tuberculous pleural effusion

Characteristics	Normal	Tuberculous	Notes
Appearance	clear	straw-coloured	Turbid in chronic tuberculous empyema.
Biochemistry			
pH	7.60 - 7.64	7.3 - 7.4	pH < 7.20 indicates more of chronic tuberculous empyema.
Glucose, mmol/L	similar to plasma	similar to plasma	Low glucose concentration is more characteristic of chronic tuberculous empyema.
Lactate dehydrogenase, U/L	< 50% of plasma	> 500	
Leucocyte count, cells/mL	< 1000	1000 - 6000 predominantly lymphocytes (usually >75%)	Fluid collected in the first few days may exhibit a neutrophil predominant effusion.
Acid-fast bacilli - Ziehl-Neelsen stain	-	positive only in 5%	Yields are higher (>20%) in: 1. HIV 2.tuberculous empyema.
Culture in solid media e.g. Lowenstein-Jensen	- -	positive in 12 - 30%	Broth medium (e.g. BACTEC) provides a higher yield and faster results. Culture-positive pleural fluid is more frequent in HIV-positive patients.
Adenosine deaminase activity (ADA)		> 40 U/L (>95% of cases are tuberculous in raised ADA when associated with lymphocytic pleural effusions)	Also elevated in empyema, lymphoma, lung cancer, mesothelioma, leukaemia, brucellosis, Q fever, rheumatoid arthritis and systemic lupus erythematosis.
Nucleic-acid amplification e.g. Xpert MTB/RIF assay		low sensitivity (60 - 80%)	Usually associated with a positive pleural fluid culture. Xpert MTB/RIF test on pleural fluid does not accurately diagnose pleural TB.

Cerebrospinal fluid specimen

Lumbar puncture should only be performed after a neurological examination but should never delay the administration of antimicrobials. A CT scan is indicated to rule out raised intracranial pressure prior to lumbar puncture.

Cerebrospinal fluid (CSF) should be analysed within an hour of collection. If there is a delay, it should be stored between 4-8°C. Do not allow CSF to sediment before partitioning into separate tubes.

CSF analysis	**Minimum volume (ml)** (may vary from lab to lab)
Microscopy and stain (Gram, Indian 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	10
Fungal antigen and culture *Aspergillus fumigatus, Cryptococcus neoformans*	3

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 ↓	1.6-2.5	↓	↓
CSF:serum glucose ratio	0.6	< 0.4	> 0.6	< 0.5	< 0.5	< 0.5
Lactate, mmol/L	< 2.9	↑↑	N	↑	↑↑	↑
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. Neutropenics may not have characteristic polymorph responses in the CSF.	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.

The standard for the diagnosis of bacterial meningitis is CSF Gram stain and culture. Gram stain has sensitivity between 60-90%, provided the patient has not received antibiotics prior to lumbar puncture. The sensitivities of CSF culture and Gram stain decrease after antibiotic therapy. Direct antigen testing or polymerase chain reaction (PCR) has recognised value in patients with clinical findings consistent with a bacterial CNS infection who have negative Gram stain or culture results.

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 infections (West Nile, St. Louis encephalitis, Eastern equine encephalitis, Japanese encephalitis viruses) since immunocompetent patients may not have these viruses in their CSF at the time of presentation.

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. Urine samples not sent immediately should be stored at 4°C, however this may affect leukocyte 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. Catheter-associated UTI is the presence of bacteriuria in a catheterized patient (≥ 48 hours) who has signs and symptoms that are consistent with UTI. Pyuria is common in catheterised patient and it has no predictive value.

	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. Its level has no predictive value.	≤ 2	undetected	Treat as UTI. Replace catheter if in place for > 7 days.
	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 • prior to genitourinary manipulation • post renal transplant • neutropenics

	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 complicated and uncomplicated UTI refer to the chapter on genitourinary tract infection.
	Absent	Asymptomatic significant bacteriuria if 2 consecutive (> 24h apart) mid-stream urine grows ≥ 10^5 cfu/ml of the same bacterial species in women and ≥ 10^3 cfu/ml in men.				Treat asymptomatic significant bacteriuria in • pregnancy • prior to genitourinary manipulation • post renal transplant • neutropenics • urinary obstruction or abnormal genitourinary tract

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. Do not take specimens for culture from in-situ abdominal drains 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 the culture, which takes 24-48 hours to demonstrate growth.

Characteristics of ascitic fluid infections

	Polymorphs count (/mm^3)	Bacterial culture	Glucose mmol/L	Protein g/dL	LDH IU/L	Treatment	Notes
Spontaneous bacterial peritonitis (SBP)	$\geq$ 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.
Culture negative neutrocytic ascites	> 250	Negative	NA	NA	NA	Treat as SBP	Causes include: prior antibiotics, peritoneal carcinomatosis, pancreatitis, tuberculous peritonitis

	Polymorphs count (/mm3)	Bacterial culture	Glucose mmol/L	Protein g/dL	LDH IU/L	Treatment	Notes
Monomicrobial non-neutrocytic bacteriascites	≤ 250	Positive (1 type of organism)	NA	NA	NA	Treat as SBP in presence of sepsis	May be early stage of SBP. In asymptomatic patients, repeat paracentesis.
Polymicrobial bacteriascites	< 250	Positive (polymicrobial)	NA	NA	NA	Antibiotics if develops 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.

Stool specimen

Stool culture should not be done routinely in all patients presenting with diarrhoea unless in the immunocompromised, elderly, those with underlying inflammatory bowel disease and with severe or bloody diarrhoea. Stool samples for ova and parasites are only recommended in patients with persistent or bloody

diarrhoea or during waterborne outbreaks. Three specimens should be sent on consecutive days since parasite excretion may be intermittent.

At least 5mls of diarrheal stool per rectal or per stoma is collected in a clean leak-proof container. The specimen should be transported to the laboratory and processed as soon as possible after collection. Culture of a single stool specimen has a sensitivity of > 95% for detection of the enteric bacterial pathogen. A negative culture for Salmonella, Campylobacter and Shigella usually rules out infection by these organisms as excretion of these pathogens is continuous. Repeat specimens are not required.

Stools should be sent for *Clostridium difficile* toxin assay for patients who develop new onset of diarrhoea while in hospital. *Clostridium difficile* toxin detection falls into two categories of laboratory tests: organism detection assay and toxin assay [enterotoxin (toxin A) and cytotoxin (toxin B)]. Toxin assays available are cytotoxin assay, enzyme immunoassay (EIA) and PCR. EIA is the preferred diagnostic assay in most clinical laboratories because the technique is relatively simple and inexpensive with results available within 24 hours. However, because of high false negative rates, three consecutive samples are recommended. Positive organism detection without toxin detection does not require treatment because this represents colonisation. Only one stool sample is required for diagnosis of *Clostridium difficile* with PCR.

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. Culturing uninfected wounds may only be used as part of an infection control surveillance protocol.

Wound culture and susceptibility testing may be done using a swab, tissue biopsy or needle aspiration. Needle aspiration and tissue biopsy are preferred methods of specimen collection, however swab cultures are acceptable as they are practical, non-invasive and cost effective. Wound infection occurs in viable wound tissue; therefore viable wound tissue must be swabbed rather than necrotic tissue or pus. At least 1cm^2 area of viable tissue is required.

To obtain wound swabs, clean the wound with sterile saline to irrigate purulent debris and ensure that skin around the wound is cleaned. Moisten the swab with sterile saline to increase the adherence of bacteria. Rotate the swab while moving it across the entire wound in a zigzag manner. Alternatively Levine's technique can be used where one rotates the swab over 1cm^2 of the cleansed wound exerting enough pressure to express exudates from within the tissue. Once collected, promptly send the swabs obtained to the laboratory in an appropriate transport media.

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COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) is associated with significant morbidity and mortality, particularly in the elderly and those with chronic diseases. Management should be guided by clinical judgement and severity of pneumonia. High severity CAP e.g. CURB-65 score of 3 to 5 carries a mortality risk of 15% to 40%.

Aetiologic pathogens remain unidentified in 35 to 70% of cases. Empirical therapy should be started after considering patients' risk factors for certain organisms e.g. patients with chronic lung disease are at higher risk of *Pseudomonas aeruginosa* pneumonia. In Asia, CAP caused by Gram-negative rods and *Staphylococcus aureus* were identified in higher proportions compared to the West, with *Mycobacterium tuberculosis* and *Burkholderia pseudomallei* reported as important causes.

Combination therapy with ß-lactams and macrolides has been shown to achieve better outcomes in patients with severe CAP. This combination confers broader coverage as a proportion of bacteraemic pneumococcal pneumonias have concomitant mycoplasma and rarely legionella infections. ß-lactams act on the bacterial wall while macrolides inhibit protein synthesis providing a dual mechanism of action. Apart from its antimicrobial activity, macrolides have anti-inflammatory properties and bacterial protein inhibition that result in less production of virulence factors.

Most patients with CAP show clinical improvement within 72 hours of initial antibiotic treatment. In those not responding to therapy, consider complications such as empyema or lung abscess or other causative

micro-organisms e.g. viruses, mycobacteria and fungi. Also consider possible non-infectious conditions e.g. congestive heart failure, pulmonary embolism, neoplasm, sarcoidosis, drug reaction and pulmonary haemorrhage.

Although recent RCTs and meta-analysis support the use of steroids in severe pneumococcal CAP, there is no clear mortality benefit. Moreover, the use of steroids has to be weighed against the risk of adverse effects.

Likely Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Streptococcus pneumoniae *Haemophilus influenzae* *Klebsiella pneumoniae* *Mycoplasma pneumoniae* *Legionella pneumophilia* *Chlamydophila pneumoniae*	IV Amoxycillin/Clavulanate 1.2g q8h X 5-7 days *PLUS* IV Azithromycin 500mg q24h X 3-5 days	IV Ceftriaxone 2g loading dose, 1g q12h X 5-7 days *PLUS* IV Azithromycin 500mg q24h X 3-5 days	The indiscriminate use of 3rd generation cephalosporins may promote the emergence of ESBL producers. If pneumococcal pneumonia is confirmed, deescalate to IV benzylpenicillin 4 million units q6h if MIC for penicillin is $\leq$ 2mcg/ml. The emergence of drug resistant *S. pneumoniae* is on the rise. A longer duration of therapy may be indicated if: • initial therapy was not active against identified pathogen • infection at extrapulmonary sites (meningitis, endocarditis) is present • causative organism is *P. aeruginosa, S. aureus, Legionella spp* or *B. pseudomallei* • empyema or lung abscess is present

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
			Duration of treatment for confirmed atypical infections: • Mycoplasma: azithromycin 5 days or fluoroquinolone 7 days • Chlamydophila: azithromycin 7-10 days. Add doxycycline if not responding. • Legionella: fluoroquinolone, azithromycin or doxycycline : if immunocompetent for 7-10 days if immunocompromised up to 3 weeks
Staphylococcus aureus	*PLUS OPTIONAL* (if MSSA suspected) IV Cloxacillin 2g q4h X 10-14 days	*PLUS OPTIONAL* (if CA-MRSA suspected) IV Vancomycin 15-20mg/kg q12h *OR* IV Linezolid 600mg q12h X 10-14 days	Suspect *S. aureus* in the presence of necrotising cavitatory infiltrates or empyema, in intravenous drug users and post influenza. CA-MRSA pneumonia is uncommon in Malaysia. For loading dose and monitoring of vancomycin refer to **Appendix C**.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pseudomonas aeruginosa	IV Piperacillin/Tazobactam 4.5g q6h OR IV Cefepime 2g q8h X 7 days	IV Imipenem 1g q8h OR IV Meropenem 1g q8h X 7 days	Risk factors are severe structural lung disease (e.g. bronchiectasis), COPD and steroid use . If *P. aeruginosa* is sensitive to ceftazidime, consider de-escalation. Dual therapy with aminoglycosides may be considered in: • neutropenics • CAP with bacteraemia • septic shock
Burkholderia pseudomallei	Refer to chapter on Melioidosis		
Pneumocystis jiroveci	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q8h-q6h X 21 days	IV Pentamidine 4mg/ kg/day *OR* PO Primaquine 30mg q24h *PLUS* IV Clindamycin 900mg q8h X 21 days	Prednisolone should be given 15-30 min before antimicrobials. PO prednisolone 40mg q12h x 5 days, then 40mg q24h x 5 days, then 20mg q24h x 11days. Consider IV methylprednisolone (75% of prednisolone dose) if unable to tolerate orally. Patients at risk: • HIV infection with CD4+ cells < 200/µL • HIV infection with other opportunistic infections e.g. oral thrush • on long term immunosuppressive or chemotherapy • primary immunodeficiency disorder

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Viral pneumonia			
Influenza A Influenza B	T. Oseltamivir 75mg q12h X 5 days		Influenza virus types A and B account for more than 50% of all community-acquired viral pneumonias in adults.
Parainfluenza viruses Respiratory syncytial virus Adenovirus Coronavirus (SARS, MERS)	No antiviral of proven value		Influenza virus impairs T lymphocytes, neutrophil and macrophage function. A high clinical suspicion of bacterial superinfection with *S. aureus* or *S. pneumoniae* should be maintained. Critically ill patients may have prolonged influenza viral replication in the lower respiratory tract. Consider longer therapy regimens, if illness is prolonged.
Varicella zoster virus Herpes simplex virus	IV Acyclovir 10mg/kg q8h X 7 days		

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ASPIRATION PNEUMONIA AND LUNG ABSCESS

Aspiration may result in chemical pneumonitis or aspiration pneumonia. The usual causative organisms in aspiration pneumonia are those that colonise the oropharynx. Risk factors for aspiration are conditions that suppress cough and mucociliary clearance. In community-acquired cases, oral anaerobes are the predominant organisms related to poor dentition or oral care and periodontal disease. Hospitalised and institutionalised patients are more likely to have oropharyngeal colonisation with Gram-negative enteric bacilli and *Staphylococcus aureus*.

