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MALAYSIAN SOCIETY OF INFECTION
CONTROL AND INFECTIOUS DISEASES

CONSENSUS GUIDELINES ON **TREATMENT OF MULTIDRUG RESISTANT GRAM NEGATIVES**



First published 2024

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Published by:

Malaysian Society of Infectious Diseases and Chemotherapy

c/o Department of Medical Microbiology & Immunology

Faculty of Medicine, 16th Floor, Pre-Clinical Building

Jalan Yaacob Latif, Badan Tun Razak

Cheras 56000, Kuala Lumpur, MALAYSIA

Designed by:

Ultra Works Sdn Bhd

This guideline was made possible by an educational grant from Pfizer Malaysia Sd Bhd. The sponsor provided financial support but had no influence over the content presented in this guidelines. The content and opinions expressed in this book are solely those of the expert panel.

C O N S E N S U S G U I D E L I N E S

**THE TREATMENT OF
MULTIDRUG
RESISTANT
GRAM
NEGATIVES**

—— FIRST EDITION ——

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Foreword

In Malaysia, the emergence of multidrug-resistant (MDR) Gram-negative infections presents a formidable challenge to the healthcare community. This consensus guideline represents the collective expertise of Adult and Paediatric infectious diseases specialists. Microbiologists and Pharmacists, who have rigorously evaluated the latest data to prepare this guideline. Our goal is to provide clinicians with a clear treatment and prevention strategy that balances efficacy, safety, and the stewardship of antimicrobial resources. The treatment recommendations within this guideline are tailored to address the complexities of local MDR pathogens, offering a tiered approach to therapy that considers pathogen type, local resistance patterns and availability of various antibiotics. We hope that by adhering to these guidelines, healthcare providers can optimise patient outcomes while contributing to the effort to curb the spread of resistance. It is our collective responsibility to ensure that these guidelines are adhered to for the benefit of patients today and the sustainability of effective antibiotics for future generations.

DISCLAIMER

The recommendations in this guideline are based on current medical knowledge and practices, which are subject to change as new information becomes available. These guidelines do not cover all possible clinical scenarios. The guidelines also do not include comprehensive drug information such as contraindications, precautions, drug-drug interactions relevant to the drugs recommended here. The complexity of clinical practice requires that in all cases, users of these guidelines understand the individual clinical situation, and exercise independent professional judgement when basing therapy on these guidelines. Hence for complicated situations, this guideline is not a substitute for appropriate expert advice. The authors and publishers of these guidelines will not be held liable for any direct, indirect, consequential or other damages arising therefrom.



Antimicrobial Stewardship (AMS) Principle

Injudicious use of antimicrobials results in the emergence of multi-drug-resistant organisms (MDRO), which are often difficult to treat and associated with high mortality. AMS is a coordinated program to guide the implementation of efforts promoting judicious antimicrobial use, advancing patient safety, and improving outcomes.

Approaches to good antimicrobial prescribing are as follows:

Documentation of the Indication

Clinical Diagnosis: Specify the clinical condition, such as pneumonia, urinary tract infection (UTI), acute gastroenteritis (AGE), line-related bloodstream infection, or meningitis.

Evidence for Bacterial Infection: Look for evidence to confirm the presence of a bacterial infection.

Diagnostic Tools: Ensure appropriate cultures are obtained based on the diagnosis and site of infection before initiating antibiotic therapy.

Drug

Selection of Antimicrobial Agent: Choose the appropriate antimicrobial agent considering the patient's drug allergy history.

- For empirical antibiotic selection, refer to local antimicrobial guidelines, such as the National Antimicrobial Therapy Guidelines (NAG)¹, Malaysia.

Dose and Route (IV or Oral): Determine the dose and frequency of antibiotic administration.

- Assess the need for any dose adjustments.
- Optimise the dose based on pharmacokinetic and pharmacodynamic parameters (e.g., prolonged infusion for β -lactam antibiotics).

Duration

Duration of Therapy: Establish the duration based on the site of infection and the organism, following relevant guidelines.

Review and Documentation: Review and document the prescription at 72 hours.

- For IV to oral conversion, refer to the protocol on AMS programs in healthcare facilities by the Ministry of Health Malaysia³.



Source Control

Debridement and Drainage: Always consider the removal of the infection source, such as an abscess or infected devices.

Optimization antibiotics

Streamlining Antibiotics: Optimise from initial broad-spectrum antibiotics to narrower spectrum antibiotics at 48-72 hours, based on culture results or clinical improvement if cultures are unavailable.

Directed Use of Antibiotics: Utilise culture susceptibility results to guide antibiotic selection. Critically evaluate microbiological results along with the clinical presentation to distinguish infection from colonisation or contamination. Select the most effective, narrow-spectrum, and least toxic antibiotic based on the identified pathogen and its antimicrobial susceptibility.

- Monotherapy is preferred unless combination therapy is proven necessary for efficacy (e.g., mixed infections), synergy, or to reduce the selection of clinically significant resistance (e.g., treatment of tuberculosis, HIV infection).

Intravenous (IV) to Oral (PO) Antimicrobials Conversion

This describes the practice of converting intravenous antimicrobial therapy to an effective oral formulation. Evidence has demonstrated the efficacy, safety and economic impact of IV to PO antimicrobials conversion. In addition to that, this strategy can minimise adverse events associated with IV therapy, increase patient comfort and mobility as well as enabling early hospital discharge.

The optimal time to consider switching a patient to oral therapy is after 48 to 96 hours of intravenous therapy. This period of time allows the clinician to evaluate the patient's microbiology results and assess their response to treatment.

Before switching to oral antimicrobial, patient must meet a number of criteria:

- A. Display signs of clinical improvement
- B. Able to tolerate oral therapy.
- C. Good compliance to oral therapy.
- D. Not having a condition in which higher concentrations of antibiotics are required in the tissue.



Conditions to consider for IV to PO Conversion:

- i. Pneumonia
- ii. Skin and soft tissue infections
- iii. Urinary tract infections
- iv. Uncomplicated Gram-negative bacteraemia
- v. Intra-abdominal infection without deep-seated collections

Suggest to consult ID physician or AMS physician prior to IV to oral conversion for conditions that may be difficult to treat such as:

- i. Osteomyelitis
- ii. Septic arthritis
- iii. Infected implant or prostheses
- iv. Necrotising soft tissue infection
- v. Melioidosis
- vi. Deep-seated infection e.g. abscesses/empyema
- vii. Complicated orbital cellulitis (abscess or other complication)



Duration Of Treatment

Duration of therapy should not differ for infections caused by MDRO compared to infections caused by more susceptible organisms. Shortening the duration of treatment appropriately reduces the anti-infective use without compromising clinical outcomes. This minimises the emergence of resistance by decreasing selection pressure⁴.

Urinary tract infection

Suggested duration:

- Uncomplicated cystitis: 3 - 5 days
- Complicated UTI: 5-10 days

Infection outside urinary tract

Suggested duration:

- Complicated intra-abdominal infection: 5-10 days
- Pneumonia/Bacteraemia: 7-10 days⁵

The duration of treatment should be calculated from the initiation of an appropriate agent.

Definitive treatment durations should be individualised according to:

- Infection sites
- Source control
- The underlying comorbidities
- The initial response to therapy



Section 1: Amp-C Beta lactamase Producing Enterobacterales

1.1 Epidemiology / Microbiology

Epidemiology/ Microbiology details	Description/Recommendations							
Introduction and epidemiology of Amp-C Beta-lactamase Producing Enterobacterales in Malaysia	- AmpC-type cephalosporinases are Ambler class C β-lactamase. - AmpC β-lactamase, aid in cell wall recycling and are capable of hydrolysing multiple β-lactam agents except cefepime and carbapenems. - There are 3 types of AmpC β-lactamases: <table border="1"> <thead> <tr> <th>Type</th><th>Features</th></tr> </thead> <tbody> <tr> <td>Inducible chromosomal gene expression</td><td> - Isolates are initially susceptible to ceftriaxone, cefotaxime, and ceftazidime. However, after exposure to a few doses of these antibiotics, resistance can be induced. - Organisms with moderate-high risk (~20%) of clinically significant inducible AmpC β-lactamases production » <i>Enterobacter cloacae complex</i> » <i>Klebsiella aerogenes</i> » <i>Citrobacter freundii</i> - Organisms with lower risk (<5%) of clinically significant inducible AmpC β-lactamases production » <i>Serratia marcescens</i> » <i>Providencia spp</i> » <i>Morganella morganii</i> </td></tr> <tr> <td>Stable chromosomal de-repression</td><td rowspan="2">These are consistently resistance to ceftriaxone, cefotaxime, and ceftazidime</td></tr> <tr> <td>Plasmid mediated-ampC genes</td></tr> </tbody> </table> - A study in a teaching hospital found 39.3% of cefotaxime and ceftriaxone-resistant <i>Enterobacter</i> spp. were positive for phenotypic AmpC⁶. - Currently, there are no national surveillance programs for AmpC β-lactamase producing Enterobacterales in Malaysia.	Type	Features	Inducible chromosomal gene expression	- Isolates are initially susceptible to ceftriaxone, cefotaxime, and ceftazidime. However, after exposure to a few doses of these antibiotics, resistance can be induced. - Organisms with moderate-high risk (~20%) of clinically significant inducible AmpC β-lactamases production » <i>Enterobacter cloacae complex</i> » <i>Klebsiella aerogenes</i> » <i>Citrobacter freundii</i> - Organisms with lower risk (<5%) of clinically significant inducible AmpC β-lactamases production » <i>Serratia marcescens</i> » <i>Providencia spp</i> » <i>Morganella morganii</i>	Stable chromosomal de-repression	These are consistently resistance to ceftriaxone, cefotaxime, and ceftazidime	Plasmid mediated-ampC genes
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Stable chromosomal de-repression	These are consistently resistance to ceftriaxone, cefotaxime, and ceftazidime							
Plasmid mediated-ampC genes								



Epidemiology/ Microbiology details	Description/Recommendations
Amp C detection	Currently, there is no CLSI-recommended test to detect AmpC β-lactamase producers. However, according to EUCAST, a potential AmpC producer is suspected when the isolate is resistant to cefoxitin (MIC > 8 mg/L or zone diameter <19 mm) combined with phenotypic resistance to ceftazidime and/or cefotaxime. EUCAST also describes on phenotypic AmpC confirmation tests based on the inhibition of AmpC by either cloxacillin or boronic acid derivatives. However, the distinction between plasmid-acquired and chromosomal AmpC is best achieved by genotypic method. Please consult your local clinical microbiologist for further information.

1.2 Infection Prevention and Control

Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Infection control precaution	Standard precaution
Hand Hygiene & PPE (Refer to page 56)	• Strict adherence to 5 moments of hand hygiene. • PPE use based on risk assessment.

1.3 Treatment

Infection details/ challenges	Recommendations Refer here for the suggested duration of treatment
Organisms with moderate risk of clinically significant inducible AmpC production (~20%) • <i>Enterobacter cloacae</i> complex • <i>Klebsiella aerogenes</i> • <i>Citrobacter freundii</i>	



Infection sites	
Uncomplicated cystitis	Confirm susceptibility before choosing antibiotic regimen Preferred Nitrofurantoin PO⁷ OR Trimethoprim/Sulfamethoxazole PO⁸⁻¹⁰ OR Single dose Aminoglycoside (Gentamicin/Amikacin) IV¹¹ Less preferred Ciprofloxacin PO¹² For patients who are already on empirical beta-lactam antibiotics (such as ceftriaxone, ceftazidime), if the agent is tested susceptible in vitro and clinical improvement is observed, complete the treatment by including the period of the empirical antibiotic given. Oral step-down to one of the drugs mentioned above is preferred in these situations.
Acute pyelonephritis or Complicated urinary tract infections (cUTI)	Confirm susceptibility before choosing antibiotic regimen Preferred Trimethoprim/Sulfamethoxazole PO⁸⁻¹⁰ OR Once Daily Aminoglycoside IV (Gentamicin/Amikacin - requires TDM monitoring)^{13,14} OR Cefepime IV Less preferred Ciprofloxacin PO¹²
Infection outside urinary tract	Cefepime susceptible isolates Preferred Cefepime IV^{8,15}



Infection sites	
Infection outside urinary tract	Cefepime susceptible dose-dependent, SDD Cefepime IV ^{8,15} OR Carbapenem ^{16,17} (Ertapenem/Meropenem/Imipenem-cilastatin) IV* *Carbapenem is preferred in high-burden infections (Appendix 1: Infection Severity Assessment) <i>Referral to an ID physician/clinical microbiologist is recommended for Cefepime Non-Susceptible isolates infection (SDD and Resistant)</i>
	Cefepime resistant isolates Preferred Carbapenem ^{8,15} (Ertapenem/Meropenem/Imipenem-cilastatin) IV <i>Referral to an ID physician/clinical microbiologist is recommended for Cefepime Non-Susceptible isolates infection (SDD and Resistant)</i>
Lower risk of clinically significant inducible AmpC production (<5%) • <i>Serratia marcescens</i> • <i>Providencia spp</i> • <i>Morganella morganii</i>	
Infection sites	
Uncomplicated cystitis	Confirm susceptibility before choosing antibiotic regimen Preferred Nitrofurantoin PO ⁷ OR Trimethoprim/Sulfamethoxazole PO ⁸⁻¹⁰ OR Single dose Aminoglycosides (Gentamicin/Amikacin) IV ¹¹



Infection sites	
	Less preferred Ciprofloxacin PO¹² If the patient was already on empirical β-lactam antibiotics (such as ceftriaxone, ceftazidime), if the agent is tested susceptible in vitro and clinical improvement is observed, complete the treatment by including the period of the empirical antibiotic given oral step-down to one of the drugs mentioned above is preferred in these situations.
Acute pyelonephritis or Complicated urinary tract infections (cUTI)	Confirm susceptibility before choosing antibiotic regimen Preferred Trimethoprim/Sulfamethoxazole PO⁸⁻¹⁰ OR Once Daily Aminoglycoside (Gentamicin/Amikacin) IV (requires TDM monitoring)^{13,14} OR Ceftriaxone/Cefotaxime IV Less preferred Ciprofloxacin PO¹²
Infection outside urinary tract	Non-severe infection, or non-high-burden disease As per susceptibility testing
	Severe, high-burden disease (Appendix 1: Infection Severity Assessment) Preferred Cefepime IV^{8,15} <i>Referral to an ID physician/clinical microbiologist is recommended for Cefepime Non-Susceptible isolates infection (SDD and Resistant)</i>
Paediatric considerations	
Antibiotic options similar to adults	



