The MSA Guide To Antimicrobial Therapy In Adult ICU

By
Intensive Care Section
Malaysian Society of Anaesthesiologists

September 2006

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FOREWORD

Antimicrobial therapy is an integral part of the intensive care management. Choosing the appropriate empiric antimicrobials in the severely septic patient remains a challenge as the appropriate selection and timely administration of antimicrobials in these patients have major impact on outcome. The rational use of antimicrobials has also shown to reduce the emergence of multidrug-resistant micro-organisms which is of an increasing problem in the intensive care units.

The aim of this guide is to provide a bedside reference on antimicrobial therapy for our local doctors managing the critically ill adults in the intensive care units. In preparing this guide, the experts have included the common infections seen in our units and have also taken into consideration the local susceptibility patterns of the micro-organisms and the antimicrobials available in Malaysia. I hope with the availability of this guide, antimicrobial therapy in patients in our intensive care units can be standardised on current evidenced-based practice.

The Intensive Care Section of the Malaysian Society of Anaesthesiologists has strived to advance the practice of intensive care in Malaysia and this guide represents one of the many efforts initiated by the section. This guide is prepared by a group of intensivists with vast clinical experience managing the critically ill adults.

I am grateful to these experts who had selflessly shared their time and expertise to produce this guide. I thank the panel of expert reviewers who had provided useful comments and suggestions to further improve on it.

Finally, I thank our sponsors, Wyeth (Malaysia) and Pfizer (Malaysia) for their financial assistance, secretarial support and the printing of this guide.

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INTRODUCTION TO SEVERE SEPSIS IN THE INTENSIVE CARE UNIT

There has been a substantial increase in the incidence of sepsis during the past 22 years, with an increasing number of deaths occurring despite a decline in overall in-hospital mortality. The mortality for patients with severe sepsis ranges from 20% to 50%. It is the second leading cause of death among patients in non-coronary intensive care units (ICUs) and the tenth leading cause of overall deaths in the United States. Furthermore, sepsis substantially reduces the quality of life of those who survive.

In Malaysia, sepsis is the leading cause of admission to the ICUs. In 2005, sepsis accounted for 26.8% of all ICU admissions.

Demographics

Over the last three decades, the average age of patients with sepsis had increased from 57 years to 60 years. The female patient tended to develop sepsis later in life when compared to male patients (mean age 62.1 vs. 56.9 years). Although men accounted for 48.1% of cases of sepsis on average per year, adjustment for sex in the population of the United States revealed that in every year, men were more likely to have sepsis than women (mean annual relative risk 1.28).

Causative Organisms

Studies from Northern America and Europe showed that from the mid-80's till now, the frequency of Gram-positive sepsis (mainly *S. aureus*, coagulase-negative staphylococci, enterococci, and streptococci) has equaled or even surpassed that of Gram-negative sepsis (mainly enterobacteriaceae especially *E. coli, K. pneumoniae* and *P. aeruginosa*). The incidence of fungal sepsis has increased three-fold between 1979 and 2000. Currently, fungi (mainly candida) account for about 5% of cases.

The predominant sites of infections are the lungs, bloodstream, abdomen, urinary tract and skin and soft tissues.

Patient outcomes

In 1979, 78.5% of surviving patients were discharged home but decreased to 56.4% in 2000. Concurrently, the rate of discharge to other health care facilities (e.g. rehabilitation centres or other long-term care facilities) increased from 16.8% to 31.8%. Over time, significantly more patients had hospitalisations of fewer than 7 days, and significantly fewer patients stayed in the hospital more than 30 days.

An audit carried out in 2002 on nosocomial infections in the ICU in Hospital Universiti Kebangsaan Malaysia showed an increase in the average length of stay in the infected patients when compared to the non-infected (13.0±12.4 vs. 3.0±2.8 days).

Organ Failure and Mortality

On a positive note, the mortality rates in these groups of patients have declined over the last two decades, currently averaging 17.9%. Despite the improved survival rates, the increasing incidence of sepsis resulted in nearly a tripling of the number of in-hospital deaths related to sepsis (21.9 in 1979 to 43.9 per 100,000 populations in 2000).

The proportion of patients with sepsis who had organ failure increased over time, from 19.1% to 30.2%. Organ failure had a cumulative effect on mortality: approximately 15% of patients without organ failure died, while the mortality in patients with three or more failing organs was 70%. The organs that failed most frequently in patients with sepsis were the lungs (18%) and kidneys (15%); less frequent were cardiovascular (7%), haematologic (6%), metabolic (4%), and neurologic (2%) failure.

Conclusion

The critically ill patient diagnosed with severe sepsis or septic shock remains one of the greater challenges faced by the intensivist in his or her day-to-day work. The outcome of these challenges has direct and indirect impact and implication on the patients themselves, their family and the community. These outcomes may be in the form of increase antimicrobial use with subsequent increase in resistant micro- organisms, increase in cost and debatable quality of life issues.

In the United States, care of patients with sepsis costs as much as US$50,000 per patient, resulting in an economic burden of nearly US$17 billion annually. In Malaysia, such figures are not readily available but it is highly presumed not to be far off from those quoted from other countries.

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PRINCIPLES OF EMPIRICAL ANTIMICROBIAL THERAPY

Introduction

Severe sepsis presents a diagnostic and management challenge to those who care for the critically ill. Besides aggressive fluid resuscitation, vasopressor therapy and support of the failing organ systems, management of the infection responsible for severe sepsis should focus on two important issues: the use of appropriate antimicrobial therapy and adequate source control of infection.

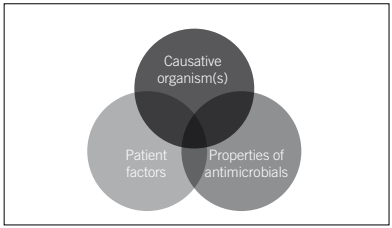
In severe sepsis, the site of infection and the causative organism is often not known. Empirical antimicrobial therapy must be started in these cases, guided by the knowledge of the most likely site of infection and the most common infecting organisms. Antimicrobials should be started within the first hour of recognition of severe sepsis as appropriate empirical antimicrobial has been shown to reduce morbidity and mortality. Microbiological specimens including blood cultures should be obtained before commencing therapy whenever possible.

Indiscriminate use of antimicrobials can lead to the emergence of resistant organisms, risk of antimicrobial-related adverse events and increase in healthcare costs.

Therefore, the use of antimicrobials requires rational prescribing and be as evidence-based as possible.

When initiating appropriate empirical antimicrobials in patients with severe sepsis, one has to consider the following factors:

1. Causative organism(s)
2. Patient factors
3. Properties of antimicrobials



Factors influencing the choice of antimicrobial

Factors influencing the choice of antimicrobial

1. **Causative organism**
   - *Decide if it is community or hospital-acquired infection*
   - *Identify the most likely source of infection*
     Attempt to identify the site of infection whenever possible. Take appropriate specimens e.g. from blood, urine, respiratory tract, wound for microscopy, culture and sensitivity testing. Imaging modalities e.g. radiography, ultrasonography or CT scan may be necessary in attempts to locate the source of infection.
   - *Local epidemiological data on potential organisms*
     Empiric antimicrobial choice depends on local susceptibility patterns of the micro-organisms. Knowing the resistance profiles in the community, hospital or unit helps in choosing antimicrobials appropriately.
2. **Patient factors**
   - *Severity of illness*
     Patients in severe sepsis or septic shock need immediate antimicrobial therapy when compared to patients with suspected minor bacterial infection who can await laboratory confirmation.
   - *Prior antimicrobial use or prolonged hospitalisation*
     Both are risk factors for the presence of resistant organisms.

- *Immunosuppressive states*
  Patients who are malnourished, have underlying malignancy or on steroids or immunosuppressive drugs may require broad-spectrum antimicrobial including antifungal.

- *Presence of renal or hepatic dysfunction*
  The risk-benefits of the antimicrobial must be determined on a case-to-case basis in these groups of patients.

- *Others e.g. pregnancy, drug allergy*

3. Antimicrobial profile

- *Route of administration*
  The intravenous route should always be used when initiating empirical antimicrobial in patients with severe sepsis or shock as oral absorption is unpredictable even in drugs with good oral bioavailability.

- *Dose and interval*
  Knowledge on pharmacodynamic principles i.e. time-dependent or concentration-dependent effect of an antimicrobial improves efficacy.

- *Achievable antimicrobial concentrations in tissue*
  Tissue penetration of antimicrobial has to be considered when treating infections. Certain antimicrobials may not penetrate to the site of infection e.g. vancomycin and aminoglycosides have poor lung tissue penetration. Antimicrobials often do not penetrate abscess cavities and require drainage.

- *Bactericidal or bacteriostatic*
  Bacteriostatic drugs should not be used in endocarditis or meningitis or immunosuppressed patients. There is decreased complement level and lack of surface phagocytosis in meningitis and neutropenia. Vegetations are impermeable to leucocytes.

- *Monotherapy or combination*
  Monotherapy with a beta-lactam is as efficacious as combination therapy with an aminoglycoside in patients with severe sepsis.

Combination therapy may be necessary if:

a. need to broaden antimicrobial coverage in life-threatening conditions when the source is not yet identified or in the immunosuppressed
b. need synergism against infecting pathogen e.g. penicillin and gentamicin in treating infective endocarditis

- *Adverse events*
  Risk-benefits 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*
  Avoid antimicrobial with known potential for selecting resistant organisms and associated risk of superinfection.

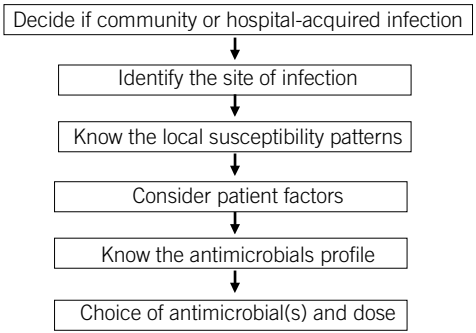
Empiric therapy should be re-evaluated when culture results become available or after 48-72 hours. Once a causative pathogen is identified, restrict the number of antimicrobials and narrow the spectrum of antimicrobial therapy.

If the patient is improving, the duration of antimicrobial therapy is usually for 7 to 10 days. There is increased resistance with prolonged use of antimicrobial. Shorter duration of antimicrobial has been shown to be equally effective in some studies. Consider switching to the oral route of administration for antimicrobials with good oral bioavailability whenever possible.

Certain conditions may require prolonged therapy e.g. *P. aeruginosa* sepsis for 2 weeks, infective endocarditis for 6 weeks, and deep-seated *S. aureus* infections for 4 weeks.

If there is no clinical response within 48-72 hours, consider:

- the possibility of a secondary infection
- the presence of resistant organisms
- abscesses, collections of pus that are not drained or infected foreign bodies that are not removed
- inadequate penetration of antimicrobial to the site of infection
- inadequate spectrum of antimicrobial coverage
- inadequate dose / 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.



Pathway in choosing the empiric antimicrobial

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MICROBIOLOGICAL INVESTIGATIONS

Identification of causative organisms is central to effective antimicrobial therapy. Appropriate cultures should always be obtained before commencing antimicrobials.