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 pulmonary parenchyma and formation of cavities caused by microbial infection. It is considered primary lung abscess when it results from existing parenchymal process and is termed secondary when it complicates another process (e.g. vascular emboli). Common causes include:

- aspiration pneumonia
- severe necrotising pneumonia due to *S. aureus* and *K. pneumoniae*
- septic emboli from right sided endocarditis (tricuspid valve endocarditis)
- suppurative (septic) thrombophlebitis of internal jugular veins (Lemierre's syndrome)

Attempts should be made to identify the causal organisms by obtaining bronchoscopic specimens and pleural fluid for cultures. Drainage of the abscess via a percutaneous catheter is recommended.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Community-acquired aspiration pneumonia/lung abscess			
Anaerobes: Peptostreptococci *Fusobacterium spp* *Prevotella melaninogenica* *Bacteroides spp* (not *Bacteroides fragilis*) *Streptococcus pneumoniae* *Haemophilus influenzae* *Staphylococcus aureus* Enterobacteriaceae *Moraxella catarrhalis*	IV Amoxicillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/Sulbactam 3g q6h	IV Ceftriaxone 2g loading dose, 1g q12h *PLUS* IV Clindamycin 600mg q8h	Oral anaerobes are sensitive to ß-lactam/ß-lactamase inhibitors. Metronidazole is added to Cefriaxone to cover *Prevotella melaninogenica*. Clindamycin is preferred in the severely ill or as a substitute in patients with unfavorable or delayed response. Duration of treatment: • Aspiration pneumonia X 7 days • Lung abscess minimum 4 weeks depending on the causative organism, clinical response or resolution by CT scan.
Healthcare-associated aspiration pneumonia/lung abscess			
Enterobacteriaceae *Pseudomonas aeruginosa* *Staphylococcus aureus* Anaerobes	IV Piperacillin/ Tazobactam 4.5g q6h	IV Imipenem 1g q8h *OR* IV Meropenem 1g q8h	Duration of treatment: • Aspiration pneumonia X 7 days • Lung abscess minimum 4 weeks depending on the causative organism, clinical response or resolution by CT scan.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Lung abscess secondary to Lemierre's syndrome			
Anaerobes *Fusobacterium spp* *Eikenella corrodens* *Porphyromonas asaccharolytica* *Streptococcus spp* Bacteroides	IV Amoxycillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/Sulbactam 3g q6h	IV Piperacillin/ Tazobactam 4.5g q6h	
Lung abscess secondary to tricuspid valve endocarditis			
Methicillin-sensitive *Staphylococus aureus* Methicillin-resistant *Staphylococcus aureus*	Refer to chapter on Infective Endocarditis		
Others			
Burkholderia pseudomallei	Refer to chapter on Melioidosis		

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HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA

Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours or more after hospitalisation while ventilator-associated pneumonia (VAP) is pneumonia that occurs after 48 hours following intubation. The term healthcare-associated pneumonia is no longer used because patients' contact with healthcare system is no longer considered a significant risk factor for multidrug-resistant (MDR) pathogens.

The single risk factor for MDR HAP is prior antibiotic use within 90 days. However the risk factors for MDR VAP include: prior antibiotic use within 90 days, septic shock at time of VAP, ARDS preceding VAP, five or more days of hospitalisation prior to occurrence of VAP and acute renal replacement therapy prior to onset of VAP.

The prevalence of causative organisms varies from unit to unit, hence empirical antibiotics must reflect local microbiological data. MDR organisms are increasing in frequency most notably the MDR Gram-negative organisms. In MRIC Report 2015, Gram-negative organisms accounted for 90.7% of VAP organisms and 60% were MDR organisms. *Acinetobacter spp, Klebsiella spp* and *Pseudomonas aeruginosa* constituted 65%, 24.8% and 4.9% of MDR strains respectively. *Staphylococcus aureus* comprises 8.1% of VAP organisms, 75% being methicillin-resistant organisms.

A positive respiratory specimen culture does not differentiate true pathogens from colonisers. Results must be interpreted in the context of the clinical condition to prevent unnecessary antimicrobial use. Candida pneumonia is very uncommon and only ever seen in severely immunocompromised patients following haematogenous spread. This needs tissue confirmation.

The treatment and management of ventilator-associated tracheobronchitis (VAT) requires further research. Treatment for VAT may be instituted if deemed necessary to reduce sputum production and facilitate weaning from mechanical ventilation after considering the risks of excess antibiotic use and adverse effects.

Recent evidence has demonstrated that duration of antibiotics could be shortened to 7 days even for MDR *Pseudomonas aeruginosa* and *Acinetobacter baumanii* organisms. Duration of treatment for MRSA pneumonia is 10 to 14 days. Longer duration may be indicated depending upon clinical, radiologic and laboratory parameters.

Likely Organisms	Antimicrobials		Notes
	Haemodynamically stable	Haemodynamically unstable	
Empirical treatment in patients with HAP or VAP without risk factors for MDR pathogens			
Streptococcus pneumoniae *Haemophilus influenzae* *Staphylococcus aureus* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*	IV Amoxycillin/Clavulanate 1.2g q8h *OR* IV Cefuroxime 1.5g q8h *OR* IV Ceftriaxone 2g loading dose, 1g q12h	IV Piperacillin/Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h	Consider Piperacilin/Tazobactam or Cefepime in patients with chronic lung disease due to increased risk of *P. aeruginosa* infections.
Empirical treatment in patients with HAP or VAP with risk factors for MDR pathogens			
Klebsiella pneumoniae *Pseudomonas aeruginosa*	IV Piperacillin/Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h	IV Imipenem 1g q8h *OR* IV Meropenem 1g q8h	

Likely Organisms	Antimicrobials		Notes
	Haemodynamically stable	Haemodynamically unstable	
Empirical treatment in patients with VAP with risk factors for MDR pathogens			
Acinetobacter baumanii (44.6%)*	IV Ampicillin/Sulbactam 9g q8h	IV Polymyxin E Loading dose and 12 hours later 4.5 million units q12h	Sulbactam component of 9g is required. Refer to **Appendix D** for dilution.
	PLUS OPTIONAL	*PLUS OPTIONAL*	The incidence of MDR Acinetobacter in VAP is 87%. Although the empirical use of polymyxin may increase the frequency of appropriate therapy, it will potentiate polymyxin resistance and increase drug toxicity rates. Hence the recommendation to use polymyxin only if patient is unstable.
Klebsiella pneumoniae (20.3%) *Pseudomonas aeruginosa (15.1%)*	IV Piperacillin/Tazobactam 4.5g q6h	IV Imipenem 1g q8h	
	OR	*OR*	For loading dose of polymyxin refer to **Appendix A**.
	IV Cefepime 2g q8h	IV Meropenem 1g q8h	
	PLUS OPTIONAL	*PLUS OPTIONAL*	Consider MRSA cover if • Antibiotic usage 90 days prior in a unit known to have more than >10% causative MRSA organism • The patient is MRSA colonised with a high quality tracheal aspirate Gram Stain showing numerous and predominant GPC in clusters
Methicillin-resistant *Staphylococcus aureus (6.4%)*	IV Vancomycin 15-20mg/kg q12h	IV Vancomycin 15-20mg/kg q12h	
	OR	*OR*	
*Data from MRIC Report 2015	IV Linezolid 600mg q12h	IV Linezolid 600mg q12h	For loading dose and monitoring of vancomycin refer to **Appendix C**.

Pathogen specific	Antimicrobials	Notes
Acinetobacter baumanii MDR *Acinetobacter baumanii*	IV Ampicillin/Sulbactam 9g q8h IV Polymyxin E Loading dose and 12 hours later 4.5 million units q12h *PLUS OPTIONAL (in VAP)* Inhaled Polymyxin E 1 million units q8h	Sulbactam component of 9g is required. Refer to **Appendix D** for dilution. Inhaled polymyxin may be used as an adjunct to IV polymyxin in patients unresponsive to IV polymyxin. Optimal dosing remains undefined. Modes of nebulisation and ventilator settings need to be addressed to ensure effective delivery. Nebulise salbutamol 15 minutes prior. For loading dose of polymyxin refer to **Appendix A**.
Klebsiella pneumoniae *Escherichia coli* (non ESBL-producing)	IV Amoxycillin/Clavulanate 1.2g q8h *OR* IV Cefuroxime 1.5g q8h *OR* IV Ceftriaxone 2g loading dose, 1g q12h	

Pathogen specific	Antimicrobials	Notes
Klebsiella pneumoniae *Escherichia coli* (ESBL-producing)	IV Ertapenem 1g q24h *OR* IV Imipenem 1g q8h *OR* IV Meropenem 1g q8h	Among the carbapenems, ertapenem is less likely to induce carbapenem resistance in *Acinetobacter spp* and *P. aeruginosa*.
Klebsiella pneumoniae *Escherichia coli* (carbapenem-resistant)	IV Polymyxin E Loading dose and 12 hours later 4.5 million units q12h *PLUS OPTIONAL (in VAP)* Inhaled Polymyxin E 1 million units q8h	Inhaled polymyxin may be used as an adjunct to IV polymyxin in patients unresponsive to IV polymyxin. Optimal dosing remains undefined. Modes of nebulisation and ventilator settings need to be addressed to ensure effective delivery. Nebulise salbutamol 15 minutes prior. For loading dose of polymyxin refer to **Appendix A**.

Pathogen specific	Antimicrobials	Notes
Pseudomonas aeruginosa	IV Ceftazidime 2g q8h *OR* IV Piperacillin/Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS OPTIONAL* IV Amikacin 15mg/kg/q24h X 3-5 days *OR* IV Ciprofloxacin 400mg q8h X 7 days	Combination therapy for pseudomonal infection has not been shown to be superior to monotherapy. Dual therapy may be considered In septic shock and those unresponsive to therapy.
Pseudomonas aeruginosa (group 1 ß-lactamase)	IV Imipenem 1g q8h *OR* IV Meropenem 1g q8h *PLUS OPTIONAL* IV Amikacin 15mg/kg/q24h X 3-5 days *OR* IV Ciprofloxacin 400mg q8h X 7 days	In VAP, if *P. aeruginosa* is only sensitive to aminoglycoside, use both IV and inhaled amikacin 400mg q8h. Optimal dosing remains undefined. Modes of nebulisation and ventilator settings need to be addressed to ensure effective delivery.

Pathogen specific	Antimicrobials	Notes
Pseudomonas aeruginosa (carbapenem resistant)	IV Polymyxin E Loading dose and 12 hours later 4.5 million units q12h *PLUS OPTIONAL (in VAP)* Inhaled Polymyxin E 1 million units q8h	Inhaled polymyxin may be used as an adjunct to IV polymyxin in patients unresponsive to IV polymyxin. Optimal dosing remains undefined. Modes of nebulisation and ventilator settings need to be addressed to ensure effective delivery. Nebulise salbutamol 15 minutes prior. For loading dose of polymyxin refer to **Appendix A**.
Methicillin-sensitive *Staphylococcus aureus* Methicillin-resistant *Staphylococcus aureus*	IV Cloxacillin 2g q4h IV Vancomycin 15-20mg/kg q12h *OR* IV Linezolid 600mg q12h	For loading dose and monitoring refer to **Appendix C**. Consider Linezolid in necrotising pneumonia.

Pathogen specific	Antimicrobials	Notes
Stenotrophomonas maltophilia	IV Trimethoprim/Sulfamethoxazole 5mg/kg (TMP component) q8h X 10-14 days	Carbapenem therapy is associated with the emergence of these organisms.
Burkholderia cepacia	IV Trimethoprim/Sulfamethoxazole 5mg/kg (TMP component) q8h X 10-14 days	Consider combination therapy with ceftazidime or meropenem in severe infections

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TUBERCULOSIS

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*, which may affect pulmonary and/or extra-pulmonary sites. It is transmitted via the airborne route. Patients at risk of TB infections include:

- the immunocompromised (e.g. malnutrition, HIV, diabetes mellitus, renal failure, silicosis, drug abuse, alcohol abuse, steroid and tumour necrosis factor-α inhibitor use)
- close contact with a person with infectious TB disease
- migrants from areas with high rates of TB
- groups with high rates of TB transmission e.g. the homeless, HIV patients and injecting drug users
- persons who work or reside with people who are at high risk of TB in facilities or institutions e.g. hospitals, prisons.

The aim of treatment is to cure and render patients non-infectious, prevent relapse and emergence of resistant tubercle bacilli. Treatment duration is a minimum of 6 months in pulmonary, abdominal, pleural, pericardial and lymph nodes infections. However may increase up to 9-12 months in TB meningitis, spine and joint infections, the immunocompromised and those with drug resistant TB.

The current drug regimen involves the four main drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol. The 6-month treatment regime involves an intensive phase of 8 weeks and a continuation phase of 4 months.

Treatment phase	Preferred agent	Notes
Intensive	Ethambutol/Isoniazid/Rifampicin/ Pyrazinamide q24h X 8 weeks or 56 daily doses	Streptomycin can be used if • Ethambutol is contraindicated • In the presence of severe liver impairment
Continuation	Isoniazid/Rifampicin daily X 4 months or 126 doses	PO pyridoxine 20-50mg q24h should be given to prevent isoniazid-induced neuropathy. Higher dose for patients with increased risk e.g. pregnancy, diabetics, malnourished, alcoholics, renal failure and advanced age. It is necessary to consult the TB specialist if: • Relapse, treatment failure or treatment after interruption. • Liver failure. • Unable to tolerate oral medications. Parenteral options include isoniazid, rifampicin, aminoglycosides and fluoroquinolones. • Co-infection with HIV.

Drug	Dose	Max. dose	Adverse reaction
Tab Isoniazid	5 (4-6) mg/kg/day	300mg	hepatitis, peripheral neuritis, hypersensitivity, skin rash
Tab Rifampicin	10 (8-12) mg/kg/day	600mg	hepatitis, vomiting, thrombocytopenia, skin rash
Tab Ethambutol	15 (15-20) mg/kg/day	1.6g	optic neuritis, gastrointestinal disturbances
Tab Pyrazinamide	25 (20-30) mg/kg/day	2g	hepatotoxicity, hyperuricemia, skin rash
IM/IV Streptomycin	15 (12-18) mg/kg/day	1g	nephrotoxicity, ototoxicity, skin rash Patients > 65 years old, dose should not exceed 750mg

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

Steroids in TB

Conditions	Steroid Dose	Notes
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 120mg q24h, taper over 6-12 weeks	Weak evidence. Only consider in those with highest risk of inflammation (large pericardial effusions or early signs of constrictive pericarditis). In HIV patients use of steroids in pericarditis has been associated with increased risk of cancers.

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5. *N Engl J Med* 2014; 371 (26): 2534

ACUTE INFECTIVE DIARRHOEA

Acute infective diarrhoea is usually self-limiting, requiring only supportive management, and is commonly caused by viral pathogens like norovirus and rotavirus. The presence of severe abdominal pain in a patient older than 50 years of age or peritoneal signs with ileus on examination should lead to a workup for more serious intraabdominal disease rather than attributing it to infective diarrhoea.