Clinical pearls	
Can I use Piperacillin-tazobactam to treat moderate-high risk of clinically significant inducible AmpC production?	Piperacillin-tazobactam is not recommended for the treatment of infections caused by Enterobacterales at moderate to high risk of clinically significant inducible AmpC production (<i>Enterobacter cloacae</i> complex, <i>Klebsiella aerogenes</i>, <i>Citrobacter freundii</i>) A higher risk of mortality and treatment failure was observed in multiple observational studies^{18–20}
Role of newer β-lactam-β-lactamase inhibitor (BLBLI) combinations to treat moderate-high risk of clinically significant inducible AmpC production	Avoid these agents. These agents are reserved for the treatment of difficult to treat Carbapenem-resistant organisms.
• Ceftazidime-avibactam • Meropenem-varbobaactam • Imipenem-cilastatin-relebactam	



SECTION 2: Extended-spectrum Beta-lactamase (ESBL) Producing Enterobacterales

2.1 Epidemiology/Microbiology

Epidemiology/ Microbiology details	Description/Recommendations																				
Introduction and Epidemiology of ESBL-producing Enterobacterales (ESBL-E) in Malaysia	- Extended-spectrum β-lactamases (ESBL) are plasmid-mediated β-lactamases capable of hydrolysing penicillin, third and fourth generation cephalosporin and monobactams excluding carbapenem and cephamycin. - In the National Antibiotic Resistance Surveillance 2022²¹, almost a quarter of <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i> clinical isolates from healthcare settings are resistant to third generation cephalosporin. - Another study conducted at Hospital Pakar Sultanah Fatimah in Johor revealed a significantly high prevalence of ESBL genes among <i>K. pneumoniae</i> isolates. ESBL genes were detected in 85.8% isolates (121/141). The predominant genes, namely blaSHV, blaTEM, and blaCTX-M-1, were identified with frequencies of 75.2%, 41.1%, and 44%, respectively²³.																				
ESBL screening test in the laboratory	- Disk Diffusion - Bacteria show high-level co-resistance to third generation cephalosporin. According to CLSI M100 34th Edition 2024, zone diameters below may indicate ESBL production. i. For <i>K. pneumoniae</i>, <i>K. oxytoca</i> and <i>E. coli</i> <table border="1"> <thead> <tr> <th>Antibiotic</th><th>Zone Diameter</th></tr> </thead> <tbody> <tr> <td>Cefpodoxime 10 μg</td><td>≤ 17 mm</td></tr> <tr> <td>Ceftazidime 30 μg</td><td>≤ 22 mm</td></tr> <tr> <td>Aztreonam 30 μg</td><td>≤ 27 mm</td></tr> <tr> <td>Cefotaxime 30 μg</td><td>≤ 27 mm</td></tr> <tr> <td>Ceftriaxone 30 μg</td><td>≤ 25 mm</td></tr> </tbody> </table> ii. For <i>Proteus mirabilis</i> <table border="1"> <thead> <tr> <th>Antibiotic</th><th>Zone Diameter</th></tr> </thead> <tbody> <tr> <td>Cefpodoxime 10 μg</td><td>≤ 22 mm</td></tr> <tr> <td>Ceftazidime 30 μg</td><td>≤ 22 mm</td></tr> <tr> <td>Cefotaxime 30 μg</td><td>≤ 27 mm</td></tr> </tbody> </table> <i>*Testing more than one antimicrobial agent improves the sensitivity of ESBL detection.</i>	Antibiotic	Zone Diameter	Cefpodoxime 10 μ g	≤ 17 mm	Ceftazidime 30 μ g	≤ 22 mm	Aztreonam 30 μ g	≤ 27 mm	Cefotaxime 30 μ g	≤ 27 mm	Ceftriaxone 30 μ g	≤ 25 mm	Antibiotic	Zone Diameter	Cefpodoxime 10 μ g	≤ 22 mm	Ceftazidime 30 μ g	≤ 22 mm	Cefotaxime 30 μ g	≤ 27 mm
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Cefpodoxime 10 μ g	≤ 22 mm																				
Ceftazidime 30 μ g	≤ 22 mm																				
Cefotaxime 30 μ g	≤ 27 mm																				



Epidemiology/ Microbiology details	Description/Recommendations
ESBL confirmatory test in the laboratory	A ≥ 5-mm increase in zone diameter for either antimicrobial agent tested in combination with clavulanate vs the zone diameter of the agent when tested alone = ESBL (e.g. ceftazidime zone = 16; ceftazidime-clavulanate zone = 21). *According to CLSI M100 34th Edition 2024, this method is only validated for <i>Klebsiella pneumoniae</i>, <i>Klebsiella oxytoca</i>, <i>Escherichia coli</i>, and <i>Proteus mirabilis</i> Other <i>Enterobacteriales</i> can produce ESBL. However, there is no CLSI-approved testing method. Please consult a clinical microbiologist.

2.2 Infection Prevention and Control

Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Infection control precaution (Refer to page 56)	- Standard precaution - Contact precaution (based on risk assessment for onward transmission) - Alert should be placed in patient's notes or electronic medical records, EMR (Tagging)
Placement (Refer to page 56)	- Single isolation room with ensuite preferred; cohorting allowed, if necessary, based on risk assessment. - Appropriate signage at the door or cohorting area.
Hand Hygiene & PPE (Refer to page 56)	- Strict adherence to 5 moments of hand hygiene. - Gloves and gowns are required upon entering the room. - PPE cart placed outside of the room. - Gowns should be removed before leaving the patient care area to avoid contaminating outside the patient care areas. - Clinical waste bin (yellow) placed inside the room.



Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Equipment (Refer to page 60)	• Use dedicated equipment. • Shared equipment must be disinfected between patients according to Spaulding's classifications.
Environmental hygiene (Refer to page 59)	• Daily cleaning with emphasis on high-touch surfaces. • Terminal cleaning on discharge, including curtain change • Adherence to hand washing sink protocol
Skin disinfectant (Refer to page 59)	Daily chlorhexidine or octenisan throughout admission.
Active surveillance (Refer to page 61)	To discuss with the ID or IPC team.
Clearance Criteria for Release from Isolation & Transmission-Based Precaution (untagging) (Refer to page 62)	• Patients should be on contact precautions throughout the hospitalisation. The exact duration of isolation is not known. • Consider discontinuation after six months have passed since the last positive culture, provided the patient does not have an active infection, is not on active treatment for ESBL infection, and has at least two consecutive negative rectal swabs at least one week apart. During the subsequent admission: • Alert should remain in patient notes • A risk assessment should be done to determine if pre-emptive contact precaution is required. • Screening may be done based on the risk assessment. • Refer to ID/Infection control for advice
Patient Movement in the Hospital, and Visitor Policy (Refer to page 65)	• Minimise the risk of environmental contamination during patient transport. • Encourage all visitors to perform hand hygiene before entering and leaving the patient's room • Advise visitors to avoid contact with other patients.
Other IPC strategies (i.e. practices in NICU/SCN etc)	For details, refer to page 66



2.3 Treatment

Infection Control Prevention	Recommendations Refer here for suggested duration of treatment
Infection sites	
Uncomplicated cystitis	Confirm susceptibility before choosing antibiotic regimen Preferred Nitrofurantoin PO ⁷ OR Trimethoprim/Sulfamethoxazole PO ⁸⁻¹⁰ Less preferred Ciprofloxacin PO ¹² OR Single dose Aminoglycosides (Gentamicin/Amikacin) IV ¹¹ OR Fosfomycin PO ⁷ (<i>for E. coli only</i>) OR Ertapenem IV ⁸ (<i>if no other available options</i>)
Acute pyelonephritis or Complicated urinary tract infections (cUTI)	Confirm susceptibility before choosing antibiotic regimen Preferred Trimethoprim/Sulfamethoxazole PO ⁸⁻¹⁰ OR Ciprofloxacin PO ¹² Less preferred Once-daily Aminoglycosides IV ^{13,14} (requires TDM monitoring) OR Carbapenems ⁸ (Ertapenem/Meropenem/Imipenem-cilastatin) IV (<i>if no other available options</i>)
Infection outside urinary tract	Preferred Carbapenems ⁸ (Ertapenem/Meropenem/Imipenem-cilastatin) IV Critically ill and hypoalbuminemia (< 25g/L)²⁶ Consider Meropenem IV or Imipenem-cilastatin IV



Paediatric considerations

Antibiotic options are similar to adults. Oral Fosfomycin is not used routinely in children below 12 years old. Paediatric ID consultation is advisable.

Clinical pearls

Can I use **Piperacillin-tazobactam** for the treatment of ESBL infections?

Piperacillin-tazobactam is not recommended for the treatment of **infections** caused by ESBL producing Enterobacterales, regardless of susceptibility.

For uncomplicated cystitis, may consider completing the empirical piperacillin-tazobactam course if the organism tested susceptible, clinical improvement is observed and oral step-down is not an option.

Can I use **Cefepime** for the treatment of ESBL infections?

Cefepime is not recommended for the treatment of **infections** caused by ESBL producing Enterobacterales, regardless of susceptibility.

For uncomplicated cystitis, may consider completing the empirical cefepime course if the organism tested susceptible, clinical improvement is observed and oral step-down is not an option.



SECTION 3: Carbapenem resistant Enterobacterales (CRE)

3.1 Epidemiology/Microbiology

Epidemiology/ Microbiology details	Description/Recommendations
Introduction and Epidemiology of Carbapenem-resistant Enterobacterales (CRE) in Malaysia	• Carbapenem-resistant Enterobacterales (CRE) isolates can be intermediate (I) or resistant (R) to one or more carbapenems. • Some Enterobacterales such as <i>Proteus spp.</i>, <i>Morganella spp.</i>, and <i>Providencia spp.</i> have intrinsic elevated minimum inhibitory concentrations (MICs) to imipenem and therefore results for meropenem, doripenem, and ertapenem should be used for these organisms to determine if these organisms meet the CRE definition. • The most predominant CRE is <i>Klebsiella pneumoniae</i> followed by <i>Enterobacter spp.</i>, and <i>Escherichia coli</i>²¹. • Increasing trend of meropenem and imipenem resistance rate observed in <i>Klebsiella pneumoniae</i>, <i>Escherichia coli</i>, and <i>Enterobacter sp.</i> from 2018 to 2022. For example, the resistance rate of <i>Klebsiella pneumoniae</i> to meropenem was 2.3% in 2018 and 2022 the resistance rate was 5.0%²¹. • The predominant mechanism of resistance in CRE is the production of carbapenemase hydrolysing enzyme²⁷. • Between 2016 and 2021, an analysis of more than 10,000 CRE isolates at IMR showed that the NDM gene was present in 83.6% of isolates, followed by OXA-48 (10.8%), IMP (1.5%), KPC (0.3%), and VIM (0.3%) genes²⁸.
Carbapenemase-producing CRE (CP-CRE)	• It is a subtype of CRE that produces carbapenemase enzyme(s). Testing of carbapenemase production can be done by laboratory using phenotypic tests such as modified carbapenem inactivation method (mCIM) or molecular tests such as PCR. • Institutional treatment guidelines, infection prevention procedures, or epidemiological investigations may necessitate the identification of carbapenemase-producing Enterobacterales.



Epidemiology/ Microbiology details	Description/Recommendations									
Non-Carbapenemase-producing CRE (Non-CP-CRE)	• CRE that is not producing carbapenemase enzymes and the mechanism of carbapenem resistance is contributed by other mechanisms such as porin modifications and efflux pumps. • Intrinsic resistance to certain carbapenem is not considered as carbapenem-resistant. For example, a <i>Proteus mirabilis</i> isolate is intrinsically resistant to imipenem but susceptible to other carbapenem are not considered as CRE.									
Phenotypic test to differentiate CP CRE and Non CP-CRE	Modified Carbapenem Inactivation Method (mCIM)²⁹ • This method demonstrated a sensitivity > 99% and specificity > 99% for detection of KPC, NDM, VIM, IMP, IMI, SPM, SME and OXA-type carbapenemases among Enterobacterales isolates investigated by Clinical and Laboratory Standards Institute (CLSI). • Meropenem disc is placed on a resistant isolate culture. The diameter of the zone of inhibition is interpreted as below: <table><tr><th>Carbapenemase positive:</th><th>Carbapenemase negative</th><th>Carbapenemase indeterminate:</th></tr><tr><td></td><td></td><td> » Zone diameter of 16–18 mm » Zone diameter of ≥ 19 mm and the presence of pinpoint colonies within the zone </td></tr><tr><td>Zone diameter of 6–15 mm or presence of pinpoint colonies within a 16–18 mm zone Report: Carbapenemase detected</td><td>Zone diameter of ≥ 19 mm (clear zone) Report: Carbapenemase not detected</td><td>Report: The presence or absence of a carbapenemase can't be confirmed</td></tr></table>	Carbapenemase positive:	Carbapenemase negative	Carbapenemase indeterminate:			» Zone diameter of 16–18 mm » Zone diameter of ≥ 19 mm and the presence of pinpoint colonies within the zone	Zone diameter of 6–15 mm or presence of pinpoint colonies within a 16–18 mm zone Report: Carbapenemase detected	Zone diameter of ≥ 19 mm (clear zone) Report: Carbapenemase not detected	Report: The presence or absence of a carbapenemase can't be confirmed
Carbapenemase positive:	Carbapenemase negative	Carbapenemase indeterminate:								
		» Zone diameter of 16–18 mm » Zone diameter of ≥ 19 mm and the presence of pinpoint colonies within the zone								
Zone diameter of 6–15 mm or presence of pinpoint colonies within a 16–18 mm zone Report: Carbapenemase detected	Zone diameter of ≥ 19 mm (clear zone) Report: Carbapenemase not detected	Report: The presence or absence of a carbapenemase can't be confirmed								



Epidemiology/ Microbiology details	Description/Recommendations		
Phenotypic test to differentiate CP CRE and Non CP-CRE	Combination of mCIM and EDTA carbapenem inactivation method can be used to differentiate metallo-β-lactamase and serine carbapenemases in Enterobacterales		
	mCIM and eCIM combination test		
	mCIM	eCIM	Report
	Negative	Do not interpret	Carbapenemase not detected
	Positive	Negative	Serine carbapenemase detected
	Positive	Positive	Metallo-β-lactamase carbapenemase detected
Inconclusive	Do not interpret	Inconclusive: The presence or absence of a carbapenemase cannot be confirmed.	