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

Blood culture

The volume of blood determines the yield of positive result in blood culture. A minimum of 20 ml of blood should be drawn; 10 ml for each aerobic and anaerobic bottle. Increasing the volume to 40-60 ml (obtaining 2-3 sets of 20 ml of blood, 10 ml per bottle) has been shown to increase the yield further. However, there is no evidence to support the practice of serial cultures. No difference in yield was shown between multiple cultures taken simultaneously and those obtained at intervals.

In the presence of a vascular access device that was inserted more than 48 hours ago (particularly central venous catheter, CVC), at least 2 sets of blood cultures should be taken. One set is drawn peripherally and another through the vascular access device.

Either one of the following will suggest catheter-related bloodstream infection:

- simultaneous quantitative cultures of blood samples with a ratio of ≥ 5:1 (CVC vs. peripheral)
- differential time to positivity i.e. a positive result of culture from a CVC is at least 2 hours earlier than is a positive result of culture from the peripheral site

Patients suspected to have ventilator-associated pneumonia should have blood taken for culture. An extrapulmonary site of infection should be considered when the respiratory culture is negative in the absence of recent change in antibiotic therapy while the blood culture is positive.

Respiratory specimen

The quality of sputum and tracheal aspirate specimens can be determined by low power field, lpf (100x) examination of epithelial and pus cells.

Epithelial cells, /lpf	Pus cells, /lpf	Comments
< 10	> 25	Good specimen
10-25	> 25	Detect predominant pathogens only
<25	< 25	Equivocal
>25		Poor specimen, to send another specimen

Most laboratories report the results of sputum and tracheal aspirate cultures semi-quantitatively; either as light, moderate or heavy growth.

Respiratory specimens can also be obtained invasively by performing bronchoalveolar lavage (BAL) or protected specimen brushing (PSB). Both specimens need to be analysed quantitatively based on the number of colony forming units (cfu). The diagnostic threshold for BAL is 10^4 or 10^5 cfu/ml and for PSB is 10^3 cfu/ml. A lower threshold value, 10^3cfu/ml for BAL and 10^2cfu/ml for PSB, may be required in patients who currently have VAP or were recently on antimicrobial therapy.

Urine specimen

Most cases of urinary tract infection (UTI) can be diagnosed using the criteria below. However, bacterial density as low as 10^2 cfu/ml may be significant in cases of partially treated UTI or over hydration.

Bacteria	No. cfu on media	Bacterial density cfu/ml	Interpretation
Gram- positive or Gram- negative	1 - 4	$< 10^4$	not significant
	5 - 25	10^4 - 10^5	equivocal
	> 25	$> 10^5$	significant

The following are positive indicators of active infection:

- positive nitrite test
- > 10 leucocyte/hpf (only in non-catheterised)
- positive leucocyte esterase test (only in non-catheterised)

Polymicrobic bacteriuria (presence of two or more culture isolates) may indicate faulty collections and/or transport, presence of indwelling catheters or anatomical abnormalities of the urinary tract. When the densities of the different isolates are $< 10^4$ cfu/ml, contamination is very likely. For isolates with densities of $> 10^4$ cfu/ml, UTI is possible and a repeat urine culture is advocated. The decision to treat with antimicrobials should be based on clinical judgement.

Urine specimen should be sent to the laboratory within 2 hours of collection, otherwise it would need to be stored at 4°C.

Cerebrospinal fluid specimen

Lumbar puncture should not delay empirical antimicrobial therapy. A CT scan is required when the patient has abnormal level of consciousness, presence of focal neurological involvement, papilloedema, risk factors for HIV/AIDS or malignancy.

Routine cerebrospinal fluid (CSF) analysis includes microscopic and biochemistry examination, Gram stain, Ziehl-Neelsen stain, India ink test and culture. Rapid latex agglutination test can be performed to detect the presence of certain bacterial antigens in the CSF. The test can qualitatively detect antigens from *S. pneumoniae*, group B Streptococcus, *H. influenzae* type B, *N. meningitidis* group A, B, C, Y or W 135 and *E. coli* K1. A negative test does not rule out infection caused by a specific pathogen. Another useful test is Cryptococcal antigen testing, which is more sensitive than India ink test in the detection of *Cryptococcus neoformans*.

Biochemical markers

Circulating levels of certain biomarkers like procalcitonin and C-reactive protein are consistently increased in sepsis. This biochemical feature has now been used in diagnosing sepsis and monitoring response to therapy.

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COMMUNITY-ACQUIRED PNEUMONIA (CAP)

CAP is associated with significant morbidity and mortality, particularly in the elderly. 10% of patients who are admitted to hospital with diagnosis of CAP will require management in the ICU and the mortality in this group is between 20% to 50%.

The common organisms are *S. pneumoniae*, *H. influenzae*, *S. aureus*, *K. pneumoniae* and atypical micro-organisms. Aetiologic pathogens remain unidentified in up to 50% of cases. It is not a routine to cover for anaerobes unless the patient is at risk for aspiration.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
S. pneumoniae *H. influenzae* *S. aureus* *K. pneumoniae*	IV Ceftriaxone 2g q24h	IV Amoxycillin / clavulanate 1.2g q8h	
	PLUS	PLUS	
M. pneumoniae *L. pneumophilia* *C. pneumoniae*	IV Erythromycin 500mg q6h OR IV Azithromycin 500mg q24h	IV Erythromycin 500mg q6h OR IV Azithromycin 500mg q24h	

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
P. aeruginosa	IV Cefepime 2g q12h OR IV Piperacillin / tazobactam 4.5g q6h PLUS IV Ciprofloxacin 400mg q8h OR IV Amikacin 15mg/kg/day	IV Imipenem 500mg q6h OR IV Meropenem 1g q8h PLUS IV Ciprofloxacin 400mg q8h OR IV Amikacin 15mg/kg/day	Risk factors are severe structural lung disease (e.g. bronchiectasis), recent antibiotic therapy or stay in hospital
Burkholderia pseudomallei	Refer to chapter on melioidosis, page 55		Risks factors are diabetes mellitus,chronic renal failure, chronic lung disease.
Methicillin-resistant *S. aureus*	IV Vancomycin 1g q12h	IV Linezolid 600mg q12 h	Refer to MRSA infections, page 76

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Pneumocystis carinii (*Pneumocystis jiroveci*)	IV Trimethoprim / sulfamethoxazole (trimethoprim comp. 15mg/kg/day) q8h x 21 days	IV Pentamidine 4mg/kg/day x 21 days	Prednisolone should be given 15-30 min. before antimicrobials. PO Prednisolone 40mg q12h x 5days then 40mg q24h x 5days then 20mg q24h x 11days

Since atypicals such as *M. pneumoniae* and Legionella are rarely diagnosed, combination treatment for typical and atypical pathogens should generally be for 7–10 days. The American Thoracic Society guidelines suggest that antimicrobials can be stopped when patient is afebrile for 72 hours.

If there is no response, consider other possible diagnosis e.g. congestive heart failure, pulmonary embolism, neoplasm, sarcoidosis, drug reaction, pulmonary haemorrhage and empyema. Also consider other causative micro-organisms e.g. mycobacteria, fungi and viruses.

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EMPYEMA

An empyema is collection of pus in the pleural space. Chest tube, video-assisted thoracoscopy or surgical drainage is the mainstay of treatment. In a large multi-centre, double-blind trial, intrapleural streptokinase did not improve mortality, the rate for surgery or the length of hospitalisation among patients with pleural infection.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Acute, usually parapneumonic			
S. pneumoniae Group A *Streptococcus* *H. influenzae*	IV Ceftriaxone 2g q24h OR IV Cefotaxime 2g q8h		Pleural fluid pH < 7.2 is highly suggestive of complicated parapneumonic effusion and hence requires drainage
S. aureus	IV Cloxacillin 1- 2 g q4h	IV Vancomycin 1g q12h (if MRSA)	

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Subacute or chronic			
Anaerobic Streptococci Bacteroides Enterobacteriaceae	IV Piperacillin / tazobactam 4.5g q8h OR IV Ampicillin / sulbactam 1.5g q6h	IV Imipenem 500mg q6h OR IV Meropenem 1g q8h OR IV Clindamycin 450-900mg q8h PLUS IV Ceftriaxone 2g q24h	If organisms are not identified, treat as subacute. Need to rule out tuberculosis or tumour.

Antimicrobial should be continued until patient is afebrile, WBC count is normal, chest tube drainage yield is < 50 ml/day and chest radiography shows considerable clearing. Normally, 7–14 days of antimicrobial therapy is required in empyema caused by *H. influenzae* or *S. pneumoniae*; and 3–4 weeks in *S. aureus* empyema. Duration of therapy for anaerobic empyema is variable and may be for as long as 6–12 weeks.

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HOSPITAL-ACQUIRED PNEUMONIA (HAP), VENTILATOR-ASSOCIATED PNEUMONIA (VAP) AND HEALTHCARE-ASSOCIATED PNEUMONIA (HCAP)

HAP is defined as pneumonia that occurs 48 hours or more after hospitalisation while VAP is pneumonia that occurs after 48–72 hours following intubation.

HCAP is defined as pneumonia in any patient who has been admitted to an acute care hospital for ≥2 days of the preceding 90 days; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy within the past 30 days; or attended a hospital or haemodialysis clinic.

The duration of hospitalisation prior to the onset of pneumonia is one of the most important determinants of potential pathogens in HAP. Patients with mild-to-moderate disease presenting < 5 days after hospitalisation generally have a better prognosis and the infecting micro-organisms are more likely to be antibiotic-sensitive.