Treatment with anti-microbials are usually not recommended for mild to moderate disease except in cases of bacteraemia and in the immunocompromised patients. Antimicrobials are also indicated for severe disease associated with extremes of age, gross blood in stool, high grade fever and persistent symptoms for more than one week. Some can lead to serious sequelae like renal failure following haemolytic-uraemic syndrome due to *Escherichia coli* 0157:H7 and Guillan-Barre syndrome following *Campylobacter* diarrhoea.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy: non bloody diarrhoea			
Salmonella typhi Salmonella non-typhi Enterotoxigenic *Escherichia coli* (ETEC) *Vibrio cholera*	IV Ceftriaxone 3g q24h *PLUS* *OPTIONAL* IV Azithromycin 1g single dose *OR* PO Doxycycline 300mg single dose	IV Ciprofloxacin 400mg q12h	Duration of therapy in salmonellosis • Immunocompetent X 7 to 10 days • Immunocompromised minimum 14 days
Empirical therapy: bloody diarrhoea			
Shigella dysenteriae Enterohaemorrhagic *Escherichia coli* 0157 (EHEC) *Entamoeba histolytica*	IV Ceftriaxone 3g q24h *PLUS OPTIONAL* IV Metronidazole 500mg q8h	IV Ciprofloxacin 400mg q12h	If E. coli 0157 is isolated, stop antibiotics and observe for haemolytic uraemic syndrome (HUS). If *S. dysenteriae* is isolated, duration of therapy: • Immunocompetent X 3 days • Immunocompromised X 7 to 10 days (if bacteraemic minimum 14 days)

***Clostridium difficile* infection (CDI)**

CDI occurs predominantly in hospitalised patients because of antibiotic usage leading to the disturbance of normal intestinal microbiota. Culprit antibiotics include clindamycin, cephalosporins, quinolones and penicillin. It is suspected when patients present with watery diarrhoea, associated with fever (T > 38.5°C) and abdominal pain. CDI may present as ileus. Diagnosis is made by the detection of *C. difficile* toxin in the stools. Colonoscopy finding of pseudomembranous colitis may aid diagnosis when laboratory confirmation is delayed or negative, or when presentation is atypical. Offending antibiotics should be discontinued if possible.

Relapse occurs in up to 27% of cases, typically between 3 days to 3 weeks after treatment is discontinued. Patients are known to excrete *C. difficile* for weeks following recovery which may present as an infection control challenge.

Metronidazole should not be used after the first recurrence. Fidaxomicin has been shown to be effective in reducing relapse rate in mild to moderate cases but use in severe disease cannot be recommended. Faecal microbiota transplant is a treatment option.

Severity of illness	Antimicrobials	Notes
First episode: Mild to moderate	PO Metronidazole 400mg q8h X 10 days	White cell count (WBC) < 15 x 10^9/L and serum creatinine < 1.5x baseline
Severe	PO Vancomycin 125mg q6h X 10-14 days	WBC >15 x 10^9/L and serum creatinine > 1.5 x baseline plus albumin < 25g/L, elevated lactate • IV formulation of Vancomycin can be given orally as the intravenous form is not effective. • When unable to tolerate oral Vancomycin adequately follow regimen for severe complicated CDI.
Severe Complicated	PO Vancomycin* 125mg q6h *PLUS* IV Metronidazole 500mg q8h *PLUS OPTIONAL* Rectal Vancomycin 500mg q6-8h (dilute in 100mls Normal saline) X 10 days	Lab results as above plus clinical deterioration e.g. shock with peritonitis or pseudomembranous colitis on colonoscopy. *Some experts advocate a higher dose of oral Vancomycin at 500mg q6h especially in severe cases though an added mortality benefit of a higher dose was not seen. Indications for surgery include: • Toxic megacolon or bowel perforation • Severe deterioration despite optimal antibiotic therapy

Severity of illness	Antimicrobials	Notes
First recurrence	As per first episode	Recurrent CDI: When CDI reoccurs within 8 weeks after resolution of symptoms from the previous episode.
Second recurrence	Tapering and pulsed oral Vancomycin 125mg PO q6h for 7-14 days then 125mg PO q12h for 7 days then 125mg PO q24 for 7 days then 125mg PO every other day for 7 days then 125mg PO every 3 days for 14 days	

Bibliography:

1. *Clin Micro Inf*: 2013 (Suppl. 2), 1-26
2. *N Eng J Med*: 2014 370; 16
3. *Int Med Journal*: 2016: doi: 10.1111/imj.13027 pg 479-493 ASID updated guidelines for the management of *Clostridium difficile* infection in adults and children in Australia and New Zealand

ACUTE INFECTIVE PANCREATITIS

Infectious complications in severe acute pancreatitis are associated with considerable morbidity and mortality. Prophylactic antibiotics are not effective in reducing the incidence of pancreatic infection and thus are not recommended. The use of antibiotics in patients with sterile necrosis to prevent the development of infected necrosis is also not recommended.

The timing of infection is variable but peaks in the second to fourth week after the onset of pancreatitis. The probability of infection is partly related to the extent of pancreatic necrosis. Infected pancreatic necrosis (IPN) should be considered in patients with pancreatic necrosis who deteriorate or fail to improve after 7-10 days of hospitalisation. A CT scan finding of gas in the pancreas is diagnostic of IPN. In these patients, empirical use of antibiotics is recommended, with or without a CT-guided fine-needle aspiration for Gram stain and culture. These antibiotics should penetrate pancreatic necrosis well e.g. ß- lactams (ceftazidime, cefepime, piperacillin-tazobactam), carbapenems, quinolones and metronidazole. Antifungal coverage should be considered, especially if multiple risk factors for invasive candidiasis are present.

Pancreatic abscess is often a late complication of acute necrotising pancreatitis occurring more than 4 weeks later. Many of these respond to percutaneous or endoscopic drainage and antibiotics.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Enterobacteriaceae *(Escherichia coli* *Klebsiella spp* *Proteus spp)* *Enterococcus spp* *Bacteroides spp*	IV Piperacillin/Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h *PLUS OPTIONAL*	IV Imipenem 1g q8h *OR* IV Meropenem 1g q8h *PLUS OPTIONAL*	Duration of treatment is guided by repeated clinical and serial radiological assessments.
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 *OR* IV Lipid formulation Amphotericin B 3-5mg/kg q24h *OR* IV Amphotericin B 0.6-1mg/kg/day	Consider echinocandins if patient has had recent azole exposure in the past 3 months.

Bibliography:

1. *Semin Respir Crit Care Med* 2011; 32: 174-180
2. *Am J Gastroenterol* 2013; 108: 1400-1415
3. *Annal Surg* 2007; 245: 674-683

BILIARY SEPSIS

Acute cholangitis can be a life-threatening infection secondary to biliary obstruction and stasis. The common causes are biliary calculi, benign stenosis and malignancy. It is also a common complication of stent placement for malignant biliary obstruction. The causative organisms are commonly Gram-negative and occasionally polymicrobial including anaerobes. This may result from translocation of bacteria from the portal system or duodenum into the biliary tree. Besides antimicrobial therapy, prompt drainage of the biliary tract need to be considered.

Acute cholecystitis is primarily an inflammatory process and secondary infection of the gall bladder can occur as a result of cystic duct obstruction and bile stasis. Antimicrobial therapy is instituted in the presence of leukocytosis or fever, and radiologic findings indicative of gallbladder rupture or necrosis. Antimicrobials are also recommended in patients of advanced age, diabetics or the immunocompromised. Obstruction to bile flow may prevent biliary excretion resulting in the inability to achieve adequate concentrations of antibiotic there.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Enterobacteriaceae *(Escherichia coli, Klebsiella spp, Enterobacter spp)* Enterococci *Pseudomonas aeruginosa* Anaerobes *(Bacteroides fragilis, Clostridium perfringens)*	IV Cefoperazone 2g 12qh *PLUS* IV Metronidazole 500mg q8h	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h *OR* IV Imipenem 1g q8h *OR* IV Meropenem 1g q8h	Consider the **alternative** regime in healthcare-associated biliary sepsis (e.g. patients with recent ERCP, presence of stents or entero-biliary surgery). Consider enterococcal cover in the immunocompromised (solid organ transplant or steroid therapy), and patients with valvular heart disease, intravascular prosthetic devices or previous antimicrobial use. Ceftriaxone may increase biliary sludging. Duration of therapy: • Post cholecystectomy following acute cholecystitis X 1 day • Post cholecystectomy for perforated, emphysematous or necrosis of the gall bladder X 4-7 days • Acute cholangitis with source of infection controlled X 4-7 days • Bacteraemia with *Enterococcus spp, Streptococcus spp* X minimum 2 weeks • Presence of residual stones or obstruction, treat until anatomical problems are resolved

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2. *World J Gastroenterol* 2012; 18(9): 865-871
3. *J Pancreat Sci* 2013; 20: 60-70

LIVER ABSCESS

Liver abscess is classified by aetiology into pyogenic (80%), amoebic (10%) and fungal abscess (10%). Pyogenic abscess is the most common and may occur following spread through the biliary tree, by extension of adjacent infection, haematogenous dissemination, trauma or following instrumentation e.g. chemoembolisation or biliary sphincterotomy. Invasive *Klebsiella pneumoniae* liver abscess syndrome (KLAS) is a community-acquired primary liver abscess that may have metastatic manifestations (endophthalmitis, meningitis, brain abscess). Abscess caused by *Burkholderia pseudomallei* should be considered in patients who present with shock. Tuberculous liver abscesses are uncommon but should be considered when typical pyogenic organisms are not recovered from cultures.

Amoebic liver abscess may be seen in patients who are from or have visited endemic areas. Serological test is positive for most patients with amoebic liver abscess. Fungal liver abscess is usually due to *Candida albicans* and occurs in patients on immunosuppressive therapy.

Besides antimicrobial therapy, drainage of the abscess may be required. Pyogenic liver abscess will require 4-6 weeks of antimicrobial therapy, and drainage of abscess needs to be considered. Amoebic liver abscess will require 7-10 days of antimicrobial therapy followed by a luminal agent for eradication of gut colonisation.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Enterobacteriaceae *(Escherichia coli* *Klebsiella pneumoniae)* *Streptococcus milleri* *Enterococcus spp* *Staphylococcus aureus* Anaerobes *(Bacteroides spp* *Fusobacterium spp* *Actinomyces spp* *Clostridium spp)*	IV Ceftriaxone 2g loading dose, 1g q12h	IV Piperacillin/Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *OR* IV Meropenem 1g q8h *OR* IV Imipenem 1g q8h	Consider alternative therapy if haemodynamically unstable. Consider carbapenem when melioidosis is suspected or recent history of antibiotic use. Consider anti-fungal therapy in immunocompromised or neutropenic patients.
Entamoeba histolytica	*PLUS* IV Metronidazole 500mg q8h		*Entamoeba histolytica* is not covered by ß-lactams or carbapenems

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2. *Lancet Infect Dis* 2012; 12: 881
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4. *Surg Clin North Am* 2010; 90: 679

PERITONITIS

Intra-abdominal infections (IAI) are usually classified as uncomplicated or complicated. In uncomplicated IAI, the infection only involves a single organ (e.g. appendicitis, diverticulitis, cholangitis) and does not extend to the peritoneum. In complicated IAI, the infectious process extends beyond the organ, causing either localised peritonitis with abscess formation or diffuse peritonitis.

Diffuse peritonitis is classified into:

1. Primary or spontaneous bacterial peritonitis (SBP): infection is usually caused by a single organism without loss of integrity of the gastrointestinal tract; typically seen in cirrhotic patients with ascites.
2. Secondary peritonitis: infection resulting from loss of integrity of the gastrointestinal tract or from infected viscera.
3. Tertiary peritonitis: persistent or recurrent infection that typically occurs at least 48 hours after apparently successful source control of secondary peritonitis.

IAIs can be further classified into community-acquired or healthcare-associated IAIs. Empiric antimicrobials with a narrower spectrum of activity are adequate in patients with community-acquired IAI. Healthcare-associated IAIs are associated with higher risk for multi-drug resistant organisms.

The treatment of IAI involves both timely source control and empiric antimicrobial therapy. Post-operative antimicrobial therapy need not be continued in uncomplicated IAI following source control (e.g. acute appendicitis). In complicated IAIs, antimicrobials are usually continued after source control. The duration of therapy should

be shortened in patients with a positive response (usually 4-7 days), except in cases of immunosuppression or ongoing infections. Prolonged antibiotic therapy does not prevent subsequent infectious complications, which is more often due to progression of the original disease or inadequate original source control. However, for patients in whom source control is known to be suboptimal, the optimal duration of antibiotic treatment is uncertain and decisions on treatment duration must be made on a case-by-case basis.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Spontaneous bacterial peritonitis			
Escherichia coli *Klebsiella pneumoniae* *Streptococcus pneumoniae* Enterococci *Staphylococcus aureus*	IV Cefotaxime 2g q8h *OR* IV Ceftriaxone 2g loading dose, 1g q12h X 5 days	IV Meropenem 1g q8h *OR* IV Imipenem 1g q8h *PLUS OPTIONAL* IV Vancomycin 15-20mg/kg q12h X 5 days	Consider alternative therapy to cover for ESBL-producing organisms and MRSA if the patient has risk factors for multi-resistant infections e.g. • nosocomial origin of infection • on fluoroquinolone prophylaxis • recent infection with multi-resistant bacteria • recent use of ß-lactam antibiotics Metronidazole is not indicated as anaerobes are rarely the causative organism in SBP. For loading dose and monitoring of vancomycin refer to **Appendix C**.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Community-acquired complicated IAI			
Escherichia coli *Klebsiella pneumoniae* *Streptococcus milleri* *Bacteroides spp*	IV Ceftriaxone 2g loading dose, 1g q12h *OR* IV Cefoperazone 2g q12h *PLUS* IV Metronidazole 500mg q8h	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h *OR* IV Meropenem 1g q8h *OR* IV Imipenem 1g q8h *OR* IV Doripenem 500mg q8h	Consider alternative therapy in patients at high risk for mortality or with risk factors for infection with multi-resistant bacteria. Factors associated with high risk for mortality are: • age > 70 years • delay in initial intervention > 24 hours • inability to achieve adequate source control • comorbidity (renal or liver disease, malignancy, malnutrition) • immunocompromised • high severity of illness • severe peritoneal involvement or diffuse peritonitis Consider carbapenems against ESBL-producing bacteria in patients with the following risk factors: • recent exposure to antibiotics (esp. ß-lactams or fluoroquinolones) within 90 days • colonisation with ESBLs • where MDR Enterobacteriaceae is widespread in the community Anti-MRSA agents or anti-fungals are not recommended in the absence of evidence of such infection.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Healthcare-associated complicated IAI			
ESBL-producing Enterobacteriaceae: *(Escherichia coli* *Klebsiella pneumoniae* *Enterobacter spp* *Proteus spp)* *Pseudomonas aeruginosa* *Acinetobacter spp* Enterococci Anaerobes	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h *PLUS OPTIONAL* IV Ampicillin 2g q6h	IV Meropenem 1g q8h *OR* IV Imipenem 1g q8h *OR* IV Doripenem 500mg q8h *PLUS OPTIONAL* IV Ampicillin 2g q6h	Consider carbapenems in patients who are haemodynamically unstable or at risk for infection with ESBL-producing bacteria: • recent exposure to antibiotics (esp. ß-lactams or fluoroquinolones) within 90 days • colonisation with ESBLs • where MDR Enterobacteriaceae is prevalent Consider anti-enterococcal agent (ampicillin or vancomycin) in these patients: • on prolonged cephalosporins • immunocompromised • valvular heart disease • prosthetic heart valves or prosthetic intravascular devices • recurrent IAI Consider anti-MRSA in those colonised with MRSA, prior MRSA treatment failure or significant antibiotic exposure. For loading dose and monitoring of vancomycin refer to **Appendix C**.
Methicillin-resistant *Staphylococcus aureus*	*PLUS OPTIONAL* IV Vancomycin 15 - 20 mg/kg q12h *PLUS OPTIONAL*		

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
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 *OR* IV Lipid formulation Amphotericin B 3-5mg/kg q24h *OR* IV Amphotericin B 0.6-1mg/kg q24h	Consider anti-fungal in patients with: • recurrent gastro-duodenal perforations • anastomotic leaks • necrotising pancreatitis • no clinical improvement despite on antibiotics Fluconazole should be the first-line anti-fungal in haemodynamically stable patients who are colonised with azole susceptible Candida or have no prior exposure to azoles. Consider alternative anti-fungals (echinocandins or amphotericin B and its lipid formulations) in haemodynamically unstable patients or those previously exposed to azoles.