3.2 Infection Prevention and Control

Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Infection control precaution (Refer to page 56)	- Contact precaution + Standard precaution - Alert should be placed in patient's notes or EMR (Tag)
Placement (Refer to page 58)	- Single isolation room with ensuite preferred; cohorting allowed, if necessary, based on risk assessment. - Appropriate signage at the door or cohorting area.
Hand hygiene & PPE (Refer to page 56)	- Strict adherence to 5 moments of hand hygiene. - Gloves and gowns are required upon entering the room. - PPE cart placed outside of the room. - Gowns should be removed before leaving the patient care area to avoid contaminating outside the patient care areas. - Clinical waste bin (yellow) placed inside the room.



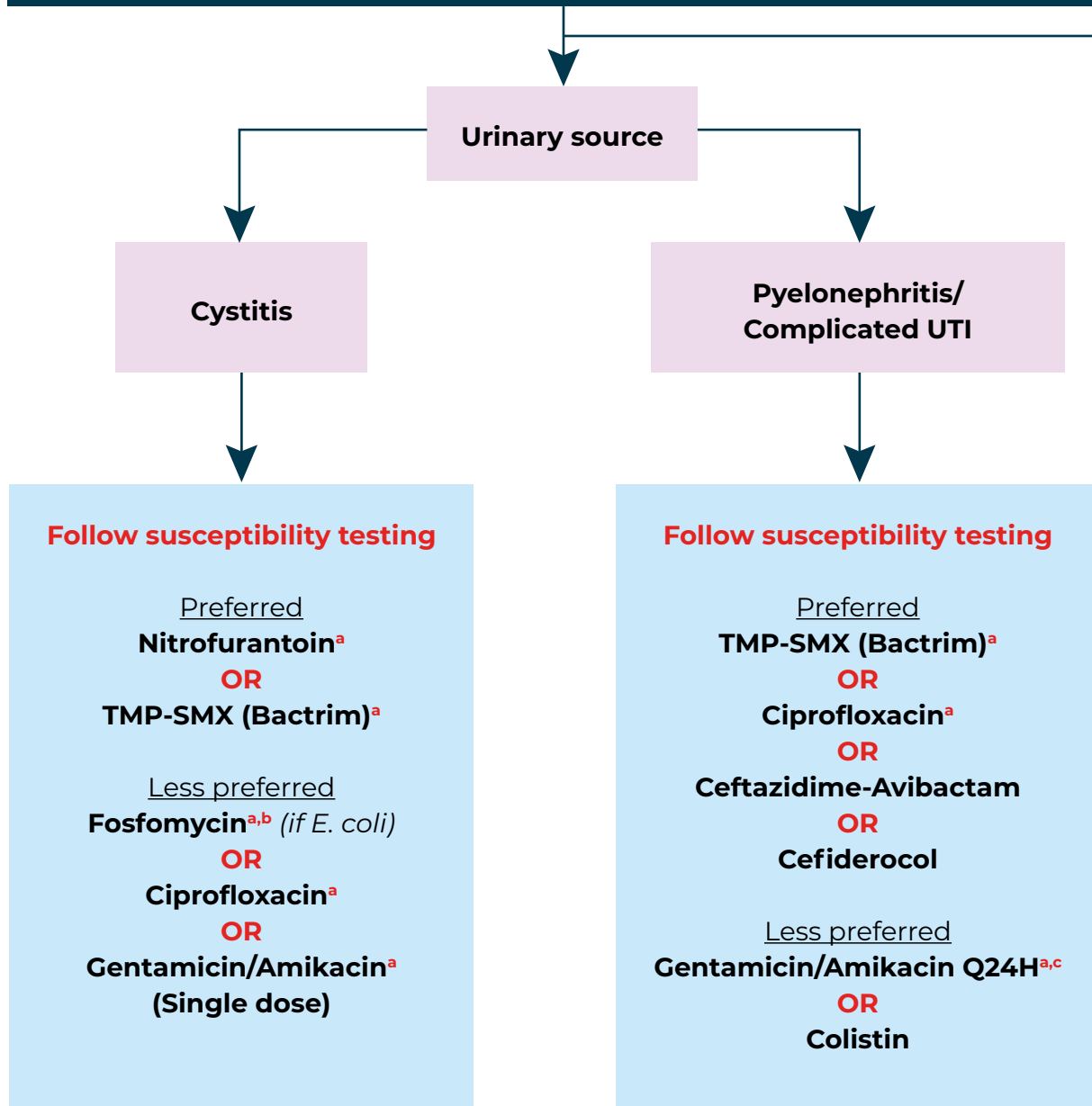
Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Equipment (Refer to page 60)	• Use dedicated equipment. • Shared equipment must be disinfected between patients according to Spaulding's classifications.
Environmental hygiene (Refer to page 59)	• Daily cleaning with emphasis on high-touch surfaces. • Terminal cleaning on discharge, including curtain change • Adherence to hand washing sink protocol.
Skin disinfectant (Refer to page 59)	Daily chlorhexidine or octenisan throughout admission.
Active surveillance (Refer to page 61)	To discuss with the ID or IPC team.
Clearance Criteria for Release from Isolation & Transmission-Based Precaution (untagging) (Refer to page 62)	Patients should be on contact precautions throughout the hospitalisation. The exact duration of isolation is not known. The recommended duration of isolation for CRE is for at least 1 year. Discontinuation of isolation (untagging) may be considered after 1 year has passed since the last positive culture, provided the patient does not have an active infection, is not on active treatment for CRE infection, has no risk for prolonged CRE carriage, and has at least two consecutive negative rectal swabs taken at least one week apart. The decision to remove from contact precaution before 1 year period may be made after consultation with ID/Infection control. For those released from isolation, during the subsequent admission: • Alert should remain in patient notes • A risk assessment should be done to determine if pre-emptive contact precaution is required. • Screening may be done based on the risk assessment. • Refer to ID/Infection control for advice



Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Patient Movement in the Hospital, and Visitor Policy (Refer to page 65)	• Minimise risks of environmental contamination during patient transport. • Encourage all visitors to perform hand hygiene before entering and leaving the patient's room • Advise visitors to avoid contact with other patients.
Other IPC strategies (i.e. practices in NICU/SCN etc)	For details, refer to page 66 .
In the event of surge of cases/ outbreak (Refer to page 66)	• Refer to ID/IPC for outbreak management & formation of the outbreak management team. • Refer to the Policies & Procedures on Infection Prevention & Control, 3rd ed., MOH Malaysia²⁴ and Responding to outbreaks of antimicrobial-resistant pathogens in health-care facilities: guidance for the Western Pacific region²⁵.



Carbapenem-resistant Enterobacterales (CRE Non-susceptible to ALL Carbapenems)



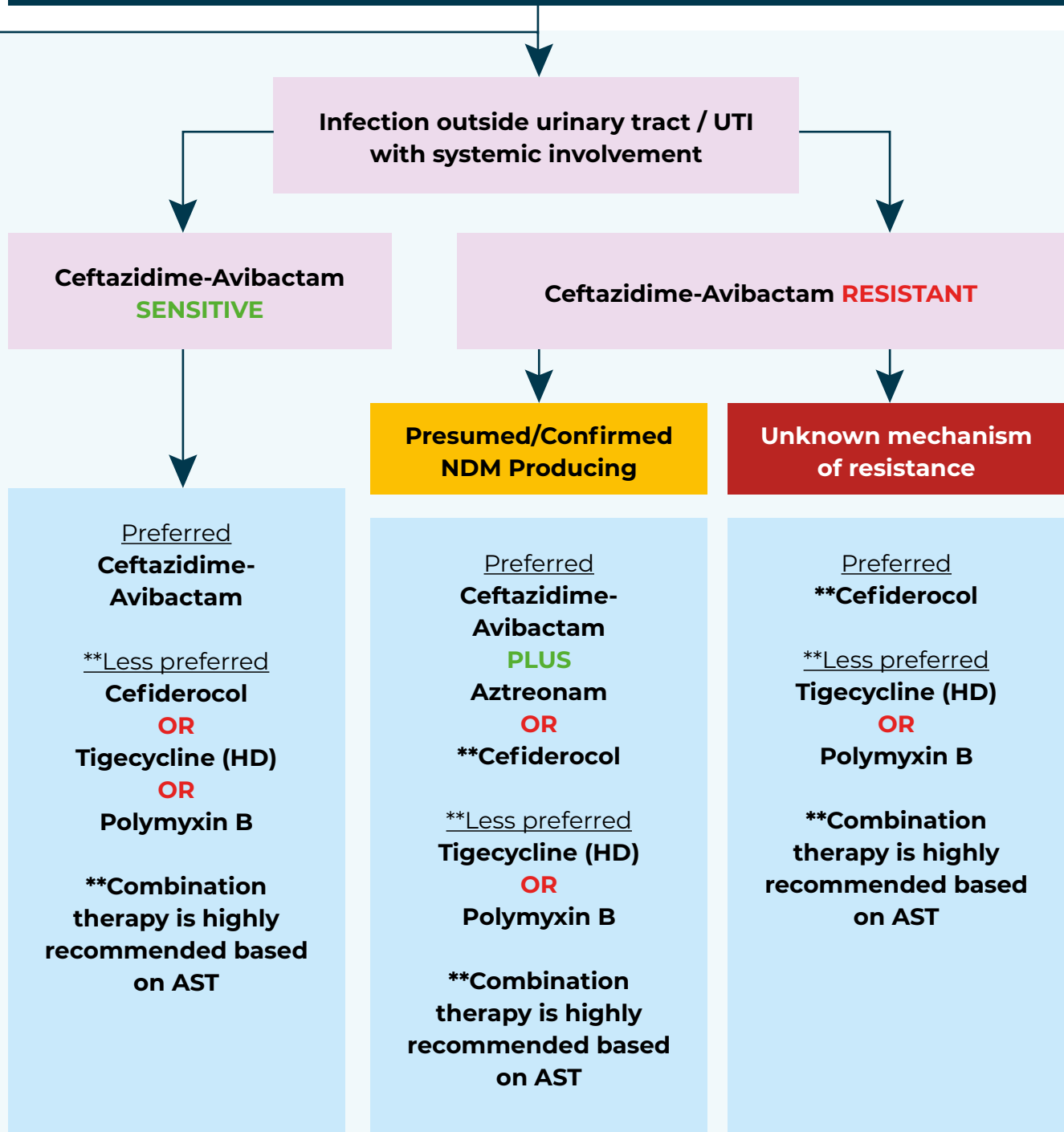
Note:

- a. Confirm susceptibility before choosing the antibiotics.
- b. Fosfomycin: Not suitable for Enterobacterales other than *E. coli* due to the possibility of harbouring FosA gene in other Enterobacterales that deactivate Fosfomycin.
- c. Aminoglycosides: Refer to pharmacist for TDM monitoring.

AST - Antimicrobial Susceptibility Testing



Carbapenem-resistant Enterobacterales (CRE Non-susceptible to ALL Carbapenems)



****If meropenem MIC $\leq$ 8mg/L, consider adding Meropenem as part of combination therapy**



3.3 Treatment

Infection details/ challenges	Recommendations Refer here for suggested duration of treatment
Non-CP CRE susceptible to Meropenem/Imipenem⁸	
CRE susceptible to Meropenem and Imipenem (MICs ≤ 1 $\mu\text{g/mL}$) and non-susceptible to Ertapenem (MICs ≥ 1 $\mu\text{g/mL}$)	High-dose carbapenem with 3 – 4 hours extended infusion (Appendix 5): Meropenem IV OR Imipenem IV
CRE Non-susceptible to Carbapenems (Meropenem/Imipenem/Ertapenem)⁸	
Infection sites	
Uncomplicated cystitis	Confirm susceptibility before choosing antibiotic regimen Preferred Nitrofurantoin PO OR Trimethoprim/Sulfamethoxazole PO Less preferred Fosfomycin PO (for <i>E.coli</i> only) OR Ciprofloxacin PO OR Single dose Aminoglycoside (Gentamicin/Amikacin) IV
Acute pyelonephritis or Complicated urinary tract infections (cUTI)	Confirm susceptibility before choosing antibiotic regimen Preferred Trimethoprim/Sulfamethoxazole PO OR Ciprofloxacin PO OR Ceftazidime/Avibactam IV OR Cefiderocol IV



Infection sites	
Acute pyelonephritis or Complicated urinary tract infections (cUTI)	Less Preferred Once Daily Aminoglycosides IV (Gentamicin/Amikacin - requires TDM monitoring) OR Colistin (Polymyxin E) IV
Infections outside of the urinary tract	Confirm susceptibility before choosing antibiotic regimen <i>Susceptible to Ceftazidime/Avibactam:</i> Preferred Ceftazidime/ Avibactam IV Less Preferred** *Cefiderocol IV OR *Tigecycline IV high dose OR *Polymyxin B IV (Colistin can be used if polymyxin B is not available) *In moderate to severe infections or high-burden diseases (Appendix 1: Infection Severity Assessment), combination therapy is preferred when using Tigecycline, Polymyxins, or Cefiderocol. The choice of companion drug is based on the susceptibility test result, which could include • IV Aminoglycosides (once daily dosing) • IV Meropenem (if MIC ≤ 8mg/L, highest dose with extended infusion over 3-4 hours) • IV Tigecycline or Polymyxins or Cefiderocol **Referral to an ID physician/clinical microbiologist is recommended.