Late-onset HAP and VAP (occurring > 5 days after hospital admission) are more likely to be caused by multidrug-resistant (MDR) micro-organisms and is associated with increased hospital mortality and morbidity. (For risk factors associated with MDR micro-organisms, refer to page 72)

The causative organisms in pneumonia may be polymicrobial. Empiric therapy should cover a wide range of Gram-positive and Gram-negative organisms as the initial antimicrobial therapy is the most important determinant of outcome.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Without risk factors for infection with MDR pathogens			
S. pneumoniae *H. influenzae* *S. aureus* *E. coli* *K. pneumoniae* *Enterobacter spp.* *Proteus spp.* *Serratia marcescens*	IV Ceftriaxone 2g q24h OR IV Ampicillin / sulbactam 1.5g q6h	IV Amoxycillin / clavulanate 1.2g q8h	*S. aureus* is more common in diabetes mellitus, head trauma. Monotherapy is recommended for early onset HAP / VAP / HCAP.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
With risk factors for infection with MDR pathogens			
P. aeruginosa **Acinetobacter spp.* **K. pneumoniae* (ESBL)	IV Piperacillin / tazobactam 4.5 g q6h OR IV Cefepime 2 g q12h PLUS IV Amikacin 20 mg/kg /day OR IV Ciprofloxacin 400mg q8h	IV Imipenem 500mg q6h OR IV Meropenem 1g q8h PLUS IV Amikacin 20 mg/kg /day OR IV Ciprofloxacin 400mg q8h	Use combination therapy if MDR pathogen is suspected. Duration of therapy is 7 days unless treating. *P.aeruginosa* or *Acinetobacter spp.*
Methicillin-resistant *S. aureus*	PLUS (if MRSA is suspected) IV Vancomycin 1g q12h	PLUS (if MRSA is suspected) IV Vancomycin 1g q12h OR IV Linezolid 600mg q12h	Aminoglycoside can be stopped after 5-7 days in patients on combination therapy who are responding to treatment

*The preferred antimicrobials for the following micro-organisms:

- *Acinetobacter spp.* : Cefoperazone/sulbactam or Ampicillin / sulbactam
- *K. pneumoniae* (ESBL) : Carbapenem

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ASPIRATION PNEUMONIA

The usual causative organisms in aspiration pneumonia are those that colonise the oropharynx. In community-acquired cases, is most likely to develop as a result of aspiration of anaerobic bacteria originating in the oropharynx. 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.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Community-acquired			
Oral anaerobes *S. pneumoniae* *H . influenzae* *M. catarrhalis*	IV Ceftriaxone 2g q24h	IV Amoxicillin / clavulanate 1.2g q8h	Oral anaerobes are sensitive to all beta-lactams and most antimicrobials used to treat CAP. Additional anaerobic (*B. fragilis*) coverage is not needed. Treat for 7-10 days in patients who respond promptly.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Community- acquired with lung abscess			
Anaerobes Gram-positive cocci *S. milleri* *K. pneumoniae* Nocardia	IV Piperacillin / tazobactam 4.5g q6h	IV Ceftriaxone 2g q24h PLUS IV Metronidazole 500mg q8h	Extend therapy to 14-21 days in highly resistant pathogens (*P. aeruginosa* or *Acinetobacter spp.*). Patients with cavitary pneumonia or lung abscess require long-term treatment (4-8 weeks)
Hospital-acquired			
Gram-negative bacilli *S. aureus* Anaerobes	IV Piperacillin / tazobactam 4.5g q6h OR IV Cefepime 2g q12h PLUS IV Metronidazole 500 mg q8h	IV Imipenem 500mg q6h OR IV Meropenem 1g q8h	

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URINARY TRACT INFECTION (UTI)

Most UTIs are uncomplicated cystitis caused by *E. Coli* in otherwise young healthy women and are easily managed with short term oral antimicrobials. In contrast, complicated UTIs are often associated with the risk of treatment failure.

Asymptomatic bacteriuria

Asymptomatic bacteriuria (ASB) is defined as the presence of $> 10^5$ cfu/ml of one or more pathogens in 2 consecutive mid-stream urine specimens or in a catheterised urine specimen in the absence of symptoms.

The recommended screening test for ASB is urine culture. Screening and treatment for ASB should be carried out in the following patients:

1. before genitourinary manipulation or instrumentation
2. first 6 months post renal transplant
3. diabetes mellitus with poor glyceamic control, autonomic neuropathy or azotemia
4. pregnancy

Complicated urinary tract infection

Complicated UTI is significant bacteriuria occurring in any of the following conditions:

1. presence of indwelling catheter or intermittently catheterised
2. incomplete emptying of bladder with > 100 mls of retained urine post voiding
3. obstructive uropathy
4. vesico-ureteric reflux and other urologic abnormalities including surgically created abnormalities
5. azotemia due to intrinsic renal disease

6. renal transplantation
7. diabetes mellitus
8. immunosuppressed e.g. febrile neutropenia / HIV
9. UTI caused by unusual pathogens or drug resistant pathogens
10. UTI in males (except young males with exclusively lower UTI symptoms)

A urine sample for culture and sensitivity testing must always be obtained before the initiation of treatment.

Optimal duration of treatment is not completely established. The IDSA guidelines recommend 2 weeks of treatment in acute uncomplicated pyelonephritis.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Acute uncomplicated UTI			
E. coli Other enterobacteriaceae *E. faecalis*	IV Amoxycillin / clavulanate 1.2g q8h OR IV Ampicillin / sulbactam 1.5g q8h OR IV Ceftriaxone 2g q24h	IV Cefuroxime 1.5g q8h	

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Acute complicated UTI			
E. coli *P. aeruginosa* *Klebsiella spp.* *Enterobacter spp.* *P. mirabilis* *E. faecalis*	IV Piperacillin / tazobactam 4.5g q8h OR IV Cefuroxime 1.5g q8h PLUS IV Gentamicin 5mg/kg/day	IV Ciprofloxacin 400 mg q12h OR IV Meropenem 1g q8h OR IV Imipenem 500mg q6h	Caution : Use of ciprofloxacin is associated with increased incidence of resistant strains Urinary catheters should be removed if not needed or replaced if still required.
Candida albicans	IV Fluconazole 200 mg q24h		Obstructive uropathy should be relieved as soon as possible Duration of therapy: 2 to 3 weeks.
Renal abscess (intrarenal or perinephric)			
Methicillin-sensitive *S. aureus* Methicillin-resistant *S. aureus* *Enterobacteriaceae*	IV Cloxacillin 2g q4-6h IV Vancomycin 1g q12h Treat as acute complicated UTI (refer above) Duration of therapy should be prolonged.	IV Linezolid 600mg q12h	Staphylococci usually cause abscesses in the cortex while enterobacteriaceae cause pyelonephritis or abscesses in the medulla. Consider image-guided aspiration or surgical drainage of abscess.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Urosepsis related to urological procedures			
P. aeruginosa *Enterobacter spp.* *Klebsiella spp.* *Serratia spp.*	IV Cefepime 2g q8-12h OR IV Piperacillin / tazobactam 4.5g q6-8 h	IV Meropenem 1g q8h OR IV Imipenem 500 mg q6h OR IV Ciprofloxacin 400 mg q12h	Usually presents within 24 hours of genitourological procedure. Not uncommon to develop septic shock. Use pre-procedural culture to guide therapy.
Pelvic inflammatory disease / tuboovarian abcess			
B. fragilis Enterobacteriaceae *N. gonorrhoeae* *C. trachomatis*	IV Ceftriaxone 2g q24h PLUS IV Metronidazole 500 mg q8h X 14 days	IV Cefepime 2g q12 h PLUS IV Metronidazole 500 mg q8h X 14 days	Add doxycycline for treatment of tuboovarian abscess (PO 100 mg q12h can be given if IV doxycycline is not available)

Bibliography:

1. The Sanford Guide to Antimicrobial Therapy 2006: 25 – 26
2. *Clin Infect Dis* 2005; 40: 643 – 654
3. Task Force on UTI 2003 - 2004, Philippines Practice Guidelines Group in Infectious Diseases.

PERITONITIS

Spontaneous bacterial peritonitis (SBP) or Primary peritonitis

SBP is a frequent and severe complication of cirrhotic patients with ascites. Most patients with SBP have systemic signs of infection with abdominal pain, alteration in GIT motility or hepatic encephalopathy which may be absent in the unconscious ICU patient. A diagnostic paracentesis should be performed in patients suspected of SBP.

Antibiotic prophylaxis, preferably quinolones is recommended in cirrhotic patients recovering from an episode of SBP as this measure is effective in preventing recurrence and improving survival.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Enterobacteriaceae *S. pneumoniae* *Enterococci*	IV Cefotaxime 2g q8h (life-threatening q4h) x 5-7 days	IV Ceftriaxone 2g q24h OR IV Amoxycillin / clavulanate 1.2g q6h x 5-7 days	Culture 10 ml ascitic fluid in each aerobic and anaerobic blood culture bottle. Diagnose SBP if > 250 WBC/mm^3 is present in ascitic fluid on microscopy

Acute peritonitis due to perforated viscus (Secondary peritonitis)

It is firmly established that optimal antimicrobial therapy for secondary peritonitis requires agents that are active against gut-derived facultative Gram-negative bacilli as well as obligate anaerobes. However, because of limitations in clinical trial design, no single regimen has been shown to be superior to others.

Anaerobic cover is essential in all patients with perforated distal small bowel or colon. However, it is not required in duodenal ulcer perforation of less than 24 hours duration.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Stomach, duodenum, proximal small bowel			
Enterobacteriaceae *Enterococci*	IV Ampicillin / sulbactam 1.5-3g q6h OR IV Piperacillin/ tazobactam 4.5g q6-8h	3rd generation cephalosporin PLUS IV Metronidazole 500mg q8h	The optimal duration of therapy is unknown but when the source control is adequate, it can be as short as 5 to 7 days
Distal small bowel, colon			
The above plus Anaerobes e.g. *Bacteroides spp.* *Clostridium spp.*	IV Cefepime 2g q12h PLUS IV Metronidazole 500mg q8h OR IV Piperacillin/ tazobactam 4.5g q6-8h	3rd generation cephalosporin PLUS IV Metronidazole 500mg q8h	

Persistent generalised peritonitis (Tertiary peritonitis)

Tertiary peritonitis occurs when secondary peritonitis fails to resolve or recurs after adequate management of primary or secondary peritonitis. It is highly important to rule out and treat any occult intra-abdominal source of infection.

The usual causative organisms are coagulase-negative staphylococci, *P. aeruginosa*, enterocci, *Enterobacter spp.*, *Acinetobacter spp.* and fungi which tend to be resistant to commonly used empiric regimens.

There is still no consensus regarding the use of antifungals in tertiary peritonitis. The isolation of fungi from peritoneal fluid is common at the time of operation. Therapy remains optional unless fungi are cultured from the blood stream, in recurrent intra-abdominal infection, or when patients are immunosuppressed.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
P. aeruginosa *Enterobacter spp.* *Acinetobacter spp.* *Enterococci* Cogulase-negative staphylococci	IV Meropenem 1g q8h OR IV Imipenem 500mg q6h PLUS OPTIONAL	IV Piperacillin / tazobactam 4.5g q8h OR IV Cefepime 2g q12h PLUS IV Metronidazole 500mg q8h	The optimal duration of therapy is unknown but when the source control is adequate, it can be as short as 5 to 7 days
Candida	IV Fluconazole 400-800mg q24h		

Bibliography:

1. *J Hepatol* 2000;32:142-53
2. *Crit Care Med* 2003;31(8):2228-37.
3. *Clin Inf Dis* 2003;37:997-1005.

BILIARY SEPSIS

The primary pathology in acute cholecystitis and cholangitis is acute inflammation and associated obstruction of bile drainage from stones, strictures or tumours. Infection is usually secondary to biliary stasis. Bacteremia is due to increased bile duct pressure, with consequent reflux of bacteria into the blood and lymphatics.

Besides antimicrobial therapy, prompt decompression and drainage of the biliary tract either surgically, percutaneously or ERCP-placed stents need to be considered.

Biliary excretion of antimicrobials is severely reduced in biliary stasis and it is important to use antimicrobials where high concentrations are achievable in the bile and blood.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Enterobacteriaceae (*E. coli, Klebsiella spp, Enterobacter spp*) *P. aeruginosa* *Enterococci* Anaerobes (*Bacteroides spp., C. perfringens*)	IV Piperacillin / tazobactam 4.5g q8h x 7-14days	IV Cefoperazone 2g 12qh OR IV Cefepime 2g q12h PLUS IV Metronidazole 500mg 8qh x 7-14 days	Ceftriaxone may increase biliary sludging. *P.aeruginosa* or *Enterobacter spp.* are common in recent instrumentation of the biliary tract. Anaerobes are more common in previous bile duct-bowel anastomosis, elderly patients and are associated with a more severe illness.