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1. *World J Emerg Surg* 2016; 11: 33-55
2. *Clin Infect Dis* 2010; 50: 133-64
3. *Hepatology* 2013; 5(4): 1-27

URINARY TRACT INFECTION

Urinary tract infections (UTI) can manifest from asymptomatic bacteriuria to severe sepsis.

Complicated UTI usually refers to an infection that occurs in a patient with a structural or functional abnormality, impeding urine flow, or in a host with altered defences or in patients with metabolic disorders like diabetes or azotemia. Antimicrobial resistance is more common and failure of therapy is higher even with agents active against the causative pathogens. UTI in males is considered complicated.

Urosepsis implies clinically evident severe infection of the urinary tract and may be associated with shock and multi-organ dysfunction. Complicated UTI is the commonest precursor of urosepsis. Patients at higher risk for developing urosepsis include the elderly, diabetics and immunosuppressed patients and renal transplant patients. Drug treatment of urosepsis often has to be complemented with endoscopic and/or surgical intervention.

Ultrasound scan is especially valuable for emergency imaging in patients presenting with urosepsis. It is helpful in defining kidney and ureteric size, and in evaluation of the prostate plus other various complications of acute pyelonephritis such as emphysematous pyelonephritis, renal abscess and perirenal abscess and to rule out obstructive uropathy.

Sterile pyuria is common in catheterised patients and does not warrant treatment. Catheter-associated urinary tract infection (CAUTI) is defined as the presence of bacteriuria ($> 10^3$ cfu/ml) in a catheterised patient ($\geq$ 48

hours) who has signs and symptoms consistent with UTI. CAUTI should be treated with antimicrobials and the catheter changed (if more than a week) or removed. Treatment duration for CAUTI varies from 7-21 days depending on organism, comorbid conditions and clinical response. In asymptomatic catheterised patients with significant bacteriuria (> 10^5 cfu/ml), treatment is indicated only in patients who are neutropenic, pregnant, undergoing genitourinary tract manipulation or post renal transplant.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Lower UTI or Acute Uncomplicated Pyelonephritis			
Escherichia coli *Klebsiella spp* *Proteus mirabilis*	IV Amoxycillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h X 10 days	IV Cefuroxime 1.5g q8h *OR* IV Ceftriaxone 2g loading dose, 1g q12h X 10 days	Duration of treatment for uncomplicated cystitis is 3-5 days.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Acute Complicated Pyelonephritis			
	Antibiotic naïve	**Recent antibiotic exposure**	
Escherichia coli *Klebsiella spp* *Proteus mirabilis* *Pseudomonas aeruginosa* *Citrobacter spp* Enterobacterteriacae (ESBL) *Enterococcus spp*	IV Amoxycillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/ Sulbactam 3g q6h *OR* IV Ceftriaxone 2g loading dose, 1g q12h X 14-21 days	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *OR* IV Imipenem 1g q8h *OR* IV Meropenem 1g q8h *OR* IV Doripenem 500mg q8h X 14-21 days	Enterococcal infections are more likely in patients post abdominal surgery, liver transplantation and prosthetic heart valves and vascular grafts. Use ampicillin/ vancomycin for enterococcal infections. Use of ciprofloxacin is associated with increased incidence of resistant strains. Obstructive uropathy should be sought and relieved. Switch to oral therapy when possible to complete course.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Acute Complicated Pyelonephritis (cont'd)			
	Antibiotic naïve	**Recent antibiotic exposure**	
Candida albicans *Candida spp*	IV Fluconazole 400mg q24h X 14-21 days	IV Amphotericin B 0.3-0.6mg/kg q24h X 14-21 days	Candiduria is often asymptomatic and is a common coloniser. Treat only prior to urinary tract instrumentation or if neutropenic. Remove indwelling catheter if possible. When infection is suspected use alternative antifungals if: • recent azole exposure in the last 3 months • known to be colonised by azole-resistant *Candida spp* Echinocandins and lipid formulations of Amphotericin B do not achieve adequate urine concentrations, and are not useful for CAUTI but can be used for pyelonephritis. Amphotericin B bladder irrigation in 50 mg/L sterile water daily for 5 days, may be useful for treatment of cystitis due to fluconazole-resistant species, such as *C. glabrata* and *C. krusei*.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Renal Abscess			
Enterobacteriaceae	Treat as acute complicated pyelonephritis		Corticomedullary and perinephric abscesses are commonly due to ascending infections by enterobacteriacae. Consider image- guided aspiration or surgical drainage of abscess.
Methicillin-sensitive *Staphylococcus aureus* Methicillin-resistant *Staphylococcus aureus*	IV Cloxacillin 2g q4h IV Vancomycin 15-20mg/kg q12h	 IV Linezolid 600mg q12h	Renal cortical abcesses are usually due to haematogenous spread of *S. aureus*. They are often multiple and not drainable. Duration of therapy should be prolonged. For loading dose and monitoring of vancomycin refer to **Appendix C**.

Bibliography:

1. The Sanford Guide to Antimicrobial Therapy 2016
2. *J Glob Infect Dis.* 2009 Jan-Jun; 1(1): 57-63
3. *Clin Infect Dis* 2011; 52(5): e103
4. *BMC Infect Dis* 2015; 15: 426
5. *Clin Infect Dis* 2016; 62(4): e1-50

CATHETER-RELATED BLOODSTREAM INFECTION

Catheter-related bloodstream infection (CRBSI) refers to bloodstream infection attributed to an intravascular catheter. It is diagnosed when the same organism with the same antibiogram is grown from paired blood samples (peripheral vein and catheter lumen) with any of the following criteria:

1. quantitative cultures of blood samples with a 3-fold greater colony count in the catheter than the peripheral sample
2. differential time to positivity of 2 hours: growth from the catheter lumen is detected at least 2 hours earlier than the periphery in an automated blood culture system.

This section deals only with CRBSI associated with short-term central venous catheters (CVC).

A patient with short-term CVC is suspected to have catheter-related infection if there is fever, chills and/or hypotension and no apparent source for the bloodstream infection except the catheter. Presence of catheter site inflammation alone does not always indicate CRBSI and vice versa.

After appropriate cultures are taken, empirical intravenous antimicrobial therapy should be initiated based on the severity of illness, underlying disease and the potential pathogens. In the Malaysian Registry of Intensive Care Report 2015 and 2016, Gram-negative organisms predominate at 68.2% and 54.6% respectively. Thus, antibiotic coverage against Gram-negative bacteria is recommended in the empirical treatment of CRBSI in our ICUs.

Following diagnosis of CRBSI, short-term CVC must be removed as soon as possible with the exception of coagulase-negative staphylococcus (CoNS) as the causative pathogen. Catheter removal is warranted in the presence of severe sepsis, haemodynamic instability, endocarditis or evidence of metastatic infection, erythema or exudate due to suppurative thrombophlebitis or persistent bacteraemia after 72 hours of antimicrobial therapy to which the organism is susceptible. Catheter salvage with antibiotic lock therapy is generally not recommended for short-term CVCs.

Echocardiography should be performed at least 1 week after the onset of bacteraemia or fungaemia in patients with CRBSI who have prosthetic valve or implantable cardiac device. It is also indicated in patients with persistent bacteraemia or fungaemia after 3 days of initiation of appropriate antimicrobial and catheter removal. Repeat echocardiography in patients with a high index of suspicion for infective endocarditis in whom the initial findings were negative.

CRBSI is classified as 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). Systemic antibiotics should be continued for 4-6 weeks and for 6-8 weeks in osteomyelitis.

The effectiveness of antibiotic or antiseptic-impregnated catheters in reducing CRBSI in ICUs remains to be studied in large clinical trials. In units where CRBSI rates remain high despite implementation of comprehensive preventive measures to reduce infection, these catheters may be recommended for use in adult patients who are expected to have CVCs in-situ for more than five days.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy in patients with CRBSI			
Gram-negative bacilli *Klebsiella spp* *Acinetobacter spp* *Pseudomonas aeruginosa* *Escherichia coli* Coagulase-negative Staphylococcus *Staphylococcus aureus* (Methicillin sensitive or resistant) *Enterococcus faecalis* (Ampicillin sensitive or resistant) *Enterococcus faecium* (Vancomycin sensitive or resistant)	IV Cefepime 2g q8h *OR* IV Piperacillin/ Tazobactam 4.5g q6h *PLUS* IV Cloxacillin 2g q4h	IV Meropenem 1g q8h *OR* IV Imipenem 1g q8h *PLUS* IV Vancomycin 15-20mg/kg q12h *PLUS OPTIONAL* IV Polymyxin E Loading dose and 12 hours later 4.5 million units q12h	Consider alternative therapy in patients who are haemodynamically unstable or immunocompromised. Antibiotic coverage for MDR gram-negative bacilli should be considered in patients with neutropenia, severe sepsis, or colonised with such pathogens. Consider MRSA cover in patients with prosthetic valves or vascular grafts, prior antibiotic use, on haemodialisis, prolonged hospital stay, HIV or reside in nursing homes. Risk factors for candida CRBSI include parenteral nutrition, femoral catheters, prolonged use of broad-spectrum antibiotics, haematological malignancy, bone marrow or solid organ transplant and candida colonisation at multiple sites. For loading dose of polymyxin refer to **Appendix A**.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy in patients with CRBSI (cont'd)			
Candida albicans Candida non- albicans	*PLUS OPTIONAL* IV Fluconazole D1 800mg followed by 400mg q24h	*PLUS OPTIONAL* 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 0.6-1mg/kg q24h	Fluconazole should be the first-line anti-fungal in haemodynamically stable patients who are colonised with azole susceptible Candida or have no prior exposure to azoles. Consider alternative anti-fungals (echinocandins or amphotericin B and its lipid formulations) in haemodynamically unstable patients or those previously exposed to azoles.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
Coagulase-negative staphylococcus (except *Staphylococccus lugdunensis)* Methicillin sensitive Methicillin resistant	IV Cloxacillin 2g q4h IV Vancomycin 15-20mg/kg q12h		Single positive cultures of CoNS should not be treated unless confirmed by follow-up cultures, the patient is immunosuppressed or critically ill, or the patient has implanted device e.g. prosthetic valves. Duration of therapy (D1 is the first day on which blood cultures are negative): • 5-7 days if catheter is removed (preferred) • 10-14 days if catheter salvage attempted
Staphylococcus aureus *Staphylococcus lugdunensis* Methicillin sensitive Methicillin resistant	IV Cloxacillin 2g q4h IV Vancomycin 15-20mg/kg q12h		All patients with *S. aureus* CRBSI should have echocardiography performed to rule out endocarditis. Duration of therapy (D1 is the first day on which blood cultures are negative): • 14 days (minimum) • 4-6 weeks in haematogenous complications (e.g. endocarditis, septic thrombosis) • 6-8 weeks in osteomyelitis Linezolid should not be used as monotherapy to treat catheter-related MRSA bacteraemia.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
Enterococcus faecalis *Enterococcus faecium*			Repeat cultures to confirm infection before starting treatment to rule out culture contamination. Perform echocardiography to rule out endocarditis if there is persistent bacteraemia after 3 days on appropriate antibiotics, presence of a prosthetic valve or vascular device. Duration of therapy (D1 is the first day on which blood cultures are negative): • 7-14 days • 4-6 weeks in presence of endocarditis or metastatic infection
Ampicillin sensitive	IV Ampicillin 2g q4h		
Ampicillin resistant, vancomycin sensitive	IV Vancomycin 15-20mg/kg q12h		
Ampicillin resistant, vancomycin resistant	IV Linezolid 600mg q12h	IV Daptomycin 10mg/kg q24h	
Escherichia coli *Klebsiella spp*			Duration of therapy (D1 is the first day on which blood cultures are negative): 7-14 days.
ESBL negative	IV Ceftriaxone 2g loading dose, 1g q12h		
ESBL positive	IV Meropenem 1g q8h *OR* IV Imipenem 1g q8h		

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
Pseudomonas aeruginosa	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS OPTIONAL* IV Amikacin 15mg/kg/day X 3 days	IV Meropenem 1g q8h *OR* IV Imipenem 1g q8h *PLUS OPTIONAL* IV Amikacin 15mg/kg/day X 3 days	Duration of therapy (D1 is the first day on which blood cultures are negative): 7-14 days.
Acinetobacter spp	IV Ampicillin/Sulbactam 9g q8h	IV Polymixin E Loading dose and 12 hours later 4.5 million units q12h	Sulbactam component of 9g is required. Refer to **Appendix D** for dilution. For loading dose of polymyxin refer to **Appendix A**. Duration of therapy (D1 is the first day on which blood cultures are negative): 7-14 days.
Enterobacter spp *Serratia spp* *Citrobacter spp* *Proteus spp*	IV Meropenem 1g q8h *OR* IV Imipenem 1g q8h	IV Cefepime 2g q8h	Deescalate to cefepime if susceptible. Duration of therapy (D1 is the first day on which blood cultures are negative): 7-14 days.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
Stenotrophomonas maltophilia	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q8h		Duration of therapy (D1 is the first day on which blood cultures are negative): 7-14 days
Burkholderia cepacia	IV Trimethoprim/ Sulfamethoxazole 5mg/kg (TMP component) q8h		Consider combination therapy with ceftazidime or meropenem in severe infections. Duration of therapy (D1 is the first day on which blood cultures are negative): 7-14 days
Corynebacterium spp *Bacillus spp*	IV Vancomycin 15-20mg/kg q12h		Confirmation of CRBSI requires at least 2 positive percutaneous blood cultures for the same organism. A single set of positive blood culture does not prove true bloodstream infection. Duration of therapy is tailored to clinical circumstances.
Elizabethkingia spp (previously known as *Chryseobacterium spp*)			Antibiotics should be selected based on antimicrobial susceptibility testing on a case-by-case basis. Combination antibiotic is encouraged.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
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 0.6-1mg/kg q24h *OR* IV Lipid formulation Amphotericin B 3 - 5mg/kg q24h	Echocardiography and abdominal ultrasound should be performed to exclude endocarditis or disseminated candidiasis, and fundoscopy to exclude endophthalmitis or chorioretinitis. Duration of therapy (D1 is the first day on which blood cultures are negative): • 14 days (without metastatic complication) If there is metastatic complication, the duration should be based on the site, clinical improvement and resolution of lesions on imaging.