Infection sites	
	<i>Non-Susceptible to Ceftazidime/Avibactam**:</i> Preferred *Cefiderocol IV Less Preferred *Tigecycline IV high dose OR *Polymyxin B IV (Colistin can be used if polymyxin B is not available) *In moderate to severe infections or high-burden diseases (Appendix 1: Infection Severity Assessment), combination therapy is preferred when using Tigecycline, Polymyxins, or Cefiderocol. The choice of companion drug is based on the susceptibility test result, which could include • IV Aminoglycosides (once daily dosing) • IV Meropenem (if MIC $\leq$ 8mg/L, highest dose with extended infusion over 3-4 hours) • IV Tigecycline or Polymyxins or Cefiderocol **Referral to an ID physician/clinical microbiologist is recommended.
	<i>Non-Susceptible to Ceftazidime/Avibactam (Presumed/ Confirmed NDM-producing):</i> Preferred Ceftazidime/ Avibactam IV PLUS Aztreonam IV Administer these two drugs simultaneously. Both these drugs are Y-site compatible OR *Cefiderocol IV Less Preferred** *Tigecycline IV high dose (should be avoided in bacteraemia) OR *Polymyxin B IV (Colistin can be used if polymyxin B is not available)



Infection sites

*In moderate to severe infections or high-burden diseases ([Appendix 1: Infection Severity Assessment](#)), combination therapy is preferred when using Tigecycline, Polymyxins, or Cefiderocol. The choice of companion drug is based on the susceptibility test result, which could include

- IV Aminoglycosides (once daily dosing)
- IV Meropenem (if MIC $\leq$ 8mg/L, highest dose with extended infusion over 3-4 hours)
- IV Tigecycline or Polymyxins or Cefiderocol

**Referral to an ID physician/clinical microbiologist is recommended.

Paediatric considerations [BNE 2022-2023](#)³⁰

Antibiotic options are similar to adults. However, the safety and efficacy of IV Ceftolozane-tazobactam and IV Cefiderocol in children is not established. Tigecycline is not recommended in children unless no alternative treatment is available³¹. Oral Fosfomycin are not used routinely in children under 12 years old. A paediatric ID consult is advisable.

Clinical pearls

Is there any role of Cefiderocol combination therapy for CRE?

To date, most literature recommends monotherapy for Cefiderocol. However, there are emerging cefiderocol resistance associated with NDM-type metallo-beta-lactamase producers³²

Is polymyxin effective against CRE?

Polymyxins did not demonstrate better clinical success and were associated with worse side effects, such as kidney injury, compared to the novel beta-lactam-beta-lactamase inhibitors, such as Ceftazidime/Avibactam⁸. However, Polymyxin remained the drug of choice in settings where newer antibiotics are not available

Is there any role of polymyxin combination therapy for CRE?

The ESCMID guidelines³³ recommend:

- Polymyxins as monotherapy only in patients with non-severe or low-risk CRE infections, when susceptibility is demonstrated.
- In others, combination therapy with more than one drug active in vitro (polymyxin, aminoglycosides, tigecycline or fosfomycin), however, no specific combinations are recommended.
- May consider combination therapy with Meropenem if Meropenem MIC $\leq$ 8 mg/mL (high dose extended infusion)



	Limited studies are available that compares various polymyxin combination therapies which include: • Polymyxin B with tigecycline combination is shown to have rapid and sustained bactericidal killing up to 120h and it is a promising combination for carbapenem-resistant E. coli³⁴. • Polymyxin B in combination with Fosfomycin IV that resulted in rapid bacterial killing in KPC-producing CRE³⁵.
What is the recommended combination therapy for Tigecycline?	• Combination with Polymyxin B has been shown to assist in rapid and sustained bacterial killing³⁵.



SECTION 4: Carbapenem-Resistant *Acinetobacter baumannii*

4.1 Epidemiology/Microbiology

Epidemiology/ Microbiology details	Description/Recommendations
Introduction & Epidemiology of <i>A. baumannii</i> in Malaysia	<i>Acinetobacter baumannii</i> is a ubiquitous, Gram-negative coccobacillus and a significant cause of nosocomial infection³⁶. <i>Acinetobacter</i> contains fimbriae that enable it to attach to surfaces and form biofilms in both biotic and abiotic environments¹²⁷. Under dry conditions, <i>A. baumannii</i> develops thicker cell walls, allowing it to survive long in the environment and making it difficult to eradicate¹²⁸⁻¹²⁹. - A study conducted at the University Malaya Medical Centre found that identical resistance patterns and PFGE profiles of <i>A. baumannii</i> from environmental samples, healthcare workers' hands, and patient isolates indicate a possible transmission route in the ICU¹³⁴. <i>A. baumannii</i> isolated from clinical specimens are mostly colonisers. Clinical correlation is important to avoid unnecessary antibiotic therapy³⁸. - When isolated, it tends to be multidrug-resistant (MDR) due to many intrinsic resistant mechanisms and can acquire resistance through mobile genetic elements³⁷. - A study conducted at Sungai Buloh Hospital from August 2017 to April 2018 revealed that <i>A. baumannii</i> is the most prevalent in High Dependency Ward with an occurrence of 42.16% followed by ICU (28.43%) and general ward (26.47%). Most <i>A. baumannii</i> isolated from this study were also MDR³⁹. - From 2009 to 2022, the nationwide carbapenem resistance rate of <i>A. baumannii</i> steadily ranges around 50-60%²¹. This resistance is mainly caused by the OXA-23 carbapenemase⁴³⁻⁴⁶. - Individual hospitals may have higher antibiotic resistance rates depending on the infection control practices and antibiotic use⁴⁰. A surveillance study in Kuala Lumpur Hospital from 2018 - 2020 revealed positive correlation of MDR <i>A. baumannii</i> to increasing carbapenem consumption⁴¹. - In a study done by Rao et al in 2020 using whole genome sequencing, 11 isolates of carbapenem-resistant <i>A. baumannii</i> (CRAB) belong to international clone II⁴².



Epidemiology/ Microbiology details	Description/Recommendations
Multidrug-resistant (MDR) <i>Acinetobacter baumannii</i>	Any <i>Acinetobacter baumannii</i> isolates that tested either (I) or (R) to at least 1 drug in at least 3 of these categories:⁴⁷ - Extended-spectrum cephalosporins (ceftazidime, cefotaxime, ceftriaxone, cefepime) - Fluoroquinolones (ciprofloxacin, levofloxacin) - Aminoglycosides (amikacin, gentamicin, tobramycin) - Carbapenems (imipenem, meropenem, doripenem) β-lactam/ β-lactam β-lactamase Inhibitor Combination (piperacillin, piperacillin/tazobactam) - Ampicillin/sulbactam

4.2 Infection Prevention and Control

Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Infection control precaution (Refer to page 56)	- Contact precaution + Standard precaution - Alert should be placed in patient's notes or EMR (Tag)
Placement (Refer to page 58)	- Single isolation room with ensuite preferred; cohorting allowed, if necessary, based on risk assessment. - Appropriate signage at the door or cohorting area.
Hand Hygiene & PPE (Refer to page 56)	- Strict adherence to 5 moments of hand hygiene. - Gloves and gowns are required upon entering the room. - PPE cart placed outside of the room. - Gowns should be removed before leaving the patient care area to avoid contaminating outside the patient care areas. - Clinical waste bin (yellow) placed inside the room.
Equipment (Refer to page 60)	- Use dedicated equipment. - Shared equipment must be disinfected between patients according to Spaulding's classifications.



Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Environmental hygiene (Refer to page 59)	• Daily cleaning with emphasis on high-touch surfaces. • Terminal cleaning on discharge. • Adherence to hand washing sink protocol
Skin disinfectant (Refer to page 59)	Daily chlorhexidine or octenisan throughout admission.
Active surveillance (Refer to page 61)	To discuss with the ID or IPC team.
Clearance Criteria for Release from Isolation & Transmission-Based Precaution (un-tagging) (Refer to page 62)	Patients should be on contact precautions throughout the hospitalisation. The exact duration of isolation is not known. During the subsequent admission: • Alert should remain in patient notes • A risk assessment should be done to determine if pre-emptive contact precaution is required. • Screening may be done based on the risk assessment. • Refer to ID/Infection control for advice
Patient Movement in the Hospital, and Visitor Policy (Refer to page 65)	• Minimise risks of environmental contamination during patient transport. • Encourage all visitors to perform hand hygiene before entering and leaving the patient's room. • Advise visitors to avoid contact with other patients.
Other IPC strategies (i.e. practices in NICU/SCN etc)	For details, refer to page 66 .



Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
In the event of surge of cases/ outbreak (Refer to page 66)	- Refer to ID/IPC for outbreak management & formation of the outbreak management team. - Observe and improve environment cleaning and equipment cleaning and disinfection. - Refer to the Policies & Procedures on Infection Prevention & Control, 3rd ed., MOH Malaysia²⁴ and Responding to outbreaks of antimicrobial-resistant pathogens in health-care facilities: guidance for the Western Pacific region²⁵

4.3 Treatment

Infection details/ challenges	Recommendations Refer here for suggested duration of treatment
Mild infections	If coloniser, DO NOT treat If susceptible to amp/sulbactam, use monotherapy with amp/sulbactam Ampicillin-sulbactam IV (6 g sulbactam/day) If non-susceptible to amp/sulbactam, use combination therapy Ampicillin-sulbactam IV (9 g sulbactam/day) PLUS *Minocycline PO/IV OR Polymyxin B IV (Colistin can be used if polymyxin B is not available. Colistin is however preferred for urinary tract infections) *Minocycline has low serum and urinary concentration.



Infection details/ challenges	Recommendations Refer here for suggested duration of treatment
Moderate to severe infection	Use combination therapy Ampicillin-sulbactam IV (9 sulbactam/day) PLUS *Minocycline PO/IV OR Polymyxin B IV (Colistin can be used if polymyxin B is not available. Colistin is however preferred for urinary tract infections) *Minocycline has low serum and urinary concentration.
Paediatric considerations	
Antibiotic options for children are similar to adults. However, IV Minocycline is used only for children above 8 years old and the usage of Tigecycline is not recommended for children unless no alternative treatment is available. A paediatric ID consult is advisable.	
Clinical pearls	
Should a standard dose of amp-sulbactam be used for infections caused by a CRAB susceptible to amp-sulbactam?	High dose is favoured over standard-dose Ampicillin-sulbactam (4 g sulbactam/day) Use 6g of sulbactam/day for mild infections and 9g/day for moderate to severe infections ^{48,49} . Rationale: High-dose sulbactam is able to saturate the PBPs of <i>A. baumannii</i> better ⁸
Which polymyxins should be used for treating CRAB infection?	Polymyxin B should be preferred over colistin (polymyxin E) for infection sites other than urinary tract infections (UTIs) due to the following reasons ⁵⁰ : • Active Form Administration: Polymyxin B is administered in its active form, whereas colistin is administered as an inactive prodrug, colistimethate sodium (CMS). This difference potentially results in better pharmacokinetics and higher drug levels in the plasma for polymyxin B. • Nonrenal Clearance: Polymyxin B is predominantly cleared via nonrenal pathways, which may lead to lower rates of nephrotoxicity compared to colistin.



Clinical pearls	
	However, colistin should be preferred over polymyxin B for UTIs because: • Renal Clearance of Prodrug: The prodrug CMS is predominantly cleared by the renal pathway, leading to better pharmacokinetics and higher drug levels in the urine, making colistin more effective for urinary tract infections.
Can I use Cefiderocol to treat CRAB infections, especially for extensively resistant CRAB (only susceptible to Cefiderocol)?	Yes, but it is preferable that the agent is combined with high-dose Ampicillin-sulbactam (Even if non-susceptibility is demonstrated against Ampicillin-sulbactam)⁸ However, data is scarce for the paediatric population.
Can I use nebulised polymyxin for HAP/VAP caused by CRAB?	• Nebulised antibiotics are not recommended^{8,51}.
Should meropenem-polymyxin combination be used for CRAB infection?	• Based on AIDA⁵² and OVERCOME⁵³ studies, the combination of meropenem and colistin was not better than colistin monotherapy for CRAB. Therefore, we recommend using other combinations.
Should I combine meropenem, polymyxin, and amp-sulbactam?	• Suggest avoiding the combination therapy as it might lead to more toxicity (e.g., neurotoxicity due to dual beta-lactam therapy + polymyxin)⁸



SECTION 5: *Pseudomonas aeruginosa* with Multidrug (MDR) or Difficult-to-Treat (DTR) Resistance

5.1 Epidemiology/Microbiology

Epidemiology/ Microbiology details	Description/Recommendations
Introduction & Epidemiology of MDR/DTR <i>P. aeruginosa</i> in Malaysia	• An aerobic, Gram-negative bacillus found ubiquitously in soil, plants and hospital water reservoirs, including showers, sinks, and toilet water. • <i>P. aeruginosa</i> is challenging to treat due to its antibiotic resistance. It can spread in healthcare settings through contaminated water, hands, equipment, or surfaces. • In the National Antibiotic Resistance Surveillance 2022, <i>P. aeruginosa</i> isolated from clinical specimens showed a reduced resistance rate to all antibiotics tested compared to 2021, with overall resistance rates to all antibiotics being less than 10%. The resistance rate to colistin was remarkably reduced by more than 6 times (1.3%) compared to the previous year (8.2%). • The susceptibility rates may differ with each individual hospital. The results from the ATLAS programme, 2013 to 2019 involving 4 centres in Malaysia, the susceptibility rate of <i>Pseudomonas aeruginosa</i> isolates to ceftazidime, cefepime, piperacillin-tazobactam, imipenem, and meropenem were 83.4%, 87.1%, 81.6%, 78.6%, and 83.4% respectively. These isolates were also highly susceptible to ceftazidime-avibactam and colistin with the rate of 93.1% and 95.6% respectively⁵⁴. • In the same study, it was found that 11.7% of isolates were MDR phenotypically and it was higher than the results from the Asia-Pacific 2012–2015 INFORM study which was 7.1%⁵⁵. These MDR isolates demonstrated high susceptibility against colistin (100%) but only 44.7% were susceptible to ceftazidime-avibactam and much lower susceptibility to other agents. • Carbapenem resistance in <i>P. aeruginosa</i> differs from Enterobacterales as it is not primarily mediated by carbapenemase expression. Acquired β-lactamases were absent in most isolates (83.7%). Resistance mechanisms typically involve OprD alterations, efflux pump expression changes, and often coincide with the overproduction of chromosomal AmpC enzymes⁵⁵.