Bibliography:

1. *Curr Treat Options Gastroenterol* 2001; 4: 139-146
2. *Clin Infect Dis* 2003; 37(8): 997-1005

ACUTE INFECTIVE PANCREATITIS

Acute pancreatitis is usually non-infectious. Infection may occur subsequently in severe acute necrotising pancreatitis and tends to develop during the 2nd and 3rd week after the onset of symptoms. Rates of organ failure and mortality appear to be highest among patients with infected pancreatic necrosis.

The gastrointestinal tract is the likely source of infective organisms. Infection is usually due to a single organism early in the course of the infective process, but later becomes polymicrobial. Gram-negative bacteria are more commonly isolated in pancreatitis of biliary aetiology while Gram-positive bacteria are more commonly isolated in pancreatic necrosis of alcoholic aetiology.

Prophylactic antimicrobials have been associated with a change in the spectrum of pancreatic isolates from enteric Gram-negative to Gram-positive organisms and fungi. Fungal infections caused by *Candida spp.*, is increasingly recognised, particularly in patients with prolonged disease and following long-term, broad-spectrum antimicrobial therapy.

There is no role of prophylactic antimicrobial in acute pancreatitis. The recent 2004 Washington consensus recommend against the routine use of prophylactic antibiotics or antifungal agents in patients with necrotising pancreatitis in light of inconclusive evidence.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Enterobacteriaceae (*E. coli, Klebsiella spp., Proteus spp .*) *P. aeruginosa* Enterococci *S. aureus* Coagulase-negative staphylococci *Bacteroides spp.* Candida	IV Cefepime 2g q12h PLUS IV Metronidazole 500mg q8h x 10 – 14days	IV Imipenem 500mg 6hrly OR IV Meropenem 1g q8h x 10–14 days	Infected pancreatic necrosis is an indication for intervention including surgical or radiological-guided drainage

Bibliography:

1. Cochrane Database Syst Rev 2003;(4): CD002941
2. *Crit Care Med* 2004; 32(12): 2524 – 2536
3. *Int J Pancreatol* 1998; 24: 187–191
4. *Pancreatology* 2005;5:145–156

CATHETER-RELATED BLOODSTREAM INFECTIONS

Below are definitions of relevant terms in catheter-related infections. Only patients diagnosed to have catheter-related blood stream infections (CRBSI) require antimicrobial therapy.

1. Catheter-tip colonisation:

Growth of > 15 colony forming units (cfu) on the agar plate using the semi-quantitative roll-plate culture technique of the central venous catheter (CVC) tip.

2. Catheter-related local infection (CRLI):

Presence of any signs of local infection (induration, erythema, heat, pain, purulent drainage) within 2 cm of catheter exit site.

3. Catheter-related bloodstream infection (CRBSI):

Bacteremia or fungemia in a patient who has an intravascular device with ≥1 positive blood culture obtained peripherally, has clinical manifestations of infection (e.g., fever, chills, and/or hypotension) and no apparent source elsewhere. One of the following should also be present:

- a positive catheter tip culture (≥15 cfu) with the same organism (species and antibiogram) isolated from a peripheral blood sample;
- simultaneous quantitative cultures of blood samples with a ratio of ≥ 5:1 (CVC vs. peripheral)
- differential time to positivity i.e. a positive result of culture from a CVC is obtained at least 2 hours earlier than that of the peripheral culture

The most common organisms isolated in CRBSI are Gram-positive cocci. Therefore the choice for empirical antimicrobial therapy would be cloxacillin or vancomycin (if MRSA is highly suspected). Repeat blood cultures before commencing therapy to rule out contamination.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Coagulase-negative staphylococci *S. aureus* Methicillin-sensitive Methicillin-resistant	 IV Cloxacillin 2g q4h-6h IV Vancomycin 1g q12h		Duration of treatment: 5-7 days in coagulase-neg. staph. bacteremia; 14 days in *S. aureus* bacteremia. Transoesophageal Echo (TOE) is desirable in *S. aureus* bacteremia to exclude endocarditis. If present, extend systemic antimicrobial to 4-6 weeks.
Enterococcus spp. Ampicillin- sensitive Ampicillin- resistant	 IV Ampicillin 2g q4h-6h IV Vancomycin 1g q12h x 10-14 days		 Optional to add IV gentamicin 1mg/kg q8h

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Gram-negative bacilli	IV Meropenem 1g q8h OR IV Imipenem 500 mg q6h x 10 -14 days	IV Cefepime 2g q12h OR IV Piperacillin / tazobactam 4.5g q8h X 10 - 14 days	
S. maltophilia	IV Trimethoprim-sulfamethoxazole 3-5mg/kg (trimethoprim component) q8h x 10-14 days		
Fungi	IV Fluconazole 400-800 mg q24h OR IV Amphotericin B 0.6 -1.0 mg/kg q24h	IV Caspofungin 70 mg x 1 dose then IV 50 mg q24h	Duration of treatment : 14 days after last positive blood culture

Bibliography:

1. *Clin Infect Dis* 2001; 32: 1249-72
2. *Curr Opin Crit Care* 2002; 8: 441-448

CENTRAL NERVOUS SYSTEM INFECTION

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

Blood samples must be obtained for culture as they are positive in 80-90% of cases of acute bacterial meningitis. The diagnosis of bacterial meningitis rests on CSF examination. The typical characteristics of CSF suggestive of bacterial meningitis are elevated WBC count (>100-5000cells/mm^3) with a neutrophil predominance, elevated protein levels (>200 mg/dL), elevated lactate levels (>4mmol/L) and ratio of CSF: serum glucose < 0.4. Gram stain examination of centrifugated CSF is the best diagnostic test in a patient who has not yet received any antimicrobial. A negative rapid CSF latex agglutination test against *S. pneumoniae*, group B Streptococcus, *H.influenzae* type B, *N. meningitidis* and *E.coli* K1 does not rule out infection caused by a specific pathogen.

Empirical antimicrobial to cover all common pathogens should be started promptly and the choice is influenced by the patient's age and conditions that may have predisposed the patient to meningitis. A repeat lumbar puncture with CSF analysis should be performed in any patient who has not responded after 48 hours of appropriate antimicrobial therapy. Antimicrobial dosing should not be reduced as the patient improves.

Intrathecal administration of antimicrobial is not recommended. Current evidence suggests the use of adjunctive dexamethasone in adults with suspected or proven pneumococcal meningitis but not in meningitis caused by other bacteria.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Acute bacterial meningitis - < 50 years			
S. pneumoniae *N. meningitidis* *H. influenzae*	IV Ceftriaxone 2g q12h	IV Meropenem 2g q8h OR IV Cefotaxime 2g q6h	IV dexamethasone 0.15 mg/kg q6h X 2–4 days in pneumococcal meningitis. Give first dose 10–20 min before, or concomitant with the first dose of antimicrobial.
	Duration of treatment: *N. meningitidis* X 7days *H. influenzae* X 7 days *S. pneumoniae* X 10 – 14 days		
Acute bacterial meningitis **> 50 years or chronic alcoholism or diabetics or impaired cellular immunity**			
S. pneumoniae *Enterobacteriaceae* *Listeria* *monocytogenes*	IV Ceftriaxone 2g q12h PLUS IV Ampicillin 2g q4h	IV Meropenem 2g q8h OR IV Cefotaxime 2g q6h PLUS IV Ampicillin 2g q4h	If culture is positive for listeria, continue with ampicillin only. In listeria meningitis treat for 21 days; or more in the immunocompro- mised

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Acute bacterial meningitis Post neurosurgery or post head trauma			
S. pneumoniae Methicillin-sensitive *S. aureus* *P. aeruginosa*	IV Cefepime 2g q8h X 14 days	IV Meropenem 2g q8h X 14 days	Treat initially for MSSA; if later identified as MRSA or MRSE, treat accordingly.
Ventriculitis due to infected VP shunt			
Coagulase-negative staphylococci *S. aureus* Coliforms	IV Cefotaxime 2gm q6h OR IV Cefepime 2gm q8h X 10 -14 days	IV Meropenem 2gm q8h PLUS IV Vancomycin 2gm q12h (if MRSA is suspected) X 10 -14 days	Remove infected shunt.
Acute encephalitis			
Herpes simplex virus -1 Arboviruses e.g. (Japanese encephalitis, Nipah) Rabies virus	IV Acyclovir 10mg/kg over 1 hr q8h x 14 – 21 days		Acyclovir is effective only in HSV-1 encephalitis
M. pneumoniae	IV / PO Doxycycline 200 mg q12h x 3 days, then 100 mg q12h X 2 – 4 weeks		Macrolides do not treat CNS infection due to poor CNS penetration

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Brain abscess – Primary			
Streptococci Bacteroides Enterobacteriaceae *S. aureus*	IV Ceftriaxone 2g q12h PLUS IV Metronidazole 500mg q8h	IV Cefotaxime 2g q6h PLUS IV Metronidazole 500mg q8h	Duration of treatment is guided by response and neuro imaging.
Brain abscess - Post surgery / post trauma			
S. aureus Enterobacteriaceae	IV Cloxacillin 2g q4h PLUS IV Ceftriaxone 2g q12h		Use vancomycin if MRSA is suspected. Duration of treatment is guided by response and neuro imaging.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Brain abscess - HIV infected			
Toxoplasma gondii	PO Pyrimethamine 200mg x 1 day then 75 mg q24h PLUS PO Sulfadiazine 1g q6h PLUS IV Folinic acid 10mg q24h X 4- 6 weeks OR PO Pyrimethamine 200mg x 1 day then 75 mg q24h PLUS PO Clindamycin 600mg q6h PLUS IV Folinic acid 10mg q24h X 4 – 6 weeks	IV Trimethoprim / sulfamethoxazole 10mg/kg/day (trimethoprim component) in 2 divided doses X 30 days	Folinic acid prevents pyrimethamine-induced haematologic toxicity Even after complete resolution of lesions on CT/MRI, patients would still need to be treated indefinitely.