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INFECTIVE ENDOCARDITIS

Duke criteria is widely used for the diagnosis of infective endocarditis (IE). Prior to initiation of antibiotic therapy, at least three sets of blood cultures should be obtained from different venipuncture sites, with the first and last samples drawn at least 1 hour apart. An echocardiogram should be done in all suspected cases to confirm the diagnosis. Transoesophageal echocardiography (TEE) should be done if initial transthoracic echocardiography (TTE) images are negative. Culture-negative endocarditis can occur up to 31% of all cases of IE. This could be due to previous antimicrobial therapy, inadequate microbiological techniques or fastidious organisms.

Treatment is guided by presentation, clinical findings, native or prosthetic valves and organism virulence. Surgery is indicated in patients with high risk features (heart failure, uncontrolled infection, fungal infection, non HACEK gram-negative infections e.g. *Pseudomonas aeruginosa*, annular/aortic abscess) that make the possibility of cure with antibiotic treatment unlikely and those at high risk of embolisation (large mobile vegetations > 10mm). Blood cultures should be taken every 48 hours until the results are negative. Duration of treatment begins from the day of first negative culture.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Empirical therapy			
Native valve	IV Ampicillin 2g q4h *PLUS* IV Gentamicin 3mg/kg q24h *PLUS OPTIONAL* IV Cloxacillin 2g q4h	IV Cefriaxone 2g loading dose, 1g q12h *PLUS OPTIONAL* IV Cloxacillin 2g q4h	Consider Cloxacillin in intravenous drug users or in acute presentation

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Empirical therapy			
Prosthetic valve	IV Vancomycin 15-20mg/kg q12h *PLUS* IV Gentamicin 3mg/kg q24h *PLUS* PO Rifampicin 450mg q12h *PLUS OPTIONAL* IV Cefepime 2g q8h		For loading dose and monitoring of vancomycin refer to **Appendix C**. Rifampicin is started 3-5 days later after vancomycin and gentamicin.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Pathogen specific			
Streptococcus viridans *Streptococcus bovis* Highly penicillin-susceptible: MIC ≤ 0.12 µg/ml	**4 weeks regimen (Native)** **6 weeks regimen (Prosthetic)** IV Benzylpenicillin 3 million units q4h *OR* IV Ceftriaxone 2g loading dose, 1g q12h	**2 weeks regimen (Native)** IV Benzylpenicillin 3 million units q4h *OR* IV Ceftriaxone 2g loading dose, 1g q12h *PLUS* IV Gentamicin 3mg/kg q24h	The **alternative** 2-week regimen is not recommended for patients age > 65 years old, creatinine clearance < 20ml/min, deafness and known cardiac or extra- cardiac abscesses and prosthetic valves. Gentamicin is used for synergy, peak level need not exceed 4µg/ml and trough should be < 1µg/ml. Benzylpenicillin: 1 million units = 600mg

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
Streptococcus viridans *Streptococcus bovis* Relatively resistant to penicillin: 0.12 µg/ml ≤ MIC < 0.5 µg/ml Group B, C and G streptococci	IV Benzylpenicillin 4 million units q4h X 4 weeks *PLUS* IV Gentamicin 3mg/kg q24h X 2 weeks	IV Ceftriaxone 2g loading dose, 1g q12h X 4 weeks *PLUS* IV Gentamicin 3mg/kg q24h X 2 weeks	Duration of treatment in prosthetic valve endocarditis: 6 weeks.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Pathogen specific			
Staphylococcus aureus (Native valve)	**Methicillin sensitive** IV Cloxacillin 2g q4h X 4-6 weeks	**Methicillin resistant** IV Vancomycin 15-20mg/kg q12h X 4-6 weeks	In uncomplicated right-sided endocarditis, duration of treatment can be shortened to 2-4 weeks. Uncomplicated right-sided endocarditis includes **absence of**: heart failure, extra-pulmonary metastatic infection such as osteomyelitis, aortic or mitral valve involvement, meningitis, MRSA infection, implanted prosthesis and AIDS. There is no evidence to routinely combine gentamicin with cloxacillin/vancomycin in native valve endocarditis. Gentamicin may help clear blood culture faster, does not affect mortality and have potential for harm. For loading dose and monitoring of vancomycin refer to **Appendix C**.

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Pathogen specific			
Staphylococcus aureus (Prosthetic valve)	**Methicillin sensitive** IV Cloxacillin 2g q4h X $\geq$ 6 weeks *PLUS* PO Rifampicin 450mg q12h X $\geq$ 6 weeks *PLUS* IV Gentamicin 1mg/kg q8h X 2 weeks	**Methicillin resistant** IV Vancomycin 15-20mg/kg q12h X $\geq$ 6 weeks *PLUS* PO Rifampicin 450mg q12h X $\geq$ 6weeks *PLUS* IV Gentamicin 1mg/kg q8h X 2 weeks	To avoid the development of resistance, start rifampicin after 3-5 days of effective therapy and/or once bacteraemia has cleared. For loading dose and monitoring of vancomycin refer to **Appendix C**.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pathogen specific			
Enterococcus spp	**Ampicillin sensitive** 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 treatment: Patient with native valve with symptoms < 3 months: 4 weeks therapy for ampicillin and 2 weeks for gentamicin. Patients with native valve with symptoms > 3 months: 6 weeks therapy for ampicillin and gentamicin. Prosthetic valves: 6 weeks. If gentamicin is contraindicated or there is gentamicin resistance, consider combination of ampicillin or vancomycin with IV ceftriaxone 2g q12h.
Enterococcus spp (Vancomycin resistant)	IV Linezolid 600mg q12h X 6-8 weeks	IV Daptomycin 10mg/kg q24 X 6-8 weeks	
HACEK *Haemophilus spp* *Aggregatibacter spp* *Cardiobacterium hominis* *Eikenella corrodens* *Kingella spp*	IV Ceftriaxone 2g loading dose, 1g q12h X 4 weeks	IV Ampicillin/ Sulbactam 3g q6h X 4 weeks	6 weeks therapy for prosthetic valve endocarditis.

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SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections (SSTIs) are usually caused by bacterial entry through breaches in the skin. Its clinical severity depends on host factors such as age, diabetes mellitus and state of immunocompetence. Purulent SSTI, cellulitis, pyomyositis, and surgical site infections (SSI) can all result in severe illness, but the most severe end of the SSTI spectrum is composed of toxic shock syndrome, gas gangrene, and necrotising fasciitis.

Purulent SSTI

Purulent SSTIs (abscesses, furuncles, and carbuncles) are predominantly caused by *S. aureus*. Cutaneous abscesses are collections of pus within dermis and deeper tissues while furuncles and carbuncles are centered on hair follicles. Polymicrobial infections are possible depending on the site of infection. Infections that include anaerobes are more likely in the pelvic and lower extremity regions (particularly in those with peripheral vascular disease and/or diabetes). Enterobacteriaceae from the gut play a role in the polymicrobial milieu of pelvic abscesses.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Staphylococcus aureus Anaerobes Enterobacteriacae	IV Cloxacillin 2g q4h X 5-10 days	IV Amoxycillin/ Clavulanate 1.2g q8h *OR* IV Cefazolin 1g q8h *PLUS* IV Metronidazole 500mg q8h X 5-10 days	Duration of treatment depends on clinical response. Incision and drainage needs to be done promptly.

Non-purulent SSTI: Cellulitis and Necrotising Fasciitis

Cellulitis is an acute diffuse infection of the epidermis, dermis and subcutaneous tissue. It is usually caused by ß-haemolytic Streptococci (most commonly Group A) or *S. aureus*. The most common presentation is a superficial spreading erythema usually associated with lymphangitis. Anaerobes and gram-negative organisms also play a role in non-purulent SSTIs of the lower extremities, particularly in patients with diabetes or peripheral vascular disease.

Necrotising fasciitis is an infection of the deeper tissues usually involving the extremities, the parapharyngeal space, the abdominal wall or the perineum (Fournier's gangrene). In the early stages, cellulitis may be difficult to differentiate from necrotising fasciitis. Presence of severe pain, bullae, crepitus, progressive spread of infection despite appropriate antibiotics, renal failure and systemic deterioration are all suggestive of necrotising fasciitis. Although supportive management of organ failure and antimicrobials play a major role, surgical debridement often extensive and repeated is essential. Tissue cultures taken at the time of debridement may help to identify the organism.

There is anatomical variation in predominant pathogens. In the neck region, oral flora including anaerobes, tend to be the more likely organism as in Ludwig's angina. Infections in the pelvic region more commonly result from Enterobacteriaceae from the genitourinary or gastrointestinal tracts. 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 caused by ß-haemolytic streptococcus. It commonly occurs in patients with no medical illnesses, predisposed by blunt trauma, varicella infection, intravenous drug abuse and surgical procedures. 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.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Cellulitis			
ß-haemolytic Streptococci *Staphylococcus aureus*	IV Cloxacillin 2g q4h X 5-10 days	IV Amoxycillin/ Clavulanate 1.2g q8h X 5-10 days	If streptococci is cultured consider IV benzylpenicillin 4 million units q6h. IV benzylpenicillin: 1 million units = 600mg Duration of treatment depends on clinical response.
Necrotising fasciitis			
Head and Neck *Streptococcus spp* Anaerobes Peptostreptococci *Fusobacterium spp* *Prevotella spp* *Bacteroides spp* *(*usually not *Bacteroides fragilis)*	IV Amoxycillin/ Clavulanate 1.2g q8h *OR* IV Ampicillin/Sulbactam 3g q6h		Includes deep neck space infections e.g. submandibular (Ludwig's angina), parapharyngeal, retropharyngeal and peritonsillar space infection. Most of these infections have an odontogenic source. Gram-negative rods to be considered in the immunocompromised host.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Necrotising fasciitis			
Abdominal/ Perineum *Bacteroides spp* *Clostridium spp* Peptostreptococci Enterobacteriaceae *Pseudomonas aeruginosa*	IV Ampicillin/ Sulbactam 3g q6h *OR* IV Ceftriaxone 2g loading dose, 1g q12h *PLUS* IV Metronidazole 500mg q8h *PLUS* IV Clindamycin 900mg q8h	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h *OR* IV Imipenem 1g q8h *PLUS* IV Clindamycin 900mg q8h	Continue treatment until surgical debridement is no longer needed and patient has clinically improved. If ESBL organisms are suspected use imipenem. If *Clostridium spp* or ß-haemolytic streptococci is confirmed, deescalate to IV benzylpenicillin 2 million units q4h but continue clindamycin. If IV Clindamycin is not available, PO Clindamycin 600mg q6h may be used.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Necrotising fasciitis			
Chest and extremities ß-haemolytic streptococci *Staphylococcus aureus* *Bacteroides spp* *Clostridium spp* Peptostreptococci Enterobacteriaceae	IV Ampicillin/ Sulbactam 3g q6h *OR* IV Ceftriaxone 2g loading dose, 1g q12h *PLUS* IV Metronidazole 500mg q8h *PLUS* IV Clindamycin 900mg q8h	IV Piperacillin/ Tazobactam 4.5g q6h *OR* IV Cefepime 2g q8h *PLUS* IV Metronidazole 500mg q8h *OR* IV Imipenem 1g q8h *PLUS* IV Clindamycin 900mg q8h	If streptococcal toxic shock syndrome is suspected consider IVIg. If ESBL organisms are suspected use imipenem. Vancomycin / Linezolid needs to be considered in cases where MRSA are likely.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Necrotising fasciitis			
Aeromonas hydrophila *Vibrio vulnificus*	IV Ceftriaxone 2g loading dose, 1g q12h *PLUS* PO Doxycycline 100mg q12h X 7-10 days	IV Ciprofloxacin 400mg q8h X 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.

Surgical Site infection

Most surgical site infections have no clinical manifestation for the first 5 days after the operation. The most important intervention is to open the wound, drain the infected material and continue to dress the wound daily. Empiric antimicrobial is usually guided by the site of infection.

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CENTRAL NERVOUS SYSTEM INFECTION

The approach to the patient with suspected acute central nervous system infection is early recognition, performance of rapid diagnostic tests, prompt antimicrobial therapy and adjunctive therapy whenever appropriate.

Acute bacterial meningitis should not be ruled out solely on the absence of classical signs and symptoms. In patients with suspected bacterial meningitis, it is strongly recommended to perform lumbar puncture to obtain 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 with high 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. Discontinue dexamethasone 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.

Meningitis associated with invasive neurological procedures or head trauma is classified as healthcare-associated ventriculitis and meningitis, with resistant Gram-negative bacilli and staphylococci being the more likely causative organisms. Intrathecal or intraventricular administration of antibiotics (aminoglycosides, polymyxins, vancomycin) is not practised routinely. It may be used with parenteral antibiotics in infections due to multi-drug resistant organisms or infections refractory to appropriate parenteral therapy. Determining the correct dosing regimen to achieve CSF antimicrobial concentrations of 10-20 times the MIC of the causative microorganism is challenging. CSF concentrations are highly variable depending on the volume of distribution, ventricular size, and CSF clearance as a result of CSF drainage.