Epidemiology/ Microbiology details	Description/Recommendations
MDR <i>P. aeruginosa</i>	NON-susceptibility to at least one antibiotic in at least three antibiotic classes of the following⁴⁷: • Traditional extended-spectrum cephalosporins (ceftazidime, cefepime) • Fluoroquinolones (ciprofloxacin, levofloxacin) • Aminoglycosides (amikacin, gentamicin, tobramycin) • Carbapenems (imipenem, meropenem, doripenem) • Traditional β-lactam-β-lactamase inhibitor (piperacillin-tazobactam)
DTR <i>P. aeruginosa</i>	Classification of difficult-to-treat (DTR) is a practical approach to classify antimicrobial resistance focusing on treatment-limiting resistance to all first-line agents, that is, all β-lactams, including carbapenems and β-lactamase inhibitor combinations, and fluoroquinolones⁵⁶. NON-susceptibility to all of the following: • Piperacillin-tazobactam • Ceftazidime • Cefepime • Aztreonam • Meropenem • Imipenem-cilastatin • Ciprofloxacin • Levofloxacin



5.2 Infection Prevention and Control

Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Infection control precaution (Refer to page 56)	• Contact precaution + Standard precaution • Alert should be placed in patient's notes or EMR (Tag)
Placement (Refer to page 58)	• Single isolation room with ensuite preferred; cohorting allowed, if necessary, based on risk assessment. • Appropriate signage at the door or cohorting area.
Hand Hygiene & PPE (Refer to page 56)	• Strict adherence to 5 moments of hand hygiene. • Gloves and gowns are required upon entering the room. • PPE cart placed outside of the room. • Gowns should be removed before leaving the patient care area to avoid contaminating outside the patient care areas. • Clinical waste bin (yellow) placed inside the room.
Equipment (Refer to page 60)	• Use dedicated equipment. • Shared equipment must be disinfected between patients according to Spaulding's classifications.
Environmental hygiene (Refer to page 59)	• Daily cleaning with emphasis on high-touch surfaces. • Terminal cleaning on discharge, including curtain change. • Adherence to hand washing sink protocol.
Skin disinfectant (Refer to page 60)	Daily chlorhexidine or octenisan throughout admission.
Active surveillance (Refer to page 61)	To discuss with the ID or IPC team.
Clearance Criteria for Release from Isolation & Transmission-Based Precaution (un-tagging) (Refer to page 62)	Patients should be on contact precautions throughout the hospitalisation. The exact duration of isolation is not known. During the subsequent admission: • Alert should remain in patient notes • A risk assessment should be done to determine if pre-emptive contact precaution is required. • Screening may be done based on the risk assessment. • Refer to ID/Infection control for advice



Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Patient Movement in the Hospital, and Visitor Policy (Refer to page 65)	- Minimise risks of environmental contamination during patient transport. - Encourage all visitors to perform hand hygiene before entering and leaving the patient's room. - Advise visitors to avoid contact with other patients.
Other IPC strategies (i.e. practices in NICU/SCN etc)	For details, refer to page 66
In the event of surge of cases/ outbreak (Refer to page 66)	- Refer to ID/IPC for outbreak management & formation of the outbreak management team. - Refer to the Policies & Procedures on Infection Prevention & Control, 3rd ed., MOH Malaysia²⁴ and Responding to outbreaks of antimicrobial-resistant pathogens in health-care facilities: guidance for the Western Pacific region²⁵.

5.3 Treatment

Infection details/ challenges	Recommendations Refer here for suggested duration of treatment
Infections by MDR <i>P. aeruginosa</i>	
Infection outside urinary tract	Not susceptible to any carbapenem agent but susceptible to other non-carbapenem β-lactam agents (i.e, piperacillin-tazobactam, ceftazidime, cefepime) and fluoroquinolones (i.e, ciprofloxacin, levofloxacin) Confirm susceptibility before choosing antibiotic regimen Preferred Ceftazidime IV OR Cefepime IV OR Piperacillin-tazobactam IV * *Piperacillin-tazobactam has added anaerobic coverage. Therefore, choose either ceftazidime or cefepime if the coverage is not needed.



Infections by MDR *P. aeruginosa*

High-dose extended-infusion therapy is recommended ([refer to Appendix 5](#))

Less preferred

Fluoroquinolones IV/PO (Ciprofloxacin/Levofloxacin)

Infections by DTR *P. aeruginosa*

Cystitis

Confirm susceptibility before choosing antibiotic regimen

Preferred

Ceftolozane-tazobactam IV

OR

Ceftazidime-avibactam IV

Less preferred

Single dose Amikacin IV

OR

Colistin IV

OR

Cefiderocol IV

Avoid Fosfomycin PO as the treatment is associated with a high likelihood of clinical failure due to the presence of intrinsic fosA gene in *P. aeruginosa*

Acute pyelonephritis or Complicated urinary tract infections (cUTI)

Confirm susceptibility before choosing antibiotic regimen

Preferred

Ceftolozane-tazobactam IV

OR

Ceftazidime-avibactam IV

Less preferred

Once daily Amikacin IV (requires TDM monitoring)

OR

*Colistin IV

OR

Cefiderocol IV

*IV Colistin should be used instead of IV Polymyxin B as it can achieve adequate concentration in the urine.



Infection outside urinary tract	Confirm susceptibility before choosing antibiotic regimen Preferred Ceftolozane-tazobactam IV OR Ceftazidime-avibactam IV Less preferred Cefiderocol IV OR Polymyxin B* IV + Second susceptible agent (*Colistin can be used if polymyxin B is not available) If no susceptible second agent is available, referral to an ID Physician/ microbiologist is recommended
Paediatric considerations	
Antibiotic options are similar to adults. However, paediatric ID consult is advisable for DTR pseudomonas since safety and efficacy of IV Ceftolozane-tazobactam and IV Cefiderocol in children is not established.	
Clinical pearls	
When Ceftazidime-avibactam and Ceftolozane-tazobactam are tested active, which one should we use in DTR- <i>P. aeruginosa</i> ?	Newer BLBLI should be reserved for DTR- <i>P.aeruginosa</i> . Ceftazidime-avibactam and ceftolozane-tazobactam may be comparable in terms of safety and efficacy based on the data from Saudi Arabia ⁵⁷ However, the most recent updates of the CACTUS data showed that Ceftolozane-tazobactam might be a better option, with a lesser impact on the microbiomes ⁵⁸
Is there any role of nebulised antibiotics in the treatment of respiratory infections caused by DTR- <i>P. aeruginosa</i> ?	Nebulised antibiotics are not recommended ^{8,51}



Clinical pearls	
Can we use IV gentamicin for <i>P. aeruginosa</i> infection?	The use of gentamicin to treat infections by <i>P. aeruginosa</i> is no longer recommended as there are no CLSI breakpoints available.
Is there a role of combination therapy for the treatment of DTR- <i>P. aeruginosa</i> infection?	Most support for combination therapy comes from observational data^{135,136}, while a recent subanalysis from a randomized controlled trial does not support it¹³⁰. Given the higher risk of adverse events associated with combination therapy and the lack of justifiable benefit in outcomes, we do not recommend its use.



SECTION 6: *Stenotrophomonas maltophilia*

6.1 Epidemiology/Microbiology

Epidemiology/ Microbiology details	Description/Recommendations
Introduction and epidemiology of <i>S. maltophilia</i> in Malaysia	• A ubiquitous, non-fermenting Gram-negative rod closely related to <i>Pseudomonas</i> spp⁵⁹. • It can be isolated from the environment, such as sinks, water, fomites, plants and hospital equipment⁶⁰. • An emerging cause of healthcare-associated infection⁶¹. • Most <i>S. maltophilia</i> isolated from clinical specimens are colonisers. However, isolation from the immunocompromised and patients with chronic illnesses warrants antibiotic therapy^{62,63}. • A study conducted in Sultan Ahmad Shah Hospital from April 2019 to October 2020 revealed that the prevalence of <i>S. maltophilia</i> in the Malaysian tertiary centre is 6.9%⁶⁴. • <i>S. maltophilia</i> prevalence and antibiotic resistance rate are currently not included in the national surveillance program. • <i>S. maltophilia</i> is intrinsically resistant to many antibiotics, including penicillin group, cephalosporin (excluding ceftazidime), aztreonam, and carbapenem⁶³. • The ceftazidime breakpoints against <i>S. maltophilia</i> were removed from the M100 CLSI document, due to lack of supporting data and poor reproducibility in susceptibility testing⁶⁵.



6.2 Infection Prevention and Control

Infection Control Prevention	Description/Recommendations (Click on the link in each row or refer to Section 7 for more details)
Infection control precaution	Standard precaution
Hand Hygiene & PPE (Refer to page 56)	• Strict adherence to 5 moments of hand hygiene. • PPE use based on risk assessment.
Equipment (Refer to page 60)	Shared equipment must be disinfected between patients according to Spaulding's classifications.
Environmental hygiene (Refer to page 59)	• Daily cleaning with emphasis on high-touch surfaces. • Terminal cleaning on discharge, including curtain change • Adherence to hand washing sink protocol

6.3 Treatment

Infection details/challenges	Recommendations Refer here for suggested duration of treatment
<i>Stenotrophomonas maltophilia</i> infection	If coloniser, DO NOT treat Preferred *Trimethoprim/Sulfamethoxazole IV/PO Less preferred *Cefiderocol IV OR Ceftazidime/Avibactam IV PLUS Aztreonam IV Administer these two drugs simultaneously. Both these drugs are Y-site compatible



*In moderate to severe infections ([Appendix 1: Infection Severity Assessment](#)) combination therapy is preferred when using Trimethoprim/Sulfamethoxazole or Cefiderocol, at least until clinical improvement is seen.

The choice of companion drug is based on susceptibility test result, which could include

Levofloxacin IV/PO

OR

Minocycline IV/PO (has low serum and urine concentration)

Paediatric consideration:

Antibiotic options for children are similar to those for adults. However, doses of TMP-SMX are higher in children, with TMP 12-15mg/kg/day (refer to paediatric dosing chart). When considering IV TMP-SMX for neonates, exercise caution due to the potential risks of hyperbilirubinemia and kernicterus. A paediatric ID consult is advisable.

IV minocycline is not recommended in children < 8 years old.

Clinical pearls

Can we use polymyxins in treating *S. maltophilia* infections?

No, there is no established breakpoint for polymyxins⁸.

What is the role of tigecycline, minocycline, and doxycycline in treating *S. maltophilia* infections?

A general concern with tetracycline derivatives is that they achieve rapid tissue distribution following administration, resulting in low drug concentrations in urine and serum⁶⁶. Therefore, tetracyclines are not recommended for treating UTI and need to be used only as part of combination therapy for bacteraemia caused by *S. maltophilia*.

CLSI provides breakpoints only for minocycline. There are no breakpoints provided for Tigecycline and Doxycycline.



SECTION 7: Infection Prevention & Control (IPC) Guideline for MDRO in Health Care Settings

7.1 Introduction

1. Case definition for a case of Multidrug-Resistant Gram-Negative (MDR GN): Laboratory confirmation of causative organism by culture (ESBL, AmpC, CR-Enterobacterales, CR-*Acinetobacter baumannii*, MDR *Pseudomonas*, *Stenotrophomonas*)
2. Patients may be colonised or have clinical infections.
3. Mode of Transmission:
 - Direct contact
 - Indirect contact with inanimate objects, e.g. a bed that was previously used by an infected patient, contaminated sinks, contaminated environments & shared equipment.
 - In healthcare settings, the transmission of MDR GN from an infected/colonised patient to another patient may occur via both direct and indirect contact, as illustrated in Figure 1 below.

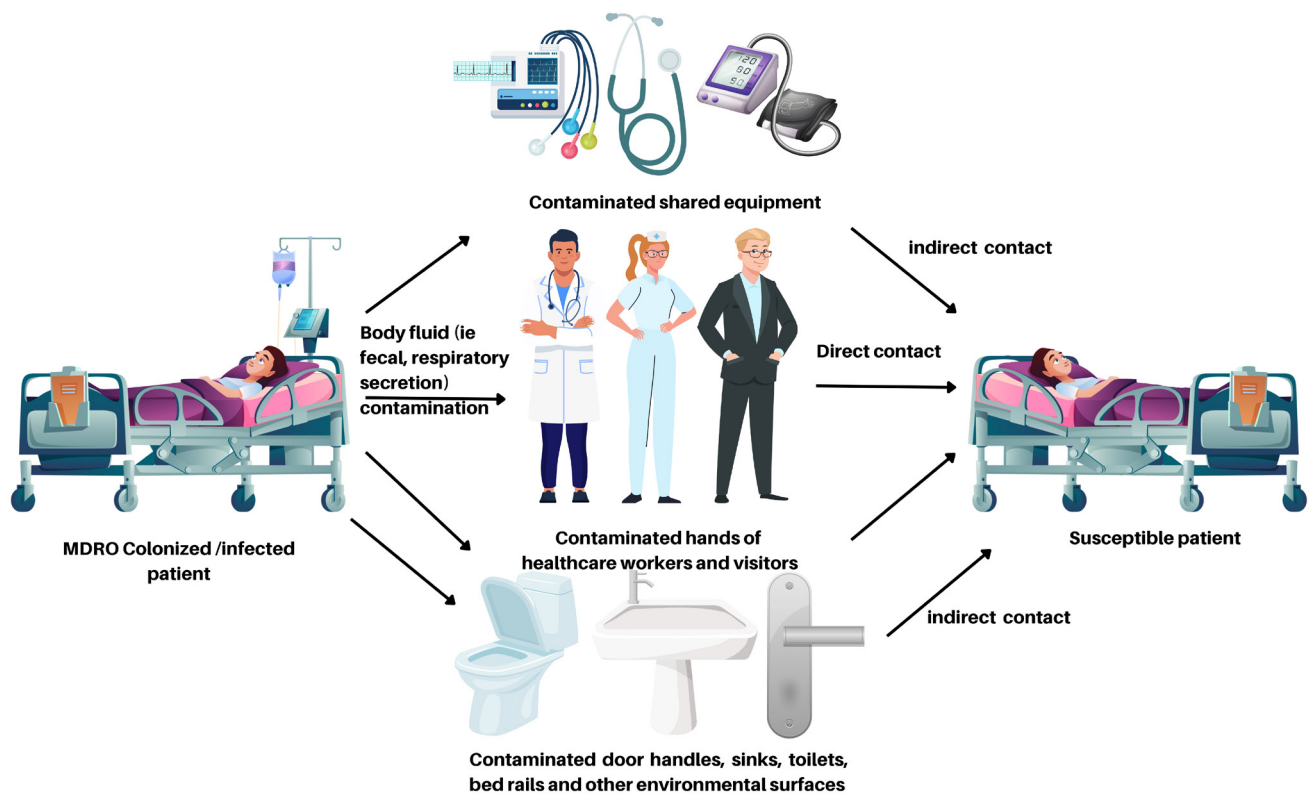


Figure 1: Potential transmission routes of hospital-acquired MDR GN infections. Image courtesy of Infection Control Dept, University Malaya Medical Centre



7.2 Strategies to Prevent & Control the Spread of MDR GN

Preventing transmission of MDRO requires meticulous hand hygiene, appropriate use of transmission-based precautions (i.e., using Contact Precautions depending on setting & organism), environmental cleaning, as well as adherence to sink and toilet hygiene practices.