Bibliography:

1. *Clin Infect Dis* 2004; 39:1267–84
2. The Sanford guide to antimicrobial therapy 2006; 5–8, 99

INFECTIVE ENDOCARDITIS

Duke's criteria is the most widely used criteria in the diagnosis of infective endocarditis (IE). The two key criteria are persistent bacteremia of typical organisms causing IE and evidence of valvular involvement. Transoesophageal echocardiography (TOE) is the preferred imaging modality as it is more sensitive in detecting vegetations and cardiac abscesses. Surgical intervention needs to be considered when there is large, persistent vegetation, recurrent embolisation, valvular dysfunction or perivalvular extension.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
S. viridans *S. bovis* Highly penicillin-susceptible: minimum inhibitory concentration (MIC) ≤0.12 µg/ml	IV Penicillin G 12-18 MU/day in 4-6 divided doses X 4 weeks OR IV Ceftriaxone 2g q24h X 4 weeks PLUS IV Gentamicin 3mg/kg/day in 3 divided doses X 2 weeks	If unable to tolerate Penicillin or Ceftriaxone: IV Vancomycin 30mg/kg/day in 2 divided doses X 4 weeks	Duration of treatment in prosthetic valve endocarditis: 6 weeks Penicillin G: 1 million units = 1 MU = 600 mg Vancomycin target concentrations Trough: 10-15 µg/ml Peak: 30-45 µg/ml (Max. 2g per day unless serum conc. very low)

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
S. viridans *S. bovis* Relatively resistant to penicillin: MIC≥ 0.12 µg/ml	IV Penicillin G 24 MU/day in 4-6 divided doses X 4 weeks OR IV Ceftriaxone 2g q24h X 4 weeks PLUS IV Gentamicin 3mg/kg/day in 3 divided doses X 2 weeks		Duration of treatment in prosthetic valve endocarditis: 6 weeks
S.aureus (Native valve)	IV Cloxacillin 12g/day in 4-6 divided doses X 6 weeks PLUS OPTIONAL IV Gentamicin 3 mg/kg/day in 2-3 divided doses X 3-5 days	If MRSA is suspected: IV Vancomycin 30mg/kg/day in 2 divided doses PLUS PO Fusidic acid 500mg q8h OR PO Rifampicin 300mg q12h X 6 weeks PLUS OPTIONAL IV Gentamicin 3 mg/kg/day in 2-3 divided doses X 3-5 days	Penetration of fusidic acid or rifampicin into the vegetation is good

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
S. aureus (Prosthetic valve)	IV Cloxacillin 12g/day in 4-6 divided doses X ≥ 6 weeks PLUS PO Fusidic acid 500mg q8h OR PO Rifampicin 300mg q12h X ≥ 6 weeks PLUS IV Gentamicin 3 mg/kg/day in 2-3 divided doses X 2 weeks	If MRSA is suspected: IV Vancomycin 30mg/kg/day in 2 divided doses X ≥ 6 weeks PLUS PO Fusidic acid 500mg q8h OR PO Rifampicin 300mg q12h X ≥ 6 weeks PLUS IV Gentamicin 3 mg/kg/day in 2-3 divided doses X 2 weeks	
Enterococcus spp.	IV Ampicillin 2g q4h OR IV Penicillin G 18-30 MU/day in 6 divided doses PLUS IV Gentamicin 3mg/kg/day in 3 divided doses	If unable to tolerate ampicillin or penicillin: IV Vancomycin 30 mg/kg/day in 2 divided doses PLUS IV Gentamicin 3mg/kg/day in 3 divided doses	Duration of treatment: Native valve with symptoms ≤ 3 mths – 4 weeks; symptoms > 3 mths – 6 weeks Prosthetic valve: min. 6 weeks

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1. *Circulation* 2005; 111: 3167-3184

SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections are usually caused by bacterial entry through breaches in the skin. Its severity ranges from trivial to lethal depending on host factors such as age, diabetes mellitus and state of immunocompetence.

Cellulitis

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. S. aureus* cellulitis is usually associated with bullae or abscesses. Lack of clinical response to antimicrobials could be due to resistant strains of organisms e.g. MRSA or infection of the deeper tissues.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Group A Streptococci	IV Penicillin G 2-4 MU q6h X 5days	IV Cloxacillin 1-2 g q4h X 5days	In cellulitis not associated with venous catheter or diabetes mellitus. IV Penicillin G: 1MU (million units) = 1 mega unit = 600 mg
Streptococci *S. aureus*	IV Cloxacillin 1-2g q4h X 5 days	IV Amoxycillin / clavulanate 1.2 gm q8h X 5 days	Blood culture results are positive in < 5 % of cases

Necrotising fasciitis

Necrotising fasciitis is an infection of the deeper tissues usually involving the extremities, the abdominal wall or the perineum. Patients are generally more ill and septic. 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.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Polymicrobial: Group A streptococci *S.aureus* *Bacteroides spp* *Clostridium spp.* *Peptostreptococci* Enterobacteriaceae	IV Imipenem 1g q6 –8h OR IV Meropenem 1g q8h	IV Piperacillin / tazobactam 4.5g q6-8h OR IV Ampicillin/ 1.5–3g q6-8h PLUS IV Clindamycin 600mg q8h	Antimicrobials are usually continued till surgical debridement is no longer needed and patient has sulbactam clinically improved. If IV clindamycin is not available, PO clindamycin 150-450mg q6h may be used.

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.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Intestinal/Genital tract			
Mixed Gram-positive and Gram-negative	IV Ampicillin / sulbactam 1.5-3g q6h X 5-7 days	IV Piperacillin / tazobactam 4.5g q6-8h X 5-7 days	
Chest/Extremities			
S. aureus Streptococci	IV Cloxacillin 1-2g q4-6h X 5-7 days	IV Amoxicillin / clavulanate 1.2g q8h X 5-7 days	
Axillary /Perineum			
Mixed Gram-positive and Gram-negative	IV Ampicillin / sulbactam 1.5-3g q6h X 5-7 days	IV Piperacillin / tazobactam 4.5g q6 -8 h X 5-7 days	

Bibliography:

1. *Clin Infect Dis:* 2005: 41; 1373 -406
2. The Sanford Guide to Antimicrobial Therapy 2006: 39-41
3. *N Engl J Med* 2004 :350(9): 904-912

DIABETIC FOOT INFECTIONS

Foot ulcers are common infectious complications in patients with diabetes mellitus. Management of patients with severe infections includes intravenous antimicrobials as well as early limb amputation for the control of sepsis.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Chronic ulcer and previously treated with antimicrobials			
S. aureus ß-hemolytic streptococci Enterobacteriaceae	IV Ampicillin / sulbactam 3g q6h	IV Piperacillin / tazobactam 4.5g q8h	If MRSA is suspected, IV vancomycin should be started. Antimicrobials are usually continued till 3-7 days after amputation of the limb.
Macerated ulcer with extensive necrosis or gangrene			
The above plus *P. aeruginosa* Anaerobes	IV Imipenem 500mg q6h OR IV Meropenem 1g q8h	IV Piperacillin / tazobactam 4.5g q8h	Antimicrobials are usually continued till 3-7 days after amputation of the limb.

Bibliography:

1. *Infect Dis Clin Pract* 2005; 13(5):216-223

ACUTE INFECTIVE DIARRHOEAS

Acute infective diarrhoea is usually self-limiting and the patient is usually not admitted to the ICU unless there is presence of systemic involvement or shock; which can be either hypovolemic or septic. However, there are certain acute infective diarrhoeas in which antimicrobials are recommended: dysenteric shigellosis, cholera and typhoid fever. The drug of choice in this clinical setting is a quinolone because the most likely organisms to be isolated are generally susceptible to the quinolones. Once a specific pathogen is isolated and sensitivities to antibiotics are identified, therapy can be modified as needed.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Shigellosis			
Shigella spp.	IV Ciprofloxacin 400mg q12h X 3-5 days		
Cholera			
Vibrio cholera	IV Ciprofloxacin 400mg q12h X 1 day		

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Typhoid fever			
Salmonella typhi	IV Ciprofloxacin 400mg q12h X 10-14 days (or until 5 days after defervescence)	IV Ceftriaxone 2g q12h X 10-14 days (or until 5 days after defervescence)	Change to PO ciprofloxacin whenever possible as oral bioavailability is good Antimicrobial is not indicated in salmonellosis caused by *Salmonella spp.* (non-typhi) unless there is systemic involvement or the patient is > 50 years, immuno-suppressed or has vascular grafts or prosthetic joints.
Pseudomembranous colitis			
Clostridium difficile	PO Metronidazole 400mg q8h X 10 days	PO Vancomycin 125mg q6h OR IV Metronidazole 500mg q8h X 10 days	Intravenous form of vancomycin can be given orally

***Clostridium difficile* associated diarrhoea**

Diagnosis is made by the detection of *C. difficile* toxin in the stools. Major risk factors are advanced age, hospitalisation and exposure to antibiotics (mainly clindamycin, cephalosporins, and penicillin). Offending antibiotics should be discontinued if possible.

C. difficile toxin can remain positive in stool for weeks. Do not treat positive result in stools unless patient has persistent diarrhoea.

Oral administration of metronidazole is preferred to oral vancomycin because it is less expensive and avoids risk of potentiating vancomycin–resistant enterococcus (VRE). If patient is too ill for oral therapy, intravenous metronidazole can be given. However the efficacy for intravenous therapy is not established.

Bibliography:

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2. *British Med J* 2005; 331:498-501
3. *N Engl J Med* 2004; 350(1):38-47
4. *Lancet* 2005; 366(9487):749-62

SEVERE SEPSIS AND SEPTIC SHOCK

Definitions for sepsis and its related syndromes were updated at the 2001 International Sepsis Definitions Conference, which included expanding the definition of sepsis while maintaining the established definition of severe sepsis and septic shock.

Term	Definition
Systemic Inflammatory Response Syndrome (SIRS)	≥ 2 of the following: – Temperature > 38.3°C or < 36°C – WBC count >12,000 or < 4,000 or >10% bands – Pulse rate > 90 beats/min or > 2 SD above normal for age – Respiratory rate > 20 breaths/min – Hyperglyceamia > 7.7 mmol/L in the absence of diabetes – Altered mental status – Lactate > 2mmol/L – Decreased capillary refill/mottling
Sepsis	Inflammatory response + presumed or identified source of infection
Severe sepsis	Sepsis + organ dysfunction, hypotension before fluid challenge, or lactate > 4 mmol/L
Septic shock	Severe sepsis + hypotension (despite 20–40 ml/kg fluid challenge)

Antimicrobial therapy should be started within the first hour of recognition of severe sepsis after appropriate cultures have been obtained.

Monotherapy is as efficacious as combination therapy with a ß-lactam and an aminoglycoside. Aminoglycoside-containing regimens have been shown to increase the risk of nephrotoxicity or ototoxicity and their risk-benefit should be evaluated on a case-to-case basis.

The antimicrobial regimen should always be reassessed after 48-72 hours on the basis of available microbiological and clinical data with the aim of using a narrow spectrum antimicrobial. The duration of therapy should typically be 7-10 days and guided by clinical response.

Whenever possible, the choice of empirical antimicrobial therapy in a patient with severe sepsis should be guided by the knowledge of the most likely site of infection and the most common infecting organisms. However, in many cases the possible infective site or organism is unidentified. The following table provides the choice of empirical antimicrobials in these situations.

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Gram-negative bacilli Gram-positive cocci	IV Cefepime 2g q12h OR IV Piperacillin/ tazobactam 4.5g q8h OR IV Meropenem 1g q8h OR IV Imipenem 500mg q6h PLUS OPTIONAL	PLUS OPTIONAL	Current evidence suggests that carbapenems, 4th generation cephalosoporins or piperacillin / tazobactam are equally effective in treatment of septic shock. If melioidosis cannot be ruled out, carbapenem should be used as the empirical agent.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Methicillin-resistant *S.aureus* Penicillin-resistant *S. pneumoniae* Ampicillin-resistant enterococci	IV Vancomycin 15 mg/kg q12h	IV Linezolid 600 mg q12h	Empirical use of these antimicrobials is only justified in areas with high endemic levels of MRSA or high levels of penicillin-resistant *S. pneumoniae*
	PLUS OPTIONAL	PLUS OPTIONAL	
Candida	IV Fluconazole 400 - 800mg q24h	IV Amphotericin B 0.6 - 1.0mg/kg q24h OR IV Caspofungin 70mg x 1 dose then 50mg q24h	Empirical antifungal agents should not be used on a routine basis. Refer to antifungal therapy for high risks patients, page 66.