Likely Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Empirical therapy in community-acquired meningo-encephalitis			
Streptococcus pneumoniae *Neisseria meningitidis* *Haemophilus influenzae* Aerobic Gram-negative bacilli (more common in age > 50, immunocompromised)	IV Ceftriaxone 2g loading dose, 2g q12h *OR* IV Cefotaxime 2g q6h		Add IV vancomycin if prevalence of cephalosporin-resistant *S. pneumoniae* is > 2%. Administer IV dexamethasone 10mg q6h X 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	
Empirical therapy in community-acquired meningo-encephalitis (cont'd)			
Listeria monocytogenes (uncommon in Malaysia)			Treat Listeria meningitis with IV ampicillin 2g q4h if CSF Gram stain reveals Gram-positive rods or when confirmed.
	PLUS OPTIONAL		Duration of treatment: • *N. meningitidis* X 7days • *H. influenzae* X 7-10 days • *S. pneumoniae* X 10-14 days • Aerobic Gram-negative bacilli X 21 days • *L. monocytogenes* X 21 days (longer if immunocompromised)
Herpes simplex virus Varicella zoster virus Enteroviruses Japanese B encephalitis virus Adenovirus Cytomegalovirus Epstein-Barr Virus	IV Acyclovir 10mg/kg q8h X 14 days		
Mycobacterium tuberculosis	Refer to chapter on Tuberculosis		

Likely Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Empirical therapy in healthcare-associated ventriculitis and meningitis			
Staphylococcus aureus Coagulase-negative staphylococcus *Propionibacterium acnes* Aerobic Gram-negative bacilli *Pseudomonas aeruginosa* *Acinetobacter spp* *Candida spp*	IV Cloxacillin 2g q4h *PLUS* IV Cefepime 2g q8h	IV Vancomycin 15 - 20mg/kg q12h *PLUS* IV Meropenem 2g q8h *PLUS OPTIONAL* IV Polymyxin E 9 million units loading dose and 12 hours later 4.5 million units q12h	Duration of therapy: • CoNS or *P. acnes* X 10 days (minimal CSF abnormalities) X 10-14 days (significant CSF abnormalities and systemic features) • *S. aureus* or Gram-negative bacilli X 10-14 days If CSF cultures are repeatedly positive despite on appropriate antimicrobial, continue for 10-14 days after last positive culture. Remove infected shunts. A new shunt can be placed after repeat CSF cultures are negative but the timing of placement varies between pathogens: • CoNS or *P. acnes* (*minimal CSF abnormalities*) - 3 days after removal • CoNS or *P. acnes* (*significant CSF abnormalities*) - 7-10 days from negative CSF culture • *S. aureus* or Gram-negative bacilli - 10 days from negative CSF culture

Brain abscesses are uncommon but can occur in immunocompetent hosts secondary to contiguous foci of infection (dental, middle ear or sinus) or haematogenous spread from an extracranial site of infection (endocarditis, lung abscess) or in cyanotic heart disease, immunocompromised hosts, and after neurosurgical procedures. It is usually difficult to diagnose brain abscess on clinical grounds alone and neuroimaging is necessary. Bacterial abscess in the brain is preceded by infarction and cerebritis. Antibiotic therapy during the early stage may prevent the progress from cerebritis to abscess.

Empiric 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 microbiological culture to allow directed therapy especially in the immunocompromised host. Surgical drainage may be necessary; especially in lesions larger than 2.5 cm. Frequent repeat neuroimaging is indicated to monitor treatment response.

Dexamethasone use is controversial but may be administered when a significant mass effect is seen on imaging and the patient's mental status is depressed. It should be discontinued once the mass effect and neurological status has improved. Steroids can retard the encapsulation process, increase necrosis, reduce antibiotic penetration into the abscess, increase the risk of ventricular rupture, and produce a rebound effect when discontinued.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess			
Immunocompetent host: contiguous or haematogenous spread, penetrating trauma or post neurosurgery			
Aerobic and anaerobic streptococci Bacteroides Enterobacteriaceae *Haemophilus influenzae* *Staphylococcus aureus* Aerobic Gram-negative bacilli *Pseudomonas aeruginosa* *Acinetobacter spp*	IV Ceftriaxone 2g loading dose, 2g q12h *OR* IV Cefotaxime 2g q6h *PLUS* IV Metronidazole 1g loading dose, 500mg q8h *PLUS OPTIONAL* IV Cloxacillin 2g q4h	IV Cefepime 2g q8h *PLUS* IV Metronidazole 1g loading dose, 500mg q8h *OR* IV Meropenem 2g q8h *PLUS OPTIONAL* IV Vancomycin 15-20mg/kg q12h	Consider alternative antimicrobial therapy to cover nosocomial aerobic Gram-negative bacilli. Metronidazole is added to cover penicillin-resistant anaerobic Gram-negative bacilli (Bacteroides) in abscess of dental, middle ear or sinus origin and in penetrating injury of paranasal sinus involvement. Empiric antibiotic to cover for *S. aureus* is indicated in abscess secondary to haematogenous spread, penetrating injury, post neurosurgery and in those at high risk for *S. aureus* sinusitis (recent endoscopic sinus surgery, chronic sinusitis, recent nasal packing). Consider anti-MRSA cover in patients with risk for MRSA infection. For loading dose and monitoring of vancomycin refer to **Appendix C**. For empirical treatment of brain abscess associated with endocarditis, refer to chapter on Infective Endocarditis.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess (cont'd)			
Immunocompetent host: contiguous or haematogenous spread, penetrating trauma or post neurosurgery			
			Duration of therapy: • cerebritis or post drainage X 4-6 weeks • encapsulated abscess with tissue necrosis, multiloculated abscess, abscess in vital locations (e.g. brain stem) X minimum 6 weeks • immunocompromised X minimum 6 weeks
Immunocompromised host: solid organ or bone marrow transplant recipients			
Aspergillus spp *Candida spp* Mucorales *Cryptococcus neoformans* Nocardia *Listeria monocytogenes* *Mycobacterium tuberculosis*	Alternative antimicrobials as per immunocompetent host *PLUS* IV Voriconazole D1 6mg/kg q12h followed by 4mg/kg q12h *OR* IV Liposomal Amphotericin B 5mg/kg q24h		Aspergillus brain abscess usually occurs in the setting of disseminated aspergillosis. Consider combination antifungal in Aspergillus CNS infection. Suspect nocardia brain abscess in presence of lung abscess. Suspect listeria brain abscess in presence of prodrome of meningoencephalitis and brain stem location of abscess.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess (cont'd)			
Immunocompromised host: HIV infected			
Toxoplasma gondii *Cryptococcus neoformans* *Mycobacterium tuberculosis* *Listeria monocytogenes*	Alternative antimicrobials as per immunocompetent host *PLUS* PO Pyrimethamine D1 200mg followed by 50mg q24h (BW < 60kg) 75mg q24h (BW ≥ 60kg) *PLUS* PO Sulfadiazine 1g q6h (BW < 60kg) 1.5g q6h (BW ≥ 60kg) *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.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess (cont'd)			
Pathogen specific			
Listeria monocytogenes	IV Ampicillin 2g q4h	IV Trimethoprim/ Sulfamethoxazole 5mg/kg q6h (TMP component)	Duration of therapy: - minimum 6 weeks
Candida spp	IV Liposomal Amphotericin B 5mg/kg q24h	IV Fluconazole 800mg q24h	Duration of therapy: - not definitively determined
Toxoplasma gondii	Induction therapy PO Pyrimethamine D1 200mg followed by 50mg q24h (BW < 60kg) 75mg q24h (BW ≥ 60 kg) *PLUS* IV/PO Clindamycin 600mg qid *PLUS* PO Folinic acid 10-25mg q24h X 6 weeks (minimum)		Duration of therapy • induction therapy X minimum 6 weeks (longer duration if clinical or radiologic disease is extensive) • maintenance therapy PO pyrimethamine 25-50mg q24h, PO clindamycin 600 mg q8h and PO folinic acid 10-25mg q24h until asymptomatic of signs and symptoms of CNS toxoplasmosis and CD4 count > 200 cells/mm^3 for > 6 months in response to anti-retroviral therapy. • If pyrimethamine is unavailable, consider Fansidar. For alternative regimen, refer ID.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess (cont'd)			
Pathogen specific			
Cryptococcus neoformans	Induction therapy IV Liposomal Amphotericin B 3-4mg/kg q24h *PLUS* PO Flucytosine 25mg/kg q6h X 2 weeks	IV Amphotericin B 0.7-1mg/kg q24h *OR* IV Amphotericin lipid-complex 5mg/kg q24h *PLUS* PO Flucytosine 25mg/kg q6h X 2 weeks	After induction therapy, continue with • consolidation therapy, IV fluconazole 400mg q24h X minimum 8 weeks • maintenance therapy, PO fluconazole 200mg X minimum 1 year Adjust flucytosine dose in patients with renal dysfunction. For alternative regimen, refer ID.
Aspergillus spp	IV Voriconazole D1 6mg/kg q12h followed by 4mg/kg q12h	IV Liposomal Amphotericin B 5mg/kg q24h	After clinical improvement following parenteral antifungal, continue therapy with PO voriconazole 200mg q12h. Duration of therapy: - until infection is resolved.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess (cont'd)			
Pathogen specific			
Nocardia spp	IV Trimethoprim/ Sulfamethoxazole 5mg/kg q6h (TMP component)		Species identification of Nocardia is important, as antimicrobial susceptibility varies. Combination therapy with carbapenems, amikacin, 3rd generation cephalosporins may be used and continued until clinical improvement occurs. Therapy may continue with oral minocycline, amoxicillin/ clavulanate and linezolid after an induction course of parenteral therapy. Duration of therapy: - minimum 12 months
Mucorales	IV Liposomal Amphotericin B 5mg/kg q24h		Duration of therapy: - minimum 6-8 weeks
Mycobacterium tuberculosis	Refer to chapter on Tuberculosis.		

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MELIOIDOSIS

Melioidosis is a potentially fatal disease caused by *Burkholderia pseudomallei*. There is no reliable pathognomonic feature and can present as bacteraemia with no obvious focal infection or as septic shock with multi-organ failure. Common sites of infection include the lung (50%), joints, spleen, liver, skin and prostate. In bacteraemic cases, CT or ultrasound of the abdomen and pelvis is required to detect any abscesses.

Predisposing host factors to melioidosis include diabetes mellitus, renal failure, chronic lung disease, alcoholism, steroid use, malignancy and HIV infection. Other risk factors include occupational and recreational exposure to surface water and mud e.g. rice farmers, construction site workers and adventure travellers. Melioidosis can also occur sporadically during the rainy seasons or floods.

Antibiotic therapy consists of 2 phases, an initial intensive treatment phase for at least 2 weeks followed by an eradication phase for 12-20 weeks to prevent relapse and recurrence. Prolonged IV therapy is necessary for complicated pneumonia, deep-seated infection including prostatic abscesses, central nervous system involvement, osteomyelitis and septic arthritis. The actual eradication phase is guided by the site of infection and the clinical response to therapy. Deep-seated abscesses may need to be drained. Infected joints also need surgical intervention.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Phase 1: Treatment			
Burkholderia pseudomallei	IV Meropenem 1g q8h (2g q8h for CNS infection) *OR* IV Imipenem 1g q8h	IV Ceftazidime 2g q6h	Carbapenem is preferred in severe sepsis as the benefits include: • higher rate of bacterial killing in vitro due to enhanced cell wall penetration • better post-antibiotic effect • decreased endotoxin release Evidence for the use of G-CSF is weak. It may be considered in septic shock patients admitted within 72 hours to ICU. IV G-CSF 300μg daily x 10 days (contraindications: acute coronary event, total WCC > 50,000 x10^6/L)
	PLUS OPTIONAL IV Trimethoprim/Sulfamethoxazole 5mg/kg (TMP component) q12h (in deep seated focal infections, CNS, joints, bones, prostate)		Add PO Folic Acid 5mg q24h
Phase 2: Eradication			
	PO Trimethoprim/Sulfamethoxazole >60kg 320:1600mg q12h 40-60kg 240:1200mg q12h <40kg 160:800mg q12h *OR* PO Amoxycillin/Clavulanate 500/125mg q8h		Add PO Folic Acid 5mg q24h

Duration of therapy for *Burkholderia pseudomallei* infections

Clinical focus	Minimum intensive intravenous phase (weeks)	Eradication oral phase (weeks)
Skin abscess	2	12
Bacteraemia with no focus	2	12
Pneumonia	2 to 4	12
Prostatic abscess, septic arthritis, organ or deep-seated tissue collection	4	12
Osteomyelitis	6	24
Central nervous system infection	8	24
Mycotic aneurysms	8	Maybe lifelong

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LEPTOSPIROSIS

Leptospirosis is a zoonotic infection caused by pathogenic spirochetes of the genus *Leptospira*. It is commonly associated with rodents in the settings of poor sanitation, high-risk occupations (sewerage workers, livestock handlers), flooding and recreational activities conducted in contaminated water or soil. The clinical manifestations of leptospirosis vary from mild febrile illness to the icteric-haemorrhagic form with severe kidney and liver involvement, myocarditis and pulmonary haemorrhage.

Presumptive diagnosis is made with a positive rapid screening test such as IgM ELISA. However, its specificity is affected by previous exposure (significant in endemic areas and may remain detectable for several years) and other diseases. Diagnosis is confirmed with a fourfold or greater rise in antibody titres or seroconversion in the microscopic agglutination test (MAT) on paired samples obtained 2 weeks apart. Hence treatment should be initiated even when the initial test is negative if the clinical picture is consistent. Blood for PCR testing can be done. Blood cultures are not routinely done as it requires specialised media and can only be recovered early in the illness.

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Leptospira spp	IV Benzylpenicillin 2 million units q6h X 7 days	IV Ceftriaxone 2g loading dose, 1g q12h X 7 days	In less severe infection: PO Azithromycin 500 mg q24h x 3 days *OR* PO Doxycyline 100mg q12h x 5-7 days *OR* PO Amoxicillin 500mg q8h x 7 days Jarisch-Herxheimer reaction can occur post ß-lactam therapy

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SEVERE MALARIA

Patients diagnosed or suspected with severe malaria should be started on parenteral anti-malarial therapy immediately. Severe malaria with multiorgan dysfunction is usually due to *Plasmodium falciparum*. Occasionally severe malaria may be due to *P. knowlesi*, *P. vivax* or a mix coinfection with *P. falciparum*. *P. knowlesi* may be misdiagnosed as *P. malariae* on blood film. Patients with severe malaria are at risk of concurrent bacterial infection.

Microscopic examination of thick and thin blood films remain the standard for detection, species identification and quantification. Rapid diagnostic kits can detect parasite antigens with high sensitivity but must be confirmed with microscopy. The PCR method is useful for confirmation and species determination in special circumstances (clinical malaria with negative blood films or microscopic diagnosis of *P. malariae*).

Likely Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Plasmodium falciparum *Plasmodium knowlesi* *Plasmodium vivax*	IV Artesunate 2.4mg/kg at 0 hrs, 12 hrs and 24 hrs then q24h X 7 days *PLUS* PO Doxycyline 200mg q24h X 7 days	IV Quinine Dihydrochloride 20mg/kg in 250mls D/5% over 4 hours and then 10mg/kg q8h *PLUS* PO Doxycyline 200mg q24h X 7 days	If artesunate is not readily available, start quinine first to avoid delay. Blood sugars and QT intervals need to be monitored regularly while on quinine. Switch to oral Artemisinin Combination Therapy (ACT) if patient is able to tolerate orally and after 24 hours of IV artesunate. Oral Riamet (lumefantrine and artemether) is available in Malaysia. Complete the 6 doses. Substitute doxycyline with PO clindamycin 450mg q8h in pregnancy. If there is no decrement in parasite counts after 72 hours, suspect reduce susceptibility to artemisinin. 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.