7.2.1 Infection control precautions

- Standard precautions should be applied to all patients.
- Contact precautions should be applied for patients with ESBL, CRE, CRAB & *Pseudomonas* with difficult-to-treat resistance^{24,67–69}. However, in the context of limited resources, the infection prevention & control team at each facility can re-stratify the recommendations for targeted infection prevention strategies, such as isolation & contact precaution for ESBL and non-CP CRE, based on the local prevalence data and risk assessment for onward transmission⁷⁰.
 - » For ESBL: A risk assessment should be done to determine the need for contact precautions based on prevalence & endemicity. Interventions aimed at controlling the horizontal spread of ESBL organisms within the hospital may be warranted in the event of clonal outbreaks⁷¹.
 - » For CRE: More aggressive interventions, like screening contacts, are generally reserved for CP-CRE, which have greater potential for spread. Most of the increase in carbapenem resistance in Enterobacteriaceae is attributed to the spread of carbapenemase genes. Therefore, CP-CRE should be targeted for intensive prevention efforts & meticulous adherence to core infection control practices^{72,73}. However, non-CP CRE may still warrant the use of targeted infection control interventions (e.g., Contact Precautions in acute care settings) to limit transmission.
- An alert (tag) should be put in patients' medical notes to remind them & ensure precautions are carried out.
- The following should be applied for patients on 'Contact Precautions':
 - » The 'Contact Precaution' sign is clearly displayed outside the room.
 - » Clinical waste yellow bin to be made available inside the room.
 - » Use dedicated equipment where possible, e.g., blood pressure cuffs and oximeter probes. Shared equipment must be disinfected using hospital-approved disinfectant between patients.
 - » Dedicated nursing staff (recommended).



- » The PPE cart should be placed outside the room and contain the following:
 - i. Disposable gloves
 - ii. Long-sleeved gowns and aprons
 - iii. Hospital-approved disinfectant wipes for surfaces
 - iv. Alcohol-based hand rub (ABHR)
- » Strict adherence to the 5 moments of hand hygiene, as illustrated in Figure 2.
- » Hand hygiene should be done before and after using gloves.
- » Change gloves after each patient or when moving from a dirty to a clean area during patient care.
- » Gowns should be removed before leaving the patient care area/surroundings to avoid contaminating outside the patient care areas.
- » Patient environment/surroundings:
 - i. In a single room, it would be the entire room
 - ii. In a multi-bedroom, the area behind the patient curtain as depicted in Figure 3

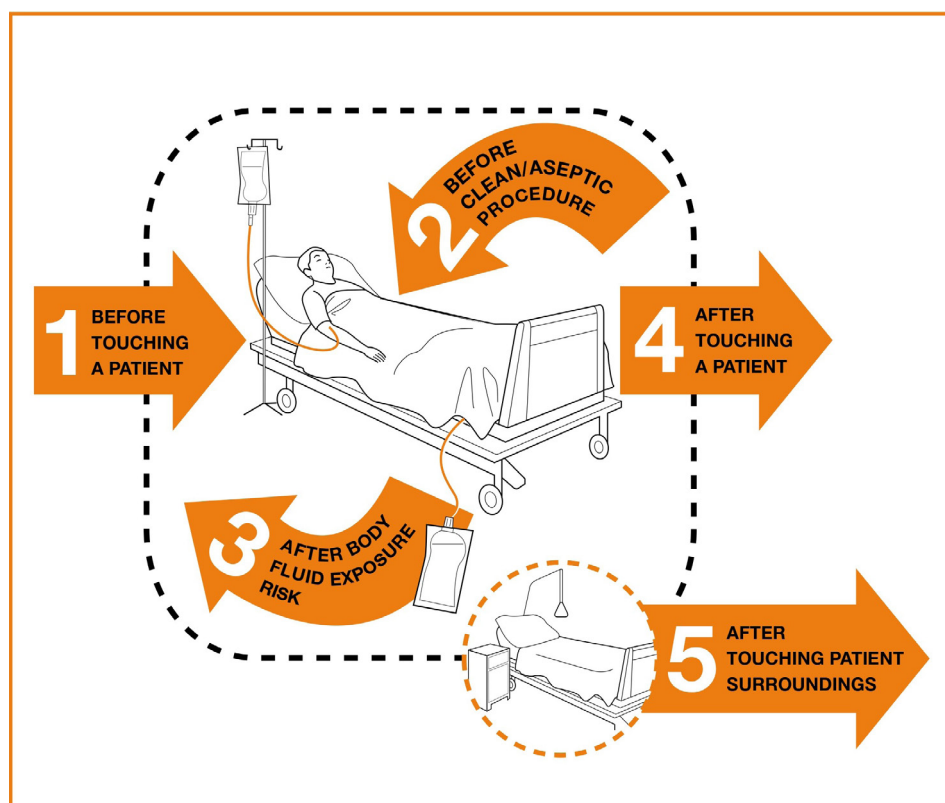


Figure 2: "My five moments for hand hygiene"
(Image source: WHO guidelines on hand hygiene in health care)

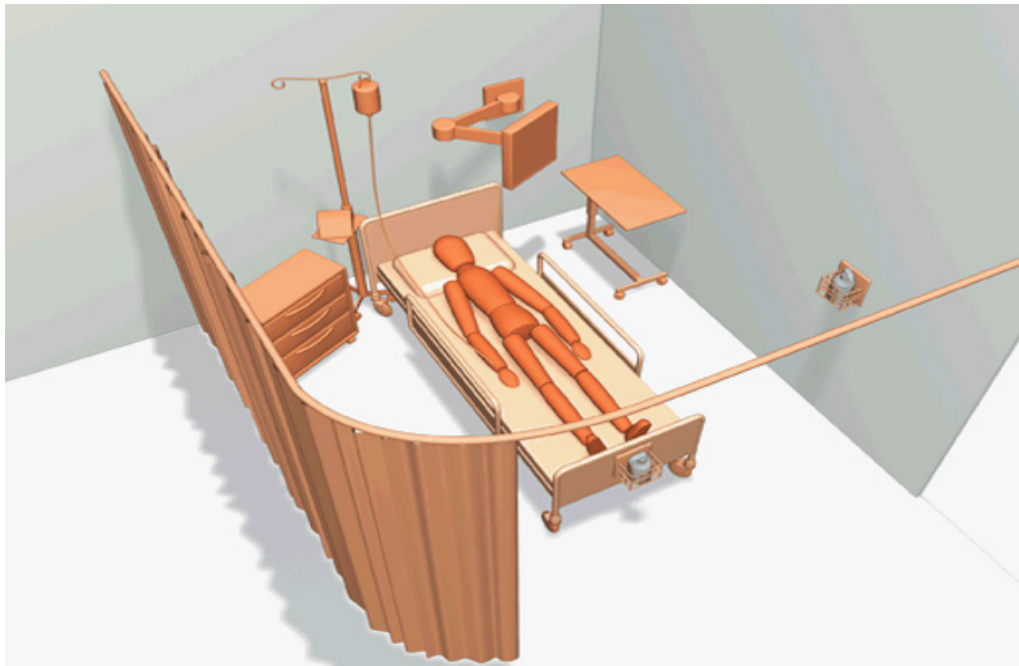


Figure 3: Patient environment includes the curtain and areas behind it.
(Image source: Public Health Ontario. *Just Clean Your Hands – Hospitals*)

7.2.2 Patient Placement / Isolation

- The patient should be prioritised to be placed in a single room with an en-suite bathroom. Patient isolation is an effective intervention to prevent onward transmission^{67,74}.
- Patient placement (in order of preference):
 - i. Single room with an attached bathroom as a priority
 - ii. Single room without attached bathroom
 - iii. Cohort in dedicated cubicle/area with attached bathroom. Cohorting can be done for patients who are colonised or infected with the same resistant organism.
 - iv. If isolation in the general ward is the only option available, dedicated toilet facilities/commode and an isolation tray/trolley beside the bed are strongly recommended⁶⁹
- Risk assessment for onward transmission to prioritise patient placement in a single isolation room⁷⁰:
 - i. Copious or uncontained drainage from wounds/abscesses
 - ii. Dressings or drains that require changing
 - iii. Faecal or urinary incontinence
 - iv. Indwelling urinary catheter/intermittent clean catheterization
 - v. Patient with abdominal drainage/ intestinal stoma/ fistula



- vi. Tracheostomy/ventilated /uncontained sputum
- vii. ≥ 2 invasive devices in situ that require frequent access.
- The minimum spatial requirement in a standard multiple-bedded room is 1.5m between beds⁷⁵
- However, if an MDRGN patient needs to be put in with other clean patients, i.e. in 2- or 4- bedded acute cubicle, to maintain the spatial distance of at least 1.5m, or more if possible:
 - » Ensure that patient and staff movement around the patient care area will not cause contamination in the neighbouring patient's zone/environment.
 - » PPE trolley and yellow bin are placed so that staff can don prior to accessing bed space & doff gown before leaving to avoid contaminating outside the patient zone.
 - » Minimise the number of patients as much as possible & avoid overcrowding in the cubicle so that the MDRO patient can be placed in isolation.
 - » Curtains are part of the patient zone/environment and HH should be performed if touched (Moment 5 for HH) and changed after patient discharge (Terminal Cleaning)⁷⁶

7.2.3 Skin Disinfectant to Reduce Bioburden

- Patients infected or colonised with MDR GN should be bathed daily with antiseptic soap or wipes, e.g., chlorhexidine or octinesan 2%. The selection of disinfectant should be approved by the hospital committee, and dilution should be based on the manufacturer's recommendation, i.e., contact time, amount, and frequency.
- Daily antiseptic bathing is aimed at reducing the patient's skin MDRO bioburden, thus can help lowering the risk of hospital-acquired infection and environmental burden/contamination^{77,78}.

7.2.4 Environmental Cleaning

- The environment is at a higher risk of getting contaminated when occupied by MDRO patients^{85–88}. Thorough environmental cleaning and disinfection can reduce environmental MDRO contamination and subsequently prevent nosocomial transmission⁸⁸.
- Daily patient environment and bathroom cleaning – with emphasis on frequently touched surfaces, should be done routinely for all patients.
- Enhanced cleaning, where the frequency of routine cleaning of high-touch surfaces is increased and/or cleaning procedures to involve certain low-touch areas, should be employed when there are patients infected or colonised with CRE, CRAB or DTR-*Pseudomonas*¹³².



- In the event of surge/outbreaks, an in-depth cleaning of the unit/ward may be required.
- Terminal cleaning should be done after patient discharge
- Fabric or disposable curtains - must be changed upon discharge
- Clean and disinfect using hospital-approved solutions for both daily and terminal cleaning
- Consider strategies to reduce the risks of transmission of MDROs from sinks, drains and plumbing⁷⁹⁻⁸³. [Refer to the section “Reducing the risks of transmission of MDROs from sinks, drains and plumbing”](#) below for details.
- Cleaning procedures should begin from cleaner areas to dirtier areas to avoid spread & contamination of clean areas⁸⁴. Refer to Policies & Procedures on Infection Prevention & Control (3rd ed.) MOH Malaysia²⁴ for details on the principles of cleaning.
- There should be clear protocols/SOPS for cleaning with defined responsible personnel for the task, and staff should be trained & monitored. Checklists and daily assignment sheets can be used to help ensure cleaning is done properly¹³¹.
- Monitoring adherence to recommended environmental cleaning practices is essential in controlling the transmission of MDROs⁸⁹. Audits should be done on a regular basis using standardised methods to assess the effectiveness & thoroughness of cleaning. [Refer to the section “Audit and Feedback”](#) for details.

7.2.5 Disinfection & Sterilisation of Patient Care Equipment

- All reusable and/or shared medical equipment should be cleaned & reprocessed (disinfection or sterilisation) based on Spaulding’s classification of medical devices prior to use on another patient.
- The table on Spaulding classification is as follows:

Spaulding Classification & Description		Type Of Cleaning Required
CRITICAL	Objects that enter normally sterile tissue or the vascular system	Sterilisation
SEMI-CRITICAL	Objects that contact mucous membranes or non-intact skin	High-Level Disinfection
NON-CRITICAL	Objects that contact intact skin but not mucous membranes	Intermediate Level Disinfection Low-Level Disinfection



- All staff involved in cleaning critical & semi-critical equipment should be trained and credentialed.
- Cleaning of non-critical items (e.g. infusion pumps, glucometer, BP cuff & monitors) requires a collaborative effort. This can be achieved by having clear protocols / SOPs on when and how cleaning should be done, as well as designating who is responsible for doing the cleaning.

7.2.6 Wastes & Linen Management

- Refer to Policies & Procedures on Infection Prevention & Control, 3rd ed., MOH Malaysia for the management of wastes and linen²⁴.