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MELIOIDOSIS

In its most acute, life-threatening form, melioidosis has no reliable pathognomonic features and presents as septic shock without obvious source of infection, severe pneumonia or septic shock with multiple abscesses in the liver, spleen or kidneys.

The majority of severe infections occur in patients with co-morbidities such as uncontrolled diabetes mellitus, chronic renal failure, alcoholic liver disease or chronic lung disease.

Observational evidence in Australia had suggested that adjunctive granulocyte-colony stimulating factor (G-CSF) may be useful in reducing the high mortality associated with septic shock due to melioidosis from 95% to 10%.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
	Intensive-phase		
Burkholderia pseudomallei	IV Ceftazidime 2g q8h X 14 days	IV Meropenem 1 g q8h OR IV Imipenem 500 mg q6h X 14 days	Consider IV G-CSF 300µg q24h for 10 days if patient has septic shock. IV therapy for minimum of 14 days or longer (4-8 weeks) in those with deep- seated infection, osteomyelitis, or septic arthritis. Look for abscesses and drain if present. Close follow-up and monitoring of adherence to therapy is important.
	Eradication-phase		
	PO Trimethoprim-sulfamethoxazole (trimethoprim comp. 5 mg/kg) q12h PLUS PO Doxycycline 100mg q12h X at least 20 weeks		

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TUBERCULOSIS

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*. It is the leading cause of death by infectious disease in Malaysia. Patients should be started on anti-TB treatment as soon they are suspected or diagnosed as having tuberculosis. The aim of treatment is to cure and render patients non-infectious, prevent relapse and resistant tubercle bacilli.

The current drug regimen involves the five main drugs: isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. The treatment regimen involves an intensive phase of 8 weeks and a continuation phase of 4 months.

Treatment phase	Preferred agent	Notes
Intensive	SHRZ or EHRZ q24h X 8 weeks or 56 daily doses	Renal profile, full blood count and liver function test should be monitored at least twice a week while the patient is in ICU
Continuation	HR biweekly X 4 months or 32 doses	PO pyridoxine 10mg q24h should be given to prevent isoniazid induced neuropathy

Drug	Dose	Max. dose	Adverse reaction
Rifampicin (R)	10 mg/kg/day	600mg	hepatitis, vomiting, thrombocytopenia
Isoniazid (H)	5-8 mg/kg/day	300mg	hepatitis, peripheral neuritis, hypersensitivity
Pyrazinamide (Z)	20-40 mg/kg/day	2 g	hepatotoxicity, hyperuricemia
Ethambutol (E)	15-25 mg/kg/day	1.2 g	optic neuritis, GI disturbances
Streptomycin (S)	15-20mg/kg/day	1 g	nephrotoxicity, ototoxcity, skin rash

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LEPTOSPIROSIS

Severe leptospirosis can be caused by infection of any serotype of Leptospira. The clinical manifestations of leptospirosis are variable, ranging from mild febrile illness to the icteric-haemorrhagic form with severe kidney and liver involvement. Weil's disease is the severe form of leptospirosis where jaundice, haemorrhage and proteinuria are the triad of important signs.

If the disease is not treated appropriately within the first 2 to 3 days, it may progress in severity, depending on the infecting serotype. There are only few well-designed controlled studies of antimicrobial therapy in leptospirosis. However, the studies showed that antimicrobial when administered early cause a significant reduction in the duration of illness.

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Leptospira spp.	IV Penicillin G 1.5 - 2MU q6h X 7 days	In less severe infection: PO Doxycylline 100mg q12h OR IV Ampicillin 0.5-1g q6h OR IV Ceftriaxone 2g q24h	

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2. *J Infect Chemother* 2001; 7(2): 59-68
3. *Clin Microbiol Rev* 2001;14(2):296-326

FALCIPARUM MALARIA

Severe malaria is almost always caused by *Plasmodium falciparum*, with its inherent complications such as haemolysis, cerebral involvement, acute renal failure and lactic acidosis. If there is clinical evidence of severe malaria but the blood smear is reported as *P. vivax, P. ovale* or *P. malariae*, the patient should be treated for falciparum malaria in case of a mixed infection or misdiagnosis. Patients diagnosed with severe malaria should be started with parenteral antimalarial immediately. Consider exchange transfusion in patients with parasitemia of more than 10%

Common Organisms	**Antimicrobials**		**Notes**
	Preferred	**Alternative**	
Plasmodium falciparum	IV quinine dihydrochloride 20mg/kg in 250ml dextrose 5% over 4 hours and then 10mg/kg over 4 hours q8h PLUS Oral doxycycline * 100mg q12h X 7 days	Arthemisinin-based combination therapy* 1. Arthemeter – lumefantrine 2. Arthesunate + amodiaquine 3. Arthesunate + mefloquine	Monitor BP, ECG and blood glucose during iv quinine infusion Switch to oral medication whenever possible Single dose of oral primaquine 0.75mg/kg may be given to patients to eradicate the gametocytes after the course of antimalarial

*Parenteral doxycycline and arthemisinin-based combination therapy is currently not available in Malaysia

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ANTIMICROBIAL THERAPY IN FEBRILE NEUTROPENIA

Febrile neutropenia is defined as an oral temperature of >38.0°C on at least 2 occasions within 24 hours, or a single oral temperature of >38.3°C, in the presence of neutropenia, defined as an absolute neutrophil count (ANC) of less than 500 cells/mm^3; or < 1000 cells/ mm^3 with a predicted decrease to <500 cells/ mm^3.

Aerobic Gram-negative bacilli used to be the predominant pathogen causing infection in neutropenic patients. There has been a steady increase in Gram-positive and polymicrobial infections from 1986 through to 2002, with a corresponding decrease in Gram-negative infections from 60% to 21% over the years. Polymicrobial infections now account for 25%–30% of bacterial infections; while 80% of them have at least one Gram-negative organism, emphasising the need for broad-spectrum antimicrobial coverage in these patients. Anaerobes are not usually isolated in patients with febrile neutropenia.

The aim of the initial evaluation of a febrile neutropenic patient is to determine whether the patient is at low or high risk for infectious complications. The choice of antimicrobial agent is made according to risk category. Most patients admitted to the ICU would be in the high risk group and warrant parenteral, empirical antimicrobial therapy for the duration of the febrile episode.

The next step in the evaluation of a high risk patient is to determine if vancomycin is required in the empirical regimen. It is recommended in the following category of patients:

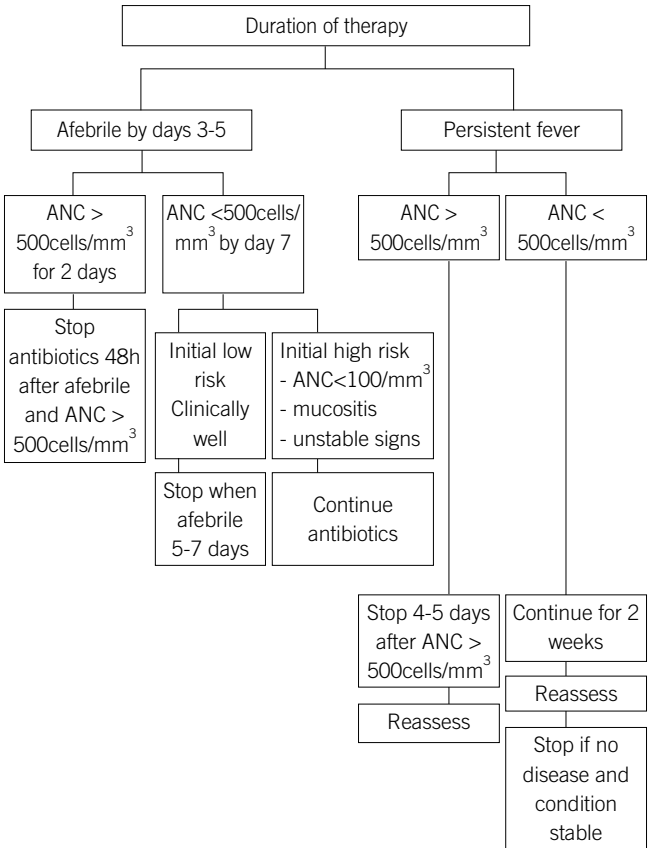
- suspected serious catheter-related infections
- evidence of colonisation with drug-resistant *S. pneumonie* or MRSA
- bacteremia by Gram-positive cocci before identification or susceptibility known
- hypotension or other evidence of cardiovascular impairment
- does not show improvement with empirical therapy after 3-5 days.

A patient who is neutropenic for > 2 weeks and develops right and/or left upper quadrant abdominal pain with increased alkaline phosphatase level should be suspected of having hepatosplenic candidiasis and treated as systemic candidiasis with antifungal (refer to antifungal therapy on page 66). Antiviral drugs are not recommended for routine use unless clinical or laboratory evidence of viral infection.

Granulocytes-colony stimulating factor (G-CSF) is not routinely used in febrile neutropenia but should be considered in certain high risk cases with predicted worsening of disease course such as septic shock, multi-organ dysfunction, pneumonia, severe cellulitis and systemic fungal infections.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Febrile neutropenia > 7days			
S. aureus Coagulase-negative staphylococci *E.Coli* *Klebsiella spp.* *P.aeruginosa*	Monotherapy: IV Cefepime 2g q8h OR IV Piperacillin/ tazobactam 4.5g q8h OR IV Imipenem 500mg q6h OR IV Meropenem 1g q8h	Combination therapy: Antimicrobials used as mono-therapy PLUS IV Amikacin 15mg/kg q24h OR IV Gentamicin 5mg/kg q24h	Use of combination therapy may be considered in complicated or severe infections. Reassess patient on days 3-5 for need to add vancomycin. Reassess for need of antifungal if febrile through days 5-7 and resolution of neutropenia is not imminent.
The above plus *Candida spp.* *Aspergillus spp.*	IV Amphotericin B 0.8-1.0 mg/kg q24h OR IV Fluconazole 800mg x 1 dose then 400mg q24h (if aspergillus unlikely)	IV Caspofungin 70mg x 1 dose then 50mg q24h	Refer to anti-fungal therapy on page 66. Vancomycin, aminoglycoside and amphothericin B should be avoided in combination if possible because of their additive nephrotoxicity.

Algorithm on duration of antibiotic therapy in febrile neutopenia



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ANTIFUNGAL THERAPY

Antifungal therapy is not routine in all cases of severe sepsis. It can be more toxic than antibacterial therapy but should be considered in certain patient population. The incidence of fungal infections varies considerably between units and this is determined mainly by the patient population.

Candida species are the most common cause of fungal infections and can cause infections that range from non life-threatening mucocutaneous illnesses to invasive processes that may involve virtually any organ.