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INVASIVE CANDIDIASIS IN THE NON-NEUTROPENIC PATIENT

Invasive candidiasis (IC) is increasingly common in ICU patients and results in high mortality if treatment is delayed or inappropriate. IC consists of candidaemia with or without metastatic complications; or deep-seated candidiasis (often blood culture negative e.g. intra-abdominal or hepatosplenic candidiasis). Although *Candida albicans* is the most common organism, there is a growing proportion of non-albican species, that is associated with fluconazole resistance. Other invasive fungal infections e.g. aspergillosis, mucormycosis are rare except in neutropenic or transplant recipients.

Colonisation with candida in the oropharynx, respiratory and urinary tract is common in ICU patients and is not an indication for treatment. Broad-spectrum antibiotic therapy increases the incidence of colonisation. Overall the risk of invasive infection increases with the number and extent of colonised sites. Candida pneumonia is very rare and only occurs in severely immunocompromised patients following haematogenous spread.

Blood culture remains the gold standard for diagnosis of IC. However, it is negative in 50% of IC and time to positivity is long (up to 72 hours and longer for species identification) contributing to poor outcomes from treatment delays. Nonculture-based diagnostic tests such as serological (mannan/antimannan, ß-D-glucan) and molecular (candida-specific PCR) techniques may be useful adjuncts to early diagnosis but are not routinely available here.

Assessing risks has become the cornerstone of empiric treatment of candida infections in the ICU setting. Patients at risk for IC are:

- High severity of illness
- Long term ICU stay
- Gastrointestinal surgery with anastomotic leakages or recurrent gastro-duodenal perforations
- Acute necrotising pancreatitis
- Immunocompromised/immunosuppressive therapy e.g. steroid use or chemotherapy
- Solid organ transplant
- Haematologic or solid organ malignancies
- Candida colonisation at multiple non-sterile sites e.g. colonisation index > 0.5 (no. of sites colonised/no. of sites cultured)
- Use of broad-spectrum antibiotics
- Presence of central venous catheters
- Parenteral nutrition
- Haemodialysis

However, there is no single factor that determines infection risk but rather a combination that may suggests a role in the initiation of anti-fungal therapy. Scoring systems and predictive rules that combine risk factors and microbiological tools lack sensitivity although have high negative predictive value.

Anti-fungals can be used as prophylactic, empiric, pre-emptive or definitive therapy. Prophylaxis therapy is initiated in asymptomatic patients with high risks for fungal infection. In ICUs with IC rates of > 5%, experts

suggest the use of prophylactic treatment for patients with recurrent GI surgery and leaks or undergoing transplantation.

Empirical therapy should be started in a patient with unexplained sepsis with risk factors for IC while pre-emptive therapy is for similar patients with radiological or serological evidence for IC. The agent of choice depends on the suspected pathogen, site of infection, severity of illness and local susceptibility patterns. If the response is positive, continue therapy for 2 weeks.

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
Empirical therapy			
	Without risk factors for resistant *Candida spp* OR Haemodynamically stable with risk factors for resistant *Candida spp*	**With risk factors for resistant *Candida spp* AND haemodynamically unstable**	
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 Lipid formulation Amphotericin B 3-5mg/kg q24h *OR* IV Amphotericin B 0.6-1mg/kg q24h	Risks factors for azole resistant candida: • previous azole exposure within last 3 months • previous abdominal surgery • solid organ tumours • haemopoietic transplant • chemotherapy with extensive mucositis In haemodynamically stable patients with risk factors, a balance must be struck between the overuse of echinocandins and inappropriate therapy. Monitor closely and change to an echinocandin if no response. There is no documented superiority of one echinocandin over another. Lipid formulation Amphotericin B (AmB) is preferred for better safety profile. AmB is the treatment of choice in pregnant women.

Likely Organisms	Antimicrobials		Notes
Pathogen specific			
	Preferred	**Alternative**	
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 Lipid formulation Amphotericin B 3-5mg/kg q24h *OR* IV Amphotericin B 0.6-1mg/kg q24h	Repeat cultures every 48 hours till negative. Duration of treatment without metastatic complication is 14 days from first negative blood culture with resolution of signs and symptoms of infection. If there are metastatic complications, the duration of treatment should be based on the site, clinical improvement and resolution of lesions on imaging. Echinocandins do not achieve therapeutic concentrations in the CNS, eye and urine. Ophthalmic examination is recommended for all patients with candidaemia within 1 week of diagnosis. Risk of endophthalmitis is up to 25%. Central venous catheters must be removed as soon as possible in candidaemia. AmB is the treatment of choice in pregnant women. Flucytosine can be added for combination with AmB for more refractory infections e.g. endophthalmitis, meningitis and endocarditis

Likely Organisms	Antimicrobials		Notes
Pathogen specific			
	Preferred	**Alternative**	
Candida parapsilosis *Candida tropicalis* *Candida lusitaniae*	IV Fluconazole D1 800mg followed by 400mg q24h	IV Lipid formulation Amphotericin B 3-5mg/kg q24h *OR* IV Amphotericin B 0.6-1mg/kg q24h	*C. lusitaniae* may be resistant to amphotericin B.
Candida glabrata *Candida krusei*	IV Anidulafungin D1 200mg followed by 100mg q24h *OR* IV Caspofungin D1 70mg followed by 50mg q24h *OR* IV Micafungin 100mg q24h	IV Lipid formulation Amphotericin B 5mg/kg q24h *OR* IV Amphotericin B 0.6-1mg/kg q24h	In *C. glabrata* that is fluconazole-susceptible, deescalate to higher dose fluconazole 800mg q24h. Consider stepdown therapy to oral voriconazole in patients with *C. krusei* that are stable.

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APPENDIX A
DOSAGE ADJUSTMENT FOR RENAL IMPAIRMENT

Below is the formula used to calculate the creatinine clearance (CrCl):

Males: CrCl (mls/min) = $\frac{(140 - \text{Age}) \times \text{IBW}^*}{0.8 \times \text{Sr. creat } (\mu\text{mol/L})}$ Females: CrCl (mls/min) = $\frac{(140 - \text{Age}) \times \text{IBW}^*}{\text{Sr. creat } (\mu\text{mol/L})}$

*In obese patients use adjusted body weight. If BMI $<$ 18.5 kg/m^2 use actual BW. Refer Appendix E for BW calculations.

§ Alternative calculation for CrCl is the CKD-EPI (Chronic Kidney Disease Epidemiology Collaborative) equation with the removal of body surface area nomalisation.

	Adjusted Maintenance Dose for Renal Impairment and Dialysis *Loading dose (LD) is required prior to Maintenance Dose (MD)*			
Drug / Normal Dose	**CrCl 30-50 ml/min**	**CrCl 10-30 ml/min**	**CrCl < 10 ml/min**	**Renal Replacement Therapy**
Amikacin	Refer Appendix C			
Acyclovir MD : 10mg/kg/dose q8h	10mg/kg/dose q12h	10mg/kg/dose q24h	5mg/kg/dose q24h	HD: 5mg/kg/dose q24h† CVVH: 10mg/kg/dose q24h CVVHD/CVVHDF: 10mg/kg q12h
Ampicillin LD : 2g MD : 2g q4h - q6h* **Higher dose range for endocarditis and meningitis*	2g q6h - q8h	2g q8h - q12h	2g q12h - q24h	HD: 2g q12h† CVVH: 2g q8h - q12h CVVHD: 2g q8h CVVHDF: 2g q6h - q8h
Ampicillin/sulbactam LD : 3g MD : 3g q6h **Refer table for dosing in MRO Acinetobacter baumanii infecion*	3g q8h	3g q12h	3g q24h	HD: 3g q24h† CVVH: 3g q12hr CVVHD: 3g q8hr CVVHDF: 3g q6h

	Adjusted Maintenance Dose for Renal Impairment and Dialysis *Loading dose (LD) is required prior to Maintenance Dose (MD)*			
Drug / Normal Dose	**CrCl** **30-50 ml/min**	**CrCl** **10-30 ml/min**	**CrCl** **< 10 ml/min**	**Renal Replacement Therapy**
Amoxicillin/clavulanate LD : 1.2g MD : 1.2g q8h	1.2g q8h	1.2g q12h	1.2g q24h	HD: 1.2g q24hr + 600mg AD CVVH: 1.2g q12hr
Benzylpenicillin LD : 4MU MD : 2-4MU q4h - q6h	1.5-3MU q4h - q6h		1-2MU q4h - q6h	HD: 1-2MU q4h - q6h† CVVH: 2MU q6h CVVHD: 2MU q4h CVVHDF: 4MU q4h
Cefepime LD : 2g MD : 2g q12h - q8h* ** Higher dose for meningitis, VAP and febrile neutropenia*	2g q12h	2g q24h	1g q24h	HD: 1g 24h + 1g AD CVVH: 2g q12h CVVHD/CVVHDF: 2g q12h or 2g q8h*
Ceftazidime LD : 2g MD : 2g q8h - q6h* ** Higher dose range for Melioidosis*	2g q12h	2g q24h	1g q24h	HD: 2g q24hr + 1g AD CVVH: 2g q12h CVVHD/CVVHDF: 2g q12h or 2g q8h
Cefuroxime LD : 1.5g MD : 1.5g q8h	Unchanged	1.5g q12h	1.5g q24h	HD: 1.5g q24h† CVVH: 1.5g q8h - q12h

	Adjusted Maintenance Dose for Renal Impairment and Dialysis *Loading dose (LD) is required prior to Maintenance Dose (MD)*			
Drug / Normal Dose	**CrCl 30-50 ml/min**	**CrCl 10-30 ml/min**	**CrCl < 10 ml/min**	**Renal Replacement Therapy**
Ciprofloxacin LD : 400mg MD : 400mg q12h - q8h* ** Higher dose for P. aeruginosa infection*	Unchanged	400mg q24h - q12h	400mg q24h	HD: 400mg q24h† CVVH: 200mg-400mg q12h CVVHD/CVVHDF: 400mg q12h
Daptomycin MD : 10 mg/kg q24h	Unchanged	10mg/kg q48h	10mg/kg q48h	HD/CVVH/CVVHD/CVVHDF: 10mg/kg q48h
Doripenem LD : 500mg MD : 500mg q8h	250mg q8h	250mg q12hr	No data	HD: 500mg q12hr on Day 1 then 500mg q24h CVVH: 250mg q12h CVVHD/CVVHDF: 500mg q8h
Ertapenem LD : 1g MD : 1g q24h	1g q24h	500mg q24h	500mg q24h	HD: 500mg q24h† CVVH/CVVHD/CVVHDF: 1g q24h
Ethambutol 15 - 20mg/kg q24h	Unchanged	15-20mg/kg q48h	15-20mg/kg q48h	HD: 15-20mg/kg q48h† CVVH/CVVHD/CVVHDF: 15-20mg/kg q24h
Fluconazole Day 1: 800mg MD : 400mg - 800mg q24h* **Higher dose for certain fungal infections*	200mg - 400mg q24h			HD: 200mg - 400mg q24h† CVVH: 400mg q24h CVVHD/CVVHDF: 400-800mg q24h

	Adjusted Maintenance Dose for Renal Impairment and Dialysis *Loading dose (LD) is required prior to Maintenance Dose (MD)*			
Drug / Normal Dose	**CrCl** **30-50 ml/min**	**CrCl** **10-30 ml/min**	**CrCl** **< 10 ml/min**	**Renal Replacement Therapy**
Gentamicin	Refer Appendix C			
Imipenem LD : 1g MD : 1g q8h	500mg q6h	500mg q8h	500mg q12h	HD: 500mg q12h†; CVVH: 500mg q8h CVVHD/CVVHDF: 500mg q6h
Levofloxacin LD : 750mg MD : 750mg q24h	750mg q48h	500mg q48h	500mg q48h	HD: 500mg q48hr CVVH: 250mg q24h CVVHD: 500mg q24h CVVHDF: 750mg q24h
Meropenem LD : 1g - 2g MD : 1g - 2g q8h **higher dose for CNS infection, MDR organisims*	1-2g 12h	500mg - 1g q12h	500mg q12h - q24h	HD: 0.5g - 1g q24h + 250-500mg AD CVVH/CVVHD/ CVVHDF: 1g - 2g q12h
Oseltamivir 75mg q12h	75mg q24h	75mg q24h	No data	HD: 75mg q24h† CVVH/CVVHD/ CVVHDF: 75mg q12h

	Adjusted Maintenance Dose for Renal Impairment and Dialysis *Loading dose (LD) is required prior to Maintenance Dose (MD)*			
Drug / Normal Dose	**CrCl** **30-50 ml/min**	**CrCl** **10-30 ml/min**	**CrCl** **< 10 ml/min**	**Renal Replacement Therapy**
Piperacillin/Tazobactam LD : 4.5g MD : 4.5g q6h	4.5g q6h	4.5g q8h	2.25g q6h	HD: 2.25g q6h† CVVH: 2.25g q6h CVVHD/CVVHDF:4.5g q8h
Pyrazinamide 20 -30mg/kg q24h	Unchanged	20-30mg/kg q48h		HD: 20 - 30mg/kg q48h†
Streptomycin* 12 - 15mg/kg/dose q24h (Max dose 1g) **Dose range for Tuberculosis*	Unchanged	12-15mg/kg q48h	12-15mg/kg q48h	HD/CVVH/CVVHD/CVVHDF: 12-15mg/kg q48h
Trimethoprim/Sulfamethoxazole 5mg/kg q8h - q6h* (TMP component) **Higher dose for PCP*	5mg/kg q8h	5mg/kg q12h	5-10mg/kg q24h*	HD: 5-10mg/kg q24h*† CVVH/CVVHD: 5mg/kg q12h CVVHDF: 10mg/kg q12h
Vancomycin	Refer Appendix C			
Voriconazole Day1 : 6mg/kg q12h MD : 4mg/kg q12h	Crcl < 50 ml/min use oral formulation as carrier vehicle of IV formulation accumulates. BW > 40kg: 400mg q12h on Day 1, then 200mg q12h BW < 40kg: 200mg q12h on Day 1, then 100 mg q12h			HD/CVVH/CVVHD/CVVHDF: As per oral dosing in CrCl < 50ml/min

HD: hemodialysis CVVH: continuous venovenous hemofiltration CVVHD: continuous venovenous hemodialysis CVVHDF: continuous venovenous hemodiafiltration AD: after dialysis †Denotes drug that is dialysable however no clear recommendations for supplemental dosing. If HD is not significantly delayed, serve the dose after HD. If HD is significantly delayed consider serving dose as scheduled.

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Polymyxin E (Colistin)

Polymyxin is increasingly used as a last resort antibiotic to treat multi-drug resistant organisms like extreme-drug resistant *Acinetobacter baumanii* and carbapenem-resistant Enterobacteriaceae or *Pseudomonas aeruginosa*. It is a hydrophilic drug that has concentration-dependent with time-dependent kill characteristics.