7.2.7 Active Surveillance

- Entry screening for colonisation can be considered, especially in the event of an outbreak.
- Weekly and exit screening for colonisation can be considered too, especially in the event of an outbreak.
- Discuss with ID/Infection Control as active surveillance for CRE and other carbapenemase-producing organisms should be guided by local epidemiology and risk assessment, taking into account:
 - i. History of previous CRE infection/colonisation,
 - ii. Contacts of CRE cases,
 - iii. History of recent hospitalisation in ward/facilities endemic with CRE or has CRE outbreaks,
 - iv. Those with an increased risk of CRE acquisition and infection, examples are as follows:
 - » Extended hospitalisation,
 - » Multiple and/or recent exposures to different antibiotic agents (e.g., broad-spectrum penicillin, cephalosporins, fluoroquinolones & carbapenems),
 - » Indwelling medical devices (i.e., CVL, CBD, biliary or wound drains)
 - » Mechanical ventilation,
 - » Admission to ICU,
 - » Burns patients, organ or stem-cell transplant recipients, or respiratory patients on long-term antibiotics
- Compared to CRE, there may be limited benefit in doing active surveillance for Carbapenemase-producing *Acinetobacter* (CPA) & Carbapenemase-producing *Pseudomonas* (CPP), unless in the event of outbreaks or follow-up of cases. Screening



may be considered only in outbreak situations after consultation with the ID/infection control team.

- When doing screening for CRE/CPE, the following samples may be considered⁷³:

Carbapenemase Producing Enterobacteriaceae (CPE)

In order of preference:

1. Faeces
2. Rectal swab + inguinal swab
3. Rectal swab alone
4. Peri-anal (e.g., neutropenic patient)

If symptoms are present or clinically relevant; send appropriate samples from

- endotracheal tube
- enterostomy
- urinary catheter
- wound

- Pre-emptive isolation and contact precautions should be implemented until the results of screening cultures are available.

7.2.8 Decolonisation Regime

- There is insufficient evidence to recommend *decolonization* in patients with MDR GN infection.

7.2.9 Un-tagging: Clearance Criteria for Release from Isolation & Transmission-based Precaution

- Patients may remain colonised for at least 6 to 12 months and some considerably longer, particularly with ongoing or repeated healthcare contact and/or antibiotic use. The exact duration of colonisation is unknown.
- When considering clearance, a risk assessment should be done to determine whether patients are still at risk of having prolonged carriage.



Predictors of prolonged carriage for CRE⁷²

- i. Exposure to antibiotics - since the initial infection/colonisation
- ii. Number of hospital admissions - e.g., multiple hospitalisation
- iii. Presence of an invasive device
- iv. Higher Charlson's co-morbidity scores
- v. Admission from another facility - esp. where CRE is endemic or has ongoing transmission/outbreak
- vi. Admission from or discharge to a long-term care facility

- For Carbapenem-resistant Enterobacterales (CRE) and Carbapenemase-producing Enterobacterales (CPE):
 - » Duration of isolation precautions is for at least 1 year.
 - » After 1 year, if the patient has no risk for prolonged CRE carriage, and has 2 negative rectal swabs 1 week apart, may consider un-tagging.
 - » Discontinuation of isolation (un-tagging) may be considered after 1 year has passed since the last positive culture, provided the patient fulfils the following criteria: does not have an active infection, is not on active treatment for CRE infection, has no risk for prolonged CRE carriage, and has at least two consecutive negative rectal swabs taken at least one week apart.
 - » The decision to remove from contact precaution before 1 year period may be made after consultation with ID/Infection control where a complete risk assessment shall be done.
 - » Despite the decision to release from contact precautions after fulfilling 'clearance criteria,' an alert (tag) should remain in the patient's medical record that CPE has been previously isolated.
- For other Carbapenemase-producing organisms i.e., *Acinetobacter* (CPA) and *Pseudomonas* (CPP):
 - » The exact duration of isolation is not known.
 - » Patients should be on contact precautions throughout the hospitalisation.
 - » In the subsequent admissions:
 - i. A risk assessment for ongoing colonisation/infection, as well as risk for onward transmission, should be made to decide whether to continue contact precautions and repeat screening, based on factors such as:
 - a. which ward they will be admitted to (e.g., ICU),
 - b. reason for admission (e.g., treatment of current infection), or
 - c. individual patient's risk factors for prolonged colonisation (e.g., COPD with history of CPP colonisation)



- ii. Despite the decision not to continue contact precautions or fulfil 'clearance criteria; an alert (tag) should remain in the patient's medical record that CPA/ CPP has been previously isolated.
- iii. Patients should be monitored for signs/symptoms of infection, and immediate investigations for Carbapenemase resistance organisms if infection is suspected.
- For ESBL organisms:
 - » ESBL protocols differ based on individual hospital policies and may range from no isolation at all to a tag duration of 3-6 months⁷¹.
 - » Consider off-tag: If negative rectal swabs at D0, D7, and D14 after completion of treatment.
 - » In the subsequent admissions a risk assessment, as CPP/CPA above, should be done to determine if patients still pose a risk.
- Decisions for de-isolation and un-tagging of all MDRO cases should be made after consultation with the Infectious Diseases or Infection Prevention and Control Team and are dependent upon a thorough assessment based on the institutional risks, priorities, and resources⁹⁰.

7.2.10 Communication

- The patient's status & required precaution (contact precaution) should be clearly communicated to all staff involved in the care of the patients
- An alert of the patient's status should be documented in clinical notes & referral letters. IT-based hospitals can consider tagging MDRO status to facilitate early recognition and isolation measures.

7.2.11 Training & Education

- All staff involved in the care of patients should receive training about standard precautions and transmission-based precautions.
- All cleaning staff (contract and those employed by the hospital) should undergo environmental (daily and terminal) cleaning training.
- All staff involved in cleaning critical & semi-critical equipment should be trained and credentialed.

7.2.12 Audit & Feedback

- It is important to monitor adherence to IPC practises & efficacy of cleaning by conducting audits. Monitoring should be done on a regular basis and as needed especially when there is a surge of cases.



- Refer to standardised audit protocol to monitor practise **adherence**:
 - » Audit of hand hygiene compliance.
Example: <https://myohar.moh.gov.my/hand-hygiene-compliance-survey/> or <https://www.who.int/teams/integrated-health-services/infection-prevention-control/hand-hygiene/monitoring-tools>
 - » Audit of transmission-based precautions practices.
Example: <https://myohar.moh.gov.my/infection-prevention-control-ipc-audit/>
 - » Environmental cleaning audits e.g., visual and fluorescent markers (glo-germ).
Example: <https://myohar.moh.gov.my/healthcare-environment-cleanliness-audit/>
- Provide feedback & report of audit results to key stakeholders

7.2.13 Patient & Visitors

- Provide information leaflets and other supportive literature as deemed appropriate to ward staff, patients, and visitors
- Encourage all visitors to perform hand hygiene before entering and leaving the patient's room
- Advise patients & visitors to avoid contact with other patients

7.2.14 Patient Movement in the Hospital

- Refer to Management of Carbapenem-resistant Enterobacteriaceae (CRE) in Healthcare Setting (4th Ed.)⁹¹ (Downloadable from: <https://myohar.moh.gov.my/publications-human-health/>) and MOH Malaysia and Policies & Procedures on Infection Prevention & Control (3rd ed.) MOH Malaysia²⁴.
- Staff should remove gloves & gowns prior to leaving patients' rooms.
- Both staff and patients are to perform hand hygiene when leaving the room.
- Minimise risk of environmental contamination during patient transport

7.2.15 Day Care Procedure, Community Dialysis Centres or Outpatient Departments

- Contact precautions at the bedside, examination chair, or whenever providing any direct patient care.
- Dedicated toilet or commode chair, if applicable to the patient care setting
- Clean the examination couch/trolley/chair and any shared patient equipment after the patient is discharged and before receiving the next patient.



7.2.16 NICU: Additional Infection Control Measures

Policies & Procedures on Infection Prevention and Control 3rd Edition 2019²⁴.

- Strict expressed breast milk (EBM) and formula milk preparation and protocol.
- Strict milk room, including sink cleaning protocol.
- Incubators change and cleaning protocol.
- Immediate diaper disposal after diaper changing to prevent environmental contamination.
- Weighing scale cleaning and disinfection protocol between patient use.
- Antiseptic bath or wipes for newborns: still lacking evidence and concern of adverse events. It could be considered in an outbreak situation. Various chlorhexidine concentrations from 0.1% to 2% have been reported.

7.2.17 Surge/Outbreak of MDR GN Cases

- Refer to the Infectious Disease/Infection Control Team for outbreak investigation and formation of the outbreak management team.
- For the steps in outbreak response, refer to the Policies & Procedures on Infection Prevention & Control, 3rd ed., MOH Malaysia²⁴ and Responding to outbreaks of antimicrobial-resistant pathogens in health-care facilities: guidance for the Western Pacific region²⁵.
- It is important to look for the causes of the surge/outbreak and implement control measures to curb the spread.
- Contaminated environments or equipment may be the cause of the outbreak and enhanced control measures may be needed to curb the outbreaks^{79,85}. Additional investigations may also be useful - to discuss with ID/IPC & microbiologists prior to environmental sampling.
- For example:
 - » In a CRE outbreak, it's worthwhile to investigate the milk preparation rooms, especially in the ICU setting.
 - » In a Carbapenem-resistant *Acinetobacter baumannii* outbreak; observe and improve environment cleaning and equipment cleaning and disinfection. A radical terminal cleaning which includes the working area and equipment, in addition to doing environmental swabs for CRAB may be helpful in halting the outbreak.
 - » In a pseudomonas outbreak, water source contamination should be investigated; this includes all sinks, intravenous fluid or heparin saline, or medication trolley. In a VAP outbreak, the respiratory tubing or suction tubing should also be investigated.



7.2.18 Reducing the Risks of Transmission of MDROs from Sinks, Drains and Plumbing

Sink drains and plumbing pose a risk for MDRO spread in hospitals. Many recent reports demonstrate that sink drainpipes become colonised with highly consequential multidrug-resistant bacteria, which then result in hospital-acquired infections⁸². Bacteria in sinks initially colonise the elbows of the drainpipe and slowly spread to the strainers. Water from the faucet directly hitting the sink strainer can splash on the surrounding counters and the floor up to three feet away from the sink and subsequently splatter to the bowl and surrounding areas.

Strategies to reduce the risks of transmission of MDROs from sinks, drains and plumbing:

General

- An alcohol-based hand rub (ABHR) is the preferred method for cleaning the hands when they are not visibly dirty.
- Regularly clean and disinfect surfaces near drains, including the sink basin, faucet, handles, and surrounding countertop, at least daily or more frequently. Each hospital should discuss with the engineer and develop a protocol for cleaning the sinks.
- Designated hand-washing sinks are only for hand washing. Do not use it for non-hand hygiene activities such as disposing of clinical waste products, patient specimens, liquid nutritional supplements, or other beverages down the sinks.
- Sinks should be in such a way and at a sufficient distance that they do not contaminate patients, clean supplies, or adjacent counters through splashing.
- Add sink splash guards to reduce counter contamination from the drain.
- Hand-washing sinks must be free-standing, wall-mounted, at least one meter away from any fixed work surface, or separated by a splash barrier.
- Avoid placement of patient care items or personal items on counters next to sinks.
- Do not place sinks next to areas for medication preparation unless barriers (splash guard) are in place to prevent splashing in medication preparation areas.

Design

- Trapless sinks are recommended
- Prevent faucets/taps from discharging directly above the drain, as this causes splashing (i.e., angle water away from the drain or offset the faucet from the drain).
- Aerators and strainers have been demonstrated to be associated with an increased risk of contamination due to the capture of biofilm¹³³. A risk assessment will determine if they should be removed.
- Use sinks in patient care areas with adequate depth and the maximum water flow as regulated to prevent splashing



- Consider selecting tap and sink designs that prevent splashing when installing new sinks⁸³. Discuss with engineers.
- Refer to Facility Guideline Documents (FGI) Guideline for Hospitals A2.1-8.4.3.2 (1) a. for recommended sink designs⁹²

Chemical disinfection of sinks

- May reduce the burden of pathogens in contaminated drains and reduce the amount of contaminated splashing that may occur from the drains.
 - » Hydrogen peroxide vapour and pouring disinfectants such as bleach, hydrogen peroxide, and acetic down sink drains have been shown to decrease bioburden and may have been useful in responding to outbreaks.
 - » However, regrowth happens within a few days.
- The most appropriate disinfection method remains unclear; no one disinfectant agent has been found to be better than others, and ideal concentrations to use are not known. Some solutions may erode the plumbing system. Discuss with engineers.



Appendix 1: Infection Severity Assessment

There is no specific guidance available in assessing the severity of infection. Here are some examples of infections that could be classified as mild or moderate to severe infections.

Mild infections:

- Skin and soft tissue infection
- Urinary tract infection
- Catheter-related infection including bloodstream infection

However, these infections may be considered severe when a patient presents with organ dysfunction or septic shock.

Moderate to severe infections:

- Infection causing organ dysfunction
- Septic shock
- Moderate to severe Pneumonia
- Infective endocarditis
- Meningitis
- Ventriculitis
- Necrotizing fasciitis

In addition, some infections may be classified as mild or moderate infections depending on patients' condition.

These include:

- Bone and joint infection
- Prosthetic joint infection

High-burden infections include infections such as infectious endocarditis, meningitis, and infections prior to source control (e.g., abscesses, necrotising fasciitis, osteomyelitis, prosthetic infections).



Appendix 2: Adults: Drug dosing and infusion in normal renal function

Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal and liver function	Extended infusion		Remark
				Loading Dose, LD	Maintenance dose, MD	
Beta lactam/ Beta lactam inhibitor	Piperacillin-tazobactam	MDR PA	4.5 gm IV Q6H	4.5 gm in 50-100 ml diluents (WFI, NS or D5). Administer	4.5 gm in 50-100 ml diluents (WFI, NS or D5). Administer over 4 hours	Although susceptible, pip/tazo has reduced potency in CR- <i>Pseudomonas</i> . High doses (4.5 gm Q6H) and extended infusion (3 hours or continuous infusion) are needed to optimise exposure.
	Ampicillin-sulbactam	Mild infection, susceptible	3 gm (1 g SUL/dose) IV Q4H over 30min ⁹³	NA	NA	IDSA suggests total daily doses of 6 gm of sulbactam per day for isolates that are sulbactam susceptible (as monotherapy) and 9 gm per day when sulbactam is resistant or unable to be determined, as combination therapy. *May administer as continuous infusion Ampicillin/sulbactam 27 gm (9 gm SUL) IV Q24H
		Mild infection, not susceptible	9 g (3 g SUL/dose) IV Q8H over 4 hr ⁴⁹	NA	NA	
		Moderate to severe infection		Dilute 9 gm dose and administer over 30 mins	Dilute 9 gm dose and administer over 4 hours	



Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal and liver function	Prolonged infusion		Remark
				Loading Dose, LD	Maintenance dose, MD	
Tetracycline	*Minocycline	<i>Steno. maltophilia</i> & Combination therapy for CRAB	200 mg IV/PO BD ^{95,96}	NA	NA	Minocycline monotherapy is not recommended for bloodstream and urinary tract infections
	**Tigecycline	Combination therapy for CRE	200 mg stat dose ^{95,97} Followed by MD 100 mg Q12H	NA	NA	Due to its extensive distribution into tissue, blood levels are low. Therefore, it is not a good choice for bacteraemia, especially those with intravascular sources of infection.

Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal and liver function	Prolonged infusion		Remark
				Loading Dose, LD	Maintenance dose, MD (To be given at the next standard administration time after LD)	
Polypeptide⁹⁸	Polymyxin B (500,000 IU/50 mg per vial)	CRE, CRAB, DTR-PA	2.0-2.5 mg/kg (20,000–25,000 IU/kg) IV as stat dose Followed by MD 1.25-1.5 mg/kg (12,500–15,000 IU/kg) Q12H	NA	NA	For obese patients, suggest using adjusted body weight, with daily dose not exceeding 250mg.
	Colistin (Polymyxin E) 1MU/vial	CRE, CRAB, DTR-PA (Urinary source)	9 MU stat dose Followed by MD 4.5 MU Q12H (12 hour after LD)	NA	NA	Renal dose adjustment is required for MD, use adjusted body weight to calculate CrCl. Suggest considering limiting dose to 360 mg (9 MU) daily, to avoid nephrotoxicity.
Sulfonamide	Trimethoprim-sulfamethoxazole (TMP-SMX)	Cystitis	TMP/SMX (160/800 mg) (2 tabs/vials) IV/PO Q12H	NA	NA	
		All other infections	8-12 mg/kg/day TMP PO/IV In 2-3 divided doses	NA	NA	



Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal and liver function	Prolonged infusion		Remark
				Loading Dose, LD	Maintenance dose, MD (To be given at the next standard administration time after LD)	
Newer Beta-lactam/Beta-lactamase inhibitor	Ceftolozane-tazobactam	Cystitis	1.5 gm IV Q8H over 1 hour	NA	NA	Doses in extended infusion of 3 hours maybe necessary for patients with severe DTR PA
		All other infections	3 gm IV Q8H	3g IV	3g IV Q8H over 3 hours	
	Ceftazidime-avibactam	All infections	2.5 gm IV Q8H over 3 hours	NA	NA	
Monobactam	Aztreonam	CRE, as combination therapy with ceftazidime-avibactam	2 gm IV Q8H over 3 hours	NA	NA	

Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal and liver function	Prolonged infusion		Remark
				Loading Dose, LD	Maintenance dose, MD (To be given at the next standard administration time after LD)	
Cephalosporin	Ceftazidime	Any infections	2 gm Q6-8H	2 gm in 50-100 ml diluents (NS or D5). Administer over 30 mins	2 gm in 50-100 ml diluents (NS or D5). Administer over 4 hours	Prolonged infusion is recommended for treatment of severe/ high burden disease
	Cefepime	Cystitis	1 gm IV Q8H	NA	NA	Prolonged infusion is recommended for treatment of severe/ high burden disease and infections with Cefepime susceptible dose-dependent (SDD) isolates
		All other infections	2 gm IV Q8H	2 gm in 50-100 ml diluents (NS or D5). Administer over 30 mins	2 gm in 50-100 ml diluents (NS or D5). Administer over 3-4 hours	
	*Cefiderocol		2 gm IV Q8H ¹	NA	NA	
Fluoro-quinolones	Levofloxacin	Any infections	750 mg IV/PO OD	NA	NA	
	Ciprofloxacin	Cystitis	400 mg IV Q12H/ 500 mg PO Q12H	NA	NA	
		All other infections	400 mg IV Q8H/ 750 mg PO Q12H	NA	NA	



Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal and liver function	Prolonged infusion		Remark
				Loading Dose, LD	Maintenance dose, MD	
Carbapenem	Meropenem	Non-CNS (AmpC/ESBL)	1 gm IV Q8H	Dilute each dose and administer over 30 mins.	Dilute each dose and administer over 3 hours.	High dose extended infusion meropenem if MIC <8mg/L as part of combination therapy for CRE and severe CRAB infections.
		Cystitis (CRE)				
		CNS infection (AmpC/ESBL)	2 gm IV Q8H			
	Imipenem	All other infections (CRE)				
		Cystitis	500 mg IV Q6H	Dilute each dose and administer over 30 mins.	Dilute each dose and administer over 3 hours.	
		All other infections	500 mg IV Q6H			
	Ertapenem	As indicated	1 gm IV Q24H	NA	NA	
	*Imipenem-cilastatin-relebactam	MDR PA	1.25 gm Q6H	NA	NA	
Amino-glycoside	Gentamicin	Cystitis	5 mg/kg IV Q24H as single dose	NA	NA	Subsequent doses and dosing interval based on TDM
		Pyelo-nephritis/ cUTI	7 mg/kg IV Q24H as single daily dose	NA	NA	
	Amikacin	Cystitis	15 mg/kg IV Q24H as single dose	NA	NA	
		Pyelo-Nephritis/ cUTI	15 mg/kg/dose IV Q24H as single daily dose	NA	NA	

Footnote:

* This product is not registered in Malaysia and not listed in MOH drug formulary. Kindly refer to this link if you want to consider bringing this product through import permit: <https://pharmacy.moh.gov.my/en/documents/application-import-manufacture-unregistered-products-treatment-life-threatening-illnesses-private.html>

**This product is not listed in MOH drug formulary, but it is registered in Malaysia



Appendix 3: Adults: Renal dosing

First, choose the dose based on the clinical conditions and then adjust the dose according to patient renal function. Due to the complexities of reference available for renal dose adjustment, you should choose according to your clinical judgement, and you may also refer to renal dosing guidelines prepared by your own facilities.

Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal function	Adjusted dose according to CrCl(ml/min)			
Beta lactam/ Beta lactam inhibitor	Piperacillin-tazobactam	MDR PA	4.5 gm IV Q6H, over 3-4 hours	20-40	<20	HD	
				4.5 gm IV Q6H	2.25 gm IV Q6H or 4.5gm IV Q12H	2.25 gm IV Q8H	
	Ampicillin-sulbactam	Mild infection, susceptible	3 gm (1 g SUL/ dose) IV Q4H ¹	30-50	15-29	<15 or HD	*post dialysis
				3 gm IV Q6H	3 gm IV Q8H	3 gm IV Q12H*	
		Mild infection, not susceptible	3 gm (1 g SUL/ dose) IV Q4H ²⁻³	3 gm IV Q6H	3 gm IV Q8H	3 gm IV Q12H*	
		Moderate to severe infection	9 gm (3 g SUL/ dose) IV Q8H ⁴	20-50	<20 or HD		
				6 gm IV Q8H	6 gm IV Q12H		
	Ceftolozane-tazobactam	Cystitis	1.5 gm IV Q8H over 1 hour	30-50	15-29	<15 or HD	*post dialysis
				750 mg IV Q8H	375 mg IV Q8H	Load with 750 mg IV, followed by 150 mg IV Q8H*	
		All other infections	3 gm IV Q8H	1.5 gm IV Q8H	750 mg IV Q8H	Load with 2.25 mg IV, followed by 450 mg IV Q8H*	



Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal function	Adjusted dose according to CrCl(ml/min)			
Beta lactam/ Beta lactam inhibitor	Ceftazidime-avibactam	Treatment for CRE as combination therapy	2.5 gm IV Q8H over 3 hours	31-50	15-30	<15 or HD	CRRT
	1.25 gm IV Q8H			0.94 gm IV Q12H	0.94 gm IV Q24H	0.94 gm IV Q48 (post dialysis)	
	Aztreonam		2 gm IV Q6-8H over 3 hours	16-30	<15 or HD		
				2 gm IV Q12H	2 gm IV Q24H		
Tetracycline	Minocycline	Steno. maltophilia & Combination therapy for CRAB	200 mg IV/PO Q12H	No dosage adjustment required			
	Tigecycline	Combination therapy for CRE	200 mg load, then 100 mg Q12H ^{5,7}	No dosage adjustment required			
Polypeptide	Polymyxin B (500,000 IU/50 mg per vial)	CRE, CRAB, DTR-PA	2.0-2.5 mg/kg IV as stat dose 1.25-1.5 mg/kg Q12H (12 hour after LD) *1 mg=10,000 IU	No dosage adjustment required			
	Colistin (Polymyxin E) 1 MU/vial	CRE, CRAB, DTR-PA (Urinary source)	9 MU stat dose, or: <50 kg: 6 MU 51-60 kg: 7 MU 61-74 kg: 8 MU >75 kg: 9 MU 4.5 MU Q12H (12 hour after LD)	50-59	40-49	30-39	10-29
4 MU IV Q12H				3.5 MU IV Q12H	3 MU IV Q12H	2.5 MU IV Q12H	
<10				HD		CRRT	
				Non-dialysis	Dialysis day		
			2 MU IV Q12H	2 MU IV Q12H	2 MU IV Q12H plus supplemental dose: 1.2 MU IV (3h HD) 1.6 MU IV (4h HD) 1.5 MU IV (4h SLED)	6.7 MU IV Q12H or 4 MU IV Q8H	
Sulfonamide	Trimethoprim-sulfamethoxazole (TMP-SMX)	Cystitis	TMP-SMX (160/800 mg) (2 tabs/vials) IV/PO Q12H	> 15	<15 or HD		
				No adjustment	No data on suitability of ESRF patient		
		All other infections	8-12 mg/kg/day IV/PO Given in 2-3 divided doses	15-30	<15 or HD		
				4-6 mg/kg/day IV/PO in 2 divided doses	2-3 mg/kg IV/PO Q24H or 4-6 mg/kg IV/PO Q24-48H (administer post dialysis)		
				Use with caution and appropriate monitoring OR consider alternative agent.			



Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal function	Adjusted dose according to CrCl(ml/min)			
Cephalosporin	Ceftazidime	As indicated	2 gm Q8H	30-50	10-29	<10	HD
				2 gm IV Q12H	2 gm IV Q24H	1 gm IV Q24H	1 gm IV Q24H or 2 gm IV Q48H
			2 gm Q6H	31-50	15-30	<15 or HD	
				2 gm IV Q8H	2 gm IV Q12H	2 gm IV Q24H (post dialysis)	
	Cefepime	Cystitis	1 gm IV Q8H	30-60	10-29	<10	HD
				1 gm IV Q12H	1 gm IV Q24H	500 mg IV Q24H	1 gm once, then 500 mg IV Q24H
	Cefiderocol	All other infections	2 gm IV Q8H, over 3-4 hours	1 gm IV Q8H or 2 gm IV Q12H	1 gm IV Q12H or 2 gm IV Q24H	1 gm IV Q24H	1 gm IV Q24H (post dialysis)
Fluoroquinolones	Levofloxacin	As indicated	750mg IV/PO OD	31-50	10-30	<10	HD
				750 mg IV/PO Q48H	500 mg IV/PO Q48H	500 mg IV/PO Q48H	500 mg IV/PO Q48H
	Ciprofloxacin	As indicated	400 mg IV Q8-12H	30-50	<30	HD or PD	
				400 mg IV Q12H	400 mg IV Q24H	200-400 mg IV Q24H	
			500mg -750 mg PO Q12H	500-750 mg PO Q12H	250-500 mg PO Q24H	250-500 mg PO Q24H	



Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal function	Adjusted dose according to CrCl(ml/min)			
Carbapenem	Meropenem	Non-CNS infection (AmpC/ESBL)	1 gm IV Q8H	30-50	10-29	<10 or HD	
		Uncomplicated cystitis (CRE)		1 gm IV Q12H	500 mg IV Q12H	500 mg IV Q24H	
		CNS infection (AmpC-E/ESBL) All other infections (CRE)	2 gm IV Q8H as prolonged infusion	1 gm IV Q8H or 2 gm IV Q12H	1 gm IV Q12H	1 gm IV Q24H	
	Imipenem	Uncomplicated cystitis	500 mg IV Q6H over 30 minutes	30-59	15-29	<15	HD
		All other infections	500 mg IV Q6H over 3 hours	500 mg IV Q8H	250 mg IV Q6H or 500 mg IV Q12H	Not recommended	250 mg IV Q6H or 500 mg IV Q12H post dialysis
		Severe infections or intermediate susceptibility	1000 mg IV Q8H over 3 hours	60-90	30-59	15-29	<15
				500 mg IV Q6H	500 mg IV Q8H	500 mg IV Q12H	Not recommended
							HD 250 mg IV Q6H or 500 mg IV Q12H
	Ertapenem	As indicated	1 gm IV Q24H	<30 or HD			
				500 mg Q24H			
	*Imipenem-cilastatin-relebactam	MDR PA	1.25 gm IV Q6H	60-89	30-59	15-29	<15
				1 gm IV Q6H	0.75 gm IV Q6H	0.5 gm IV Q6H	No data



Antibiotic classification	Name of drug	Clinical condition	Suggested dosing in normal renal function	Adjusted dose according to CrCl(ml/min)			
Aminoglycoside	Gentamicin	Uncomplicated cystitis	5 mg/kg IV 24H as single dose	60-80	40-60	30-40	<30
				4 mg/kg IV Q24H	3.5 mg/kg IV Q24H	2.5 mg/kg IV Q24H	<i>SDD is not recommended, please dose according to multiple daily dosing</i>
		Pyelonephritis	7 mg/kg IV 24H as single daily dose (SDD