Superficial colonisation with candida is common and not an indication for treatment. Broad-spectrum antibiotic therapy increases the incidence of enteric colonisation. Non-neutropenic patients with isolation of candida from respiratory samples (tracheal aspirates, bronchoscopic samples), even in high concentrations, are unlikely to have invasive candidiasis. Candida is frequently cultured from the urine, especially when an indwelling catheter is present but the patient is usually asymptomatic. However, in the immunocompromised patient, it may be the source of systemic fungal infection.

In the absence of definitive clinical findings indicative of candidiasis, such as candida endophthalmitis or tissue histology, diagnosis is largely based on the presence of candida in blood cultures. The incidence of candida bloodstream infections is increasing and is associated with a high mortality. A single positive blood culture of candida is highly predictive and should never be considered as contaminant.

Accurate early diagnostic tools for invasive candidiasis are lacking and empiric antifungal therapy may be indicated. However, widespread use of inappropriate antifungal therapy may have deleterious epidemiological consequences, including selection of resistant organisms and should be limited to patients with (1) Candida colonisation (preferably at multiple sites), (2) multiple risks factors, and (3) absence of other causes of fever. The absence of colonisation by candida indicates a lower risk for invasive candidiasis and warrants delaying empiric therapy.

Patients at risk for invasive fungal infection are:

- Immunocompromised/immunosuppressive therapy
- Neutropenia (neutrophil count < 1000 mm^3)
- Solid organ and bone marrow transplantation
- Candida colonisation at multiple non-sterile sites
- Burns (>50% BSA)
- Recent severe trauma
- Major surgery e.g. abdominal, urological
- Faecal contamination of the peritoneum
- Hyperalimentation
- High severity illness score
- Malignancy
- Acute renal failure
- Diabetes mellitus
- Mechanical ventilation
- Haemodialysis
- Prolonged ICU stay
- Prolonged use of antibacterial
- Presence of central venous catheters
- Presence of urinary catheter

Newer antifungal agents

All the newer antigungal agents are much more expensive than fluconazole or amphotericin B and are not recommended to be used routinely as the first line empirical antifungal therapy in our local setting. They should only be used in selected patients after weighing the risks and benefits.

1. **Lipid-associated formulation of amphotericin B**
   - 3 formulations available:
     1) amphotericin B lipid complex
     2) amphotericin B colloidal dispersion
     3) liposomal amphotericin B
   - Not superior to amphotericin B for treatment of candidiasis
   - Patients who may benefit are those who require prolonged therapy, pre-existing renal dysfunction or require continued concomitant use of another nephrotoxic agent.

2. **Caspofungin**
   - Spectrum is limited to candida and aspergillus (fungistatic against aspergillus) with no activity against cryptococcus.
   - Shown to be as effective as amphotericin B or fluconazole when used in oropharyngeal and oesophageal candidiasis.
   - Equivalent in efficacy to amphotericin B but better tolerated in invasive candidiasis.
   - Toxicity profile is good with only occasional liver enzyme changes.

3. **Voriconazole**
   - Broader spectrum of activity against candida species (including *C. krusei*)
   - More effective than amphotericin B in a randomised trial of immunosuppressed patients with invasive aspergillosis. Appears particularly advantageous in cerebral aspergillosis.

Common Organisms	Antimicrobials		Notes
	Preferred	**Alternative**	
Clinically stable with or without central venous catheter	IV / PO Fluconazole 400mg q24h OR IV Amphotericin B 0.6 mg/kg q24h (total dose 5-7 mg/kg)	Fail to respond or deteriorating: IV Amphotericin B 0.8-1.0 mg/kg q24h OR IV / PO Fluconazole 800 mg q24h OR IV Caspofungin 70 mg loading followed by 50mg q24h OR IV Voriconazole 6 mg/kg q12h X2 doses then maintenance IV 3 mg/kg q12h or PO 200mg q12h, after at least 3 days of IV therapy.	Remove and replace venous catheter (do not change over guidewire). Mortality 21% vs. 45% if catheter not removed. Ophthalmic examination is recommended for all patients with candidaemia. Duration of treatment is 14 days after last positive blood culture and resolution of signs and symptoms of infection

Common Organisms	Antimicrobials		Notes
	Preferred	Alternative	
Bloodstream, Unstable or deteriorating, Neutropenia, Disseminated (pulmonary, hepatosplenic, eye)	IV Amphotericin B 0.8-1.0 mg q24h ± PO Flucytosine 37.5 mg/kg q6h OR IV Fluconazole 800 mg q24h	IV Voriconazole 6 mg/kg q12h X2 doses then 3 mg/kg q12h (at least 3 days) followed by PO 200mg q12h OR IV Caspofungin 70mg loading followed by IV 50 mg q24h	Hydration before and after infusion of amphotericin B with 500ml saline has been shown to reduce renal toxicity. Reduce Caspofungin to 35 mg q24h in moderate hepatic insufficiency Duration of treatment is 14 days after last positive blood culture and resolution of signs and symptoms of infection

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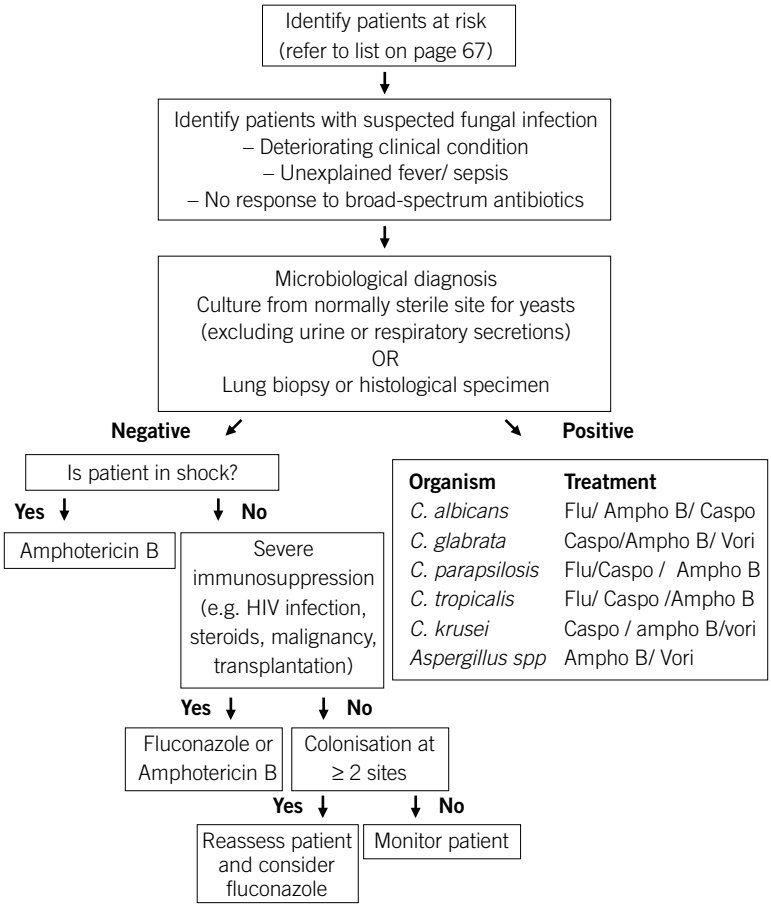
3. *Curr Anaes Crit Care* 2005;1: 231-241

Algorithm for antifungal therapy in suspected/proven invasive fungal infection in the ICU patient



MICRO-ORGANISMS OF CONCERN IN ICU

Infections due to resistant micro-organisms in the intensive care setting have been increasing in recent years where few antimicrobials are available as therapeutic options. Such dependence on these few antimicrobials further perpetuates the problem by increasing the emergence of "superbugs".

Infections in the following groups of patient are more likely to be due to multidrug- resistant (MDR) micro-organisms.

1. Prolonged hospital stay (> 5 days)
2. Previous hospitalisation of > 2 days within past 90 days
3. Was on antibiotics within past 90 days, especially broad-spectrum antibiotics
4. Antibiotic resistance in the area
5. Admission from long-term care institution
6. Chronic renal dialysis within past 30 days
7. Poor underlying condition
8. Immunocompromised or neutropenic patient/ immunosuppressive therapy
9. Presence of invasive catheters e.g. central venous catheters

A. Extended-spectrum beta-lactamase (ESBL) producing enterobacteriaceae e.g. *Klebsiella spp., E. coli*

In 2001 in the US, the incidence of ESBL-producing enterobacteriaceae ranges from 1.3% to 8.6% and 1 out of 5 isolates are resistant not only to 3rd generation cepahalosporins but also to aminoglycosides, quinolones and trimethoprim-sulfamethoxazole. 3rd generation cepahalosporins use, ceftazidime in particular has been implicated as an important factor in nosocomial infections caused by ESBL producers.

For typical ESBL-producing enterobacteriaceae infections, it is generally accepted that the therapy of choice is a carbapenem.

Preferred antimicrobial: IV Imipenem 500mg q6h OR IV Meropenem 1g q8h

Other treatment options include:

1. Fluroquinolones, trimethoprim/sulfamethoxazole and aminoglycosides may be used if organisms are known to be susceptible.
2. If active in-vitro, beta-lactam/beta-lactamase inhibitor combinations may be used at higher concentrations. ESBL hyperproducers are resistant to piperacillin / tazobactam and ticarcillin/clavulanate.
3. For carbapenem-resistant strains, polymyxin B or colistin (polymyxin E) are among the first-line agents for treatment in patients with these serious infections.

B. Multidrug-resistant *Acinetobacter baumannii*

Acinetobacter spp. is one of the most important Gram-negative organism associated with nosocomial outbreaks as it can be disseminated easily and survive in the environment for prolonged periods. MDR *A. baumannii* is now recognised as one of the most difficult nosocomial infections to control and treat. Carbapenem-resistant *Acinetobacter* is increasingly being reported.

Preferred therapy: IV Cefoperazone / sulbactam 2g q12h
OR
IV Ampicillin / sulbactam 1.5-3g q6-8h

Alternative therapy: IV Meropenem 1g q8h
OR
IV Imipenem 500mg q6-8h

In strains resistant to both carbapenems and sulbactams, IV polymyxin B or colistin remains the only treatment options. Acinetobacter isolates resistant to colistin and polymyxin B have also been reported.

C. *Pseudomonas aeruginosa*

Nosocomial infections caused by *P. aeruginosa* are frequently life-threatening and often challenging to treat. Selection of resistance during anti-pseudomonal therapy among initially susceptible isolates occurs frequently with this pathogen, resulting in the emergence of resistance to multiple drugs.

Multidrug-resistant *P. aeruginosa* (MDRPA) is defined as isolates intermediate or resistant to at least three drugs in the following classes: ß-lactams, carbapenems, aminoglycosides, and fluoroquinolones.

Patients with severe MDRPA infections should be treated with combination therapy, consisting of an anti-pseudomonal ß-lactam with an aminoglycoside or fluoroquinolone rather than aminoglycoside and fluoroquinolone combinations, to provide adequate therapy. Although use of double ß-lactam combinations has been discouraged in clinical practice, the results from in-vitro synergy testing indicate frequent synergy without antagonism. Because of the adverse-effect profile, polymyxins are usually reserved as a salvage therapy. Intravenous colistin or ploymyxin B with or without adjunctive therapy, such as a ß-lactam or rifampin are used. When treatment options become limited, the above are still used despite resistance to one or both agents in the combination.