Polymyxin E is available as Colistimethate Sodium (CMS) while its active drug is colistin. The following are some measures to optimise the use of polymyxin:

- Administer a loading dose as CMS conversion to Colistin is slow and incomplete.
- For isolates of MIC < 1mg/ml, target plasma concentration of 2mg/L is recommended.
- The main side effects are nephrotoxicity and neurotoxicity. The risk of nephrotoxicity must be balanced against the severity of infection and potential for treatment failure. Signs of neurotoxicity may not be apparent in ventilated patients.
- Beware of underdosing in patients with augmented renal clearance (CrCl > 130ml/min/1.73m^2 e.g. burns, sepsis, trauma).
- Combination therapy may need to be considered on case-to-case basis if MIC of organism is > 1mg/L in patients.
- Colistin is efficiently cleared by HD. On dialysis day, dialyse towards end of a dosage interval and administer a supplemental dose. On a non-HD day, dose as for creatinine clearance < 10ml/min.
- Colistin is also effectively cleared during CRRT hence the new higher dosing recommendations of 4 million units q8h (which averages about 0.5 million units/hour). This dose has been safely administered during CRRT using AN69 ST (Surface Treated) membrane filters (which has high colistin adsorption) with citrate anticoagulation. However use with other filters may shorten the filter life and lead to toxicity.

Loading Dose

Ideal Body Weight (kg)*	Loading Dose
> 75	9 million units
61-74	8 million units
51-60	7 million units
< 50	6 milliion units

*Refer Appendix E for IBW calculation

Maintenance Dose

Creatinine Clearance (ml/min)	Maintenance Dose (MD) in million units (MU)	Starting time of MD after LD (hours)
> 50	4.5 MU q12h	12
30-50	3 MU q12h	12
10-30	2.5 MU q12h	12
< 10	2 MU q12h	12
CVVH/CVVHDF	4 MU q8h* ***IMPORTANT:** Cease this dosing regimen when CVVH stops to prevent toxicity	8
HD	2MU q12h + 1.5 MU AD	8
SLED 4 hour SLED 6 hour	2 MU q12h + 1.5 MU after SLED 2 MU q12h + 2.5 MU after SLED	8

Sulbactam

In Ampicilin/Sulbactam (Unasyn), the ratio of ampicillin to sulbactam is 1:0.5

	Estimated creatinine clearance (ml/min)			Renal Replacement Therapy	
	> 50	20-50	< 20	HD	CVVH/CVVHD/CVVHDF
Sulbactam	9g/day	6g/day	4g/day	4g/day	9g/day
Ampicillin/Sulbactam (Unasyn)	9g q8h	6g q8h	6g q12h	6g q12h	9g q8h

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APPENDIX B
DOSAGE ADJUSTMENT FOR HYPOALBUMINAEMIA

Recommendations for dosing highly protein-bound antibiotics in patients with hypoalbuminaemia (serum albumin < 30g/L)

Antibiotic	Standard ICU dosing	Recommended Loading Dose	Recommended Maintenance Dose
Ertapenem	1g q24h	2g	Increase frequency of administration: 1g q12h
Ceftriaxone	1g q12	2g	Increase frequency of administration: 1g q8h
Cloxacillin	2g q4h	2g	Consider continuous infusion: 12g q24h
Vancomycin	1g q12h (15-20mg/kg q12h)	20-30mg/kg	Increase dosing: 1.5g q12h Or consider continuous infusion (e.g. 3g q24h) Monitor trough concentrations to target concentrations > 15mg/L

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APPENDIX C
THERAPEUTIC DRUG DOSING AND MONITORING

GENTAMICIN IN ENDOCARDITIS

CrCl (ml/min)	Dose and interval*
> 60	1mg/kg q8h or 3mg/kg q24h
40-60	1mg/kg q12h or 2 mg/kg q24h
20-40	1mg/kg q24h
< 20	1mg/kg q24h then redose when trough level < 1mg/L
HD	1mg/kg q24h then redose when trough level < 1mg/L
CVVH/CVVHD/CVVHDF	Loading dose 3mg/kg followed by 1mg/kg q24h

*Use actual BW if malnourished and adjusted BW if > 20% ideal BW. In others, use ideal BW. Refer **Appendix E** for BW formulae.

Initial assay: Trough and peak with 3rd dose

Repeat assay: Every 3-7 days or more frequent if changing renal profile

Sampling time: Trough: ½ hour before next dose
Peak: 30 mins after completion of 30 mins infusion

Target serum concentration (mg/ml):	Trough (< 1mg/L) and peak (10-12mg/L)
Dose adjustment / Interpretation:	Consult pharmacist

Aminoglycoside (high dose extended interval dosing/single daily dosing)

Exclusion criteria:	- Age < 13 - Burns > 20% - Ascites - Synergistic dosing for gram-positive infections (e.g. endocarditis) - History of ototoxicity - Pregnancy
Initial dose:	Gentamicin: 7mg/kg Amikacin: 15mg/kg (Use actual BW if malnourished and adjusted BW if > 20% ideal BW. In others, use ideal BW. Refer **Appendix E** for BW formulae)
Initial assay:	Single assay 6-14 hours after infusion of first dose. Peak and trough serum levels are not routinely done.

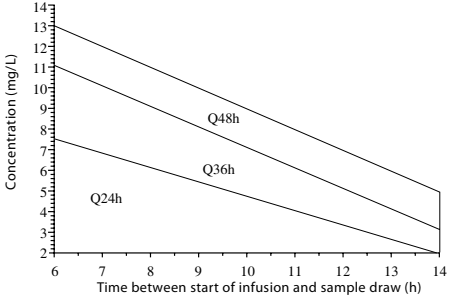
Repeat assay: Once weekly or more frequent in patients requiring q36h or q48h dosing, changing renal function or on other nephrotoxic drugs.

Dosing interval following 1st dose: For gentamicin, plot concentration on the Hartford nomogram below to determine the dosing interval. If the level:

- falls on a borderline, use the longer interval.
- falls above the q48h dosing interval, reevaluate the need for continued therapy
- is < 2 µg/ml, and continue current regimen if the patient is clinically stable or improving. If not, re-evaluate clinical situation (e.g. repeat level, change to traditional dosing, change antibiotics)

For amikacin, divide the measured concentration by 2 before plotting on the nomogram to determine the dosing interval.

Hartford Hospital High Dose Extended Interval Aminoglycoside Nomogram



Applicable only to gentamicin dosing of 7mg/kg (or amikacin 15mg/kg)

Unit: mg/L = ug/ml

Vancomycin

Loading Dose: 15-20mg/kg/dose or 25-30mg/kg/dose in severely ill (Use actual BW. Refer Appendix E for BW formulae.) (Not to exceed 2g per dose, infusion rate max 1g per hour to avoid Red Man Syndrome)

Maintenance dose: 15-20mg/kg/dose (Use actual BW Refer **Appendix E** for BW formulae.)

Dosing interval (Based on creatinine clearance):

CrCl (mL/min)	Dosing Interval
> 50	q12h
30-50	q24h
< 30	Need longer intervals, determine by serum concentration monitoring
Haemodialysis	Following loading dose of 15-20mg/kg, given 500mg to 1000mg after each dialysis session.
CVVH	1g every 48 hours or 500mg every 24hours
CVVHD/CVVHDF	1g every 24 hours

Initial assay: Normal renal function: After 3rd dose
Impaired renal function: After 24 hours

Repeat assay: Once weekly monitoring in hemodynamically stable patients. More frequent or daily monitoring in patients who are hemodynamically unstable and changing renal function.

Sampling time:	**Trough:** Regular interval dosing: just before next dose Stat/Intermittent dosing: Random level: 12-36 hours after stat dose Peak: not recommended due to extreme inter-patient variability and lack of correlation with either efficacy or toxicity
Target serum concentration:	Trough: 10-15 µg/ml in conditions other than listed below 15-20 µg/ml in bacteremia, endocarditis, osteomyelitis, meningitis, pneumonia
Dose adjustment: (Based on trough concentration)	If level is < 10µg/ml (or < 15µg/ml in target levels of 15-20µg/ml), decrease the dosing interval by one step, in steps of q12h, q24h, q36h, and q48h. If receiving the dose q12h, increase the dose by 250-500mg or consider q8h. If the trough level is > 15µg/ml (or > 20µg/ml if target level is 15-20µg/ml), increase the dosing interval by one step.

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APPENDIX D
EXTENDED OR CONTINUOUS INFUSIONS OF ß-LACTAMS

The use of extended or continuous infusions of ß-lactam antibiotics has been shown to improve the time the free drug remains above MIC which predicts the killing characteristic of the antibiotic. This is pertinent when dealing with multi-drug resistant organisms. A loading dose must be given prior to regular dosing of the antimicrobial followed by either:

- Extended infusion: Infusion lasting 3-4 hours, usually 50% of dosing interval.
- Continuous infusion: Infusion over 24 hours at a fixed rate.

The diluted antibiotic should be stable throughout the infusion duration at room temperature of less than 24°C and has no incompatibilities with other medication administered concurrently. The stability may differ with different manufacturers.

Antibiotic	Loading dose over 30mins	Duration of infusion	Notes
Ampicillin/ Sulbactam* **For high dose sulbactam*		Extended over 4 hours	3g of ampicillin/sulbactam dilute in 70mls of normal saline or dextrose 5%.
Cefepime	2g	Extended over 4 hours Or Continuous infusion over interval prescribed	1 or 2g of cefepime in 50mls normal saline.
Ceftazidime	2g	Extended over 4 hours Or Continuous infusion over interval prescribed	1-2g dilute in 50mls normal saline.
Doripenem	500mg	Extended over 4 hours	500mg: dilute in 50mls normal saline.
Imipenem	1g q8h	Extended over 4 hours	500mg or 1g: dilute in 100-200mls normal saline (5mg/ml).
Meropenem	1-2g	Extended over 4 hours	500mg or 1g: dilute in 50mls normal saline. 2g: dilute in 100mls normal saline.
Piperacillin/ Tazobactam	4.5gm	Extended over 4 hours Or Continuous infusion over interval prescribed	2.25g or 4.5g: dilute in 50mls normal saline.

APPENDIX E
DRUG DOSING IN THE OBESE (BMI > 30kg/m^2)

Obese patients have a significant increase in fat mass as well as a smaller increase in lean tissue. This can make it difficult to determine a dosing weight for an obese patient. A number of different body weights (BW) are used for different purposes (actual, ideal and adjusted BW). Some antibiotics have sufficient data to be able to make recommendations, whereas others may need to use doses at the upper end of the recommended range or use modifications based on pharmacokinetic/pharmacodynamic principles. In obese patients:

- Oral bioavailability does not change.
- For hydrophilic drugs, generally no change in volume of distribution (V_d) since they have limited distribution in body fat, hence loading dose is unaffected. For lipophilic drugs, there are large increases in V_d and larger loading doses are required.
- The renal and hepatic clearance of many drugs is increased. However, patients with severe fatty infiltration of liver have poor hepatic function and reduced drug clearance. For drugs with increased clearance, maintenance dose should be based on adjusted body weight.
- Creatinine clearance using the Cockcroft and Gault formula is calculated base on adjusted body weight. Alternative calculation for CrCl is the CKD-EPI (Chronic Kidney Disease Epidemiology Collaborative) equation with the removal of body surface area nomalisation.

Abbrev.	Definition	How to estimate	Application
ABW	Actual body weight	Weigh patient	Loading dose for lipophilic drugs.
IBW	Ideal body weight	Male: 50 + [0.91 x (height{cm} - 152.4)	Maintenance dose of drugs where clearance is unchanged in obesity
AdjBW	Adjusted body weight (Estimate of fat free mass)	Female: 45.5 + [0.91 x (height{cm} - 152.4) IBW +[0.4 x (ABW - IBW)]	Maintenance dose of drugs with increased clearance in obesity

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

		Weight used for dosing			Remarks
No	**Drug**	**IBW**	**ABW**	**AdjBW**	
1	IV Acyclovir	√			
2	IV Amikacin	√			BMI ≥ 40kg/m^2: use AdjBW, followed by TDM-based dose adjustment. Consider capping at 2-2.5g per dose.
3	IV Amphotericin B		√		Both conventional & liposomal products.
4	IV Ampicillin		√		Use upper end of recommended doses or use more frquently.
5	IV Benzylpenicillin				Use higher end of recommended dose. (3-4MU q4-6h) in severe infections.
6	IV Cefazolin		√		Use a 2g per dose in adult obese patients.

		Weight used for dosing			Remarks
No	**Drug**	**IBW**	**ABW**	**AdjBW**	
7	IV Ceftriaxone				Use higher end of recommended dose. Loading dose 2g followed by 2g q12h.
8	IV Ciprofloxacin			√	4-5mg/kg/dose. It is also suggested that 600mg q12h is better than 400mg q8h Doses of 800mg q12h in morbid obesity have been used.
9	IV Clindamycin				Serious infection: 600mg - 1.2g in divided 2-4 divided doses. In life threatening infections - use doses up to 4.8g daily in divided doses (1200mg q6h). Doses of < 10mg/kg/24h have been shown to worsen outcomes in morbidly obese.
10	IV Colistimethate (Polymyxin E)	√			Refer to **appendix A**.
11	IV Daptomycin		√		
12	Oral Ethambutol		√		Max daily dose 1.6g.
13	IV Fluconazole		√		Based on higher end of 6-12mg/kg.
14	IV Flucytosine	√			
15	IV Ganciclovir			√	

		Weight used for dosing			Remarks
No	**Drug**	**IBW**	**ABW**	**AdjBW**	
16	IV Gentamicin			√	AdjBW used for initial dose followed by TDM-based dose adjustment.
17	Oral Isoniazid	√			Max daily dose 300mg.
18	IV Linezolid	√			Patients weighing ≤ 150kg, use 600mg q12h. Sufficient for treating skin & soft tissue infections.
19	IV Metronidazole				Use standard dosing. Doses up to 7.5mg/kg (up to 1g) q6h can be used for treatment of anaerobic bacterial infections.
20	IV Meropenem				Use standard dosing, however consider dosing of upper end of recommended dose e.g. 2g q8h.
21	IV Piperacillin/Tazobactam		√		Give as continuous infusion especially for isolates with high MIC.
22	Oral Pyrazinamide		√		Max 2g/day.
23	Oral Rifampicin	√			Max daily dose 1.2g.
24	IV/IM Streptomycin	√			Max daily dose 1g.
25	IV Trimethoprim / Sulfamethoxazole			√	Use AdjBW if > 20% ideal BW. In others, use ideal BW.

		Weight used for dosing			Remarks
No	**Drug**	**IBW**	**ABW**	**AdjBW**	
26	IV Vancomycin		√		ABW used for initial dose followed by TDM-based dose adjustment. May need to shorten interval to maintain increased trough level of 15-20mg/L e.g. q8h.
27	IV Voriconazole			√	Use IBW or Adj BW in morbidly obese.
28	IV Anidulafungin IV Doripenem IV Ertapenem				Use standard dosing.

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