Specific pathogen	Antimicrobials		Notes
	Preferred	**Alternative**	
	Monotherapy		
P. aeruginosa	IV Cefepime 2g q12 h OR IV Piperacillin / tazobactam 4.5g q8h	IV Meropenem 1g q8h OR IV Imipenem 500 mg q6 - 8h	Though often recommended, there is little clinical evidence that combination therapy with aminoglycosides is superior in preventing treatment failure and reducing the emergence of resistant organisms. Therefore, combination with aminoglycosides should be reserved for the severely ill patients. Generally, polymyxin E is preferred over polymyxin B as there is increased nephrotoxicity associated with polymyxin B.
	Combination therapy		
	The above PLUS IV Amikacin 15 mg/kg q24 h OR IV Ciprofloxacin 400mg q8 h		
MDR *P. aeruginosa*	Combination therapy as above	IV Colistin (Polymyxin E) 2.5-5 mg/kg/day in 3 divided doses (1 mg = 12500 units) OR IV Polymyxin B 2.5-3 mg/kg/day in 2 divided doses (1 mg = 10000 units)	

D. Methicillin-Resistant *Staphylococcus aureus* (MRSA)

According to data published in 1999 by the US Centers for Disease Control and Prevention (CDC) as part of their National Nosocomial Infection Surveillance (NNIS) System, about 50% of ICU isolates from documented infections are caused by MRSA. In the Malaysian setting, MRSA isolates are also on the rise.

Preferred therapy: IV Vancomycin 1g q12h

Alternative therapy: IV Linezolid 600 mg q12h
OR
IV Teicoplanin 6mg/kg q12h X 2 doses; then 6mg/kg q24h

Higher vancomycin plasma levels should be targeted when treating MRSA pneumonia (see section on Therapeutic drug monitoring on page 78). Linezolid has good lung penetration.

Other newer therapeutic options include daptomycin, quinipristin-dalfopristin and tigecycline but these drugs are currently not available in Malaysia. Daptomycin should not be used for pneumonia due to high failure in clinical trials.

E. Vancomycin-Resistant Enterococcus (VRE)

In 2000, a report from the NNIS System reported that up to 29% of all enterococcal blood isolates grew *E. faecium*. *E. faecium* are less susceptible to ß-lactam antibiotics and more often resistant to vancomycin and ampicillin than *E. faecalis*. The past two decades have witnessed the rapid emergence of MDR enterococci. Well established association exists between colonisation or infection with VRE with the use of vancomycin, 3rd generation cephalosporins and antianaerobic drugs such as metronidazole, clindamycin or carbapenems. Other risk factors include prolonged hospitalisation, high severity of illness score, intraabdominal surgery and renal insufficiency.

Preferred therapy: IV Linezolid 600mg q12h

Daptomycin and tigecycline have good in-vitro activity against VRE but currently are awaiting further clinical studies. Quinupristin-dalfopristin is an alternative antimicrobial for treating VRE infections but it is a bacteriostatic agent, potentially allowing emergence of resistance.

Nitrofurantoin can be considered for treating enterococci urinary tract infections.

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THERAPEUTIC DRUG MONITORING

Monitoring of drug concentration for aminoglycosides and vancomycin ensures achievement of therapeutic drug level and reduces the risks of toxicity.

Peak and trough levels should be monitored at steady states (usually 3rd or 4th dose) with dosing adjustments made accordingly. Blood sample for the trough level is taken just prior to administration of the dose while for the peak level, it should be taken 30–60 minutes after the dose is administered.

Drug	Trough concentration	Peak concentration	Notes
Gentamicin	ODD: < 2 µmol/L (< 1 µg/ml) MDD: < 4 µmol/L (<2 µg/ml)	ODD: 32-48 µmol/L (16-24 µg/ml) MDD: 8-20 µmol/L (4-10 µg/ml)	Use multiple daily dosing for treating endocarditis
Netilmicin	ODD: < 2 µmol/L (< 1 µg/ml) MDD: < 4 µmol/L (<2 µg/ml)	ODD : 32-48 µmol/L (16-24 µg/ml) MDD: 8-20 µmol/L (4-10 µg/ml)	
Amikacin	ODD: < 1.7 µmol/L (< 1µg/ml) MDD: < 17.2 µmol/L (<10 µg/ml)	ODD: 95-109 µmol/L (56-64 µg/ml) MDD: 34-51 µmol/L (20-30 µg/ml)	
Vancomycin	3-7 µmol/L (5-10 µg/ml)	14-28µmol/L (20-40 µg/ml)	Higher levels may be required in pneumonia and infective endocarditis. Trough: 10-15 µg/ml Peak: 30-45 µg/ml

ODD: once daily dosing MDD: multiple daily dosing

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2. TDM protocol guide: Pharmacy Dept. HKL, 2006

APPENDIX A
Dosage adjustment for renal impairment

Below is the formula used to calculate the creatinine clearance:

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

Drug	Normal dose	Cr clearance 10 -50ml/min	Cr clearance < 10ml/min	Comments
Acyclovir	5 – 12.5 mg/kg q8h	5-12.5mg/kg q12h – q24h	2.5mg/kg q24h	
Amphotericin B	0.4 – 1 mg/kg q24h	ND q24h	ND q 24-48h	
Ampicillin/sulbactam	1.5 – 3g q6h	q8-12h	q24h	CVVH no data
Amoxicillin/clavulanate	500/125mg q8h	200-500mg Am. component q12h	200-500mg Am. component q24h	
Cefepime	2g q12h (max. dose 6g/day)	2gm q12-24h	1g q24h	HD: extra 1g AD
Cefotaxime	2g q8h	q12-24h	q24h	
Ceftazidime	2g q8h	q24 -48h	q48h	
Ceftriaxone	2g q24h	Unchanged	Unchanged	
Ciprofloxacin	400mg q12h	50% -75%	50%	
Cloxacillin	2g q4-6h	100%	50%	
Fluconazole	200-400mg q24h	100-200mg q24h	100-200mg q24h	
Ganciclovir	Induction:5mg/kg q12h Maintenance: 5mg/kg q24h	Induction: 1.25 -2.5mg/kg q24h Maintenance:0.6–1.25mg/kg q24h	Induction: 1.25mg/kg 3X/week Maintenance:0.625mg/kg 3X/week	
Imipenem	0.5g q6h	250mg q6 -12h	125 -250mg q12h	CVVH:0.5-1g12h
Itracanazole	200mg q12h	Do not use if Cr Cl < 30 due to accumulation of carrier, cyclodexin		
Meropenem	1g q8h	1g q12h	0.5g q24h	CVVH: 1g q12h
Metronidazole	500mg q8h	100%	50%	
Penicillin G	2-4 MU q6h	75%	50%	
Piperacillin	3-4 m q4-6h	q6-8h	q8h	
Piperacillin/tazobactam	4.5g q6 - 8h	2.25g q6h	2.25g q8h	
Trimethprim/ Sulfamethoxazole	5mg/kg q12h	50%	Not recommended	
Vancomycin	1g q12h	1g q24 – 96h	1g q4-7days (same for HD)	CVVH: 500mg q24 - 48h

CVVH: continuous veno-venous haemofiltration. HD: haemodialysis AD: after dialysis ND: Normal dose

Estimated creatinine clearance (ml/min)	Once daily dosing (ODD)			Multiple daily dosing (MDD)	
	Gentamicin/ Tobramycin	Amikacin	Netilmicin	Gentamicin/tobramycin/ Netilmicin	Amikacin
>80	5mg/kg	15mg/kg	6.5mg/kg	2mg/kg q8h	5 -7.5mg/kg q12h
60-79	4mg/kg	12mg/kg	5mg/kg	2mg/kg q12h	5 -7.5mg/kg q12h
40 -59	3.5/kg	7.5mg/kg	4mg/kg	2mg/kg q18h	5 -7.5mg/kg q18h
30 -39	2.5mg/kg	4mg/kg	2mg/kg	2mg/kg q24h	5 -7.5mg/kg q24h
20-29	4mg/kg q48h	7.5mg/kg q48h	3mg/kg q48h	2mg/kg q24h	5 -7.5mg/kg q24h
10 – 19	3mg/kg q48h	4mg/kg q48h	2.5mg/kg q48h	2mg/kg q48h	5 -7.5mg/kg q48h
<10	2mg/kg q72h	3mg/kg q72h	2mg/kg q72h	2mg/kg q72h	5 -7.5mg/kg q72h

Estimated creatinine clearance (ml/min)	Colistin (Polymyxin E)	Polymyxin B
>50	1 – 1.5mg/kg q8h	2.5 – 3mg/kg q24h (in 2 divided doses)
30 - 50	1 – 1.5mg/kg q24h	2.5 – 3mg/kg X 1 loading dose then 1 – 1.5mg/kg q24h
10 - 29	1 – 1.5mg/kg q24h	2.5 -3mg/kg X 1 loading dose then 1 – 1.5mg/kg q48 – 72h
<10	1 – 1.5mg/kg q48h	2.5 -3mg/kg X 1 loading dose then 1 – 1.5mg/kg q48 – 72h

Appendix B
Antimicrobials and FDA pregnancy risk categories

Antimicrobial	Risk category	Antimnicrobial	Risk category
Antibacterial agents:			
Aminoglycosides:			
Amikacin, gentamicin, isepamicin, netilmicin, streptomycin, tobramycin	D	Antiparasitic agents:	
		Albendazole/mebendazole	C
Beta lactams:		Praziquantel	B
Penicillins; pens+BLI; cephalosporins; aztreonam	B	Pyrimethamine/pyrisulfadoxine	C
Imipenem/cilastatin	C	Quinidine	C
Meropenem, ertapenem	B	Quinine	X
Chloramphenicol	C	Antimycobacterial agents:	
Ciprofloxacin, oflox, levoflox, gatiflox, gemiflox, moxiflox	C	Dapsone	C
Clindamycin	B	Ethambutol	"safe"
Colistin	C	Ethionamide	"do not use"
Dalbavancin	C	INH, pyrazinamide	C
Daptomycin	B	Rifabutin	B
Linezolid	C	Rifampicin	C
Macrolides:		Antiviral agents:	
Erthromycin/azithromycin	B	Acyclovir	B
Clarithromycin	C	Amantadine	C
Metronidazole	B	Ganciclovir	C
Nitrofurantoin	B	Interferons	C
Sulfonamides/trimethoprim	C	Lamivudine	C
Tetracyclines, tigecycline	D	Oseltamivir	C

Appendix B
Antimicrobials and FDA pregnancy risk categories

Antimicrobial	Risk category	Antimnicrobial	Risk category
Vancomycin	C	Ribavirin	X
Antifungal agents:			
Amphotericin B preparations	B	Rimantadine	C
Caspofungin	C	Zidovudine	C
Fluconazole, itraconazole, ketoconazole, flucytosine	C		
Voriconazole	D		

FDA Pregnancy Risk Categories:

A – studies in pregnant women no risk;

B – animal studies no risk, but human not adequate or animal toxicity but human studies no risk;

C – animal studies show toxicity, human studies inadequate but benefit of use may exceed risk;

D – evidence of human risk, but benefits may outweigh;

X – fetal abnormalities in humans, risk more than benefit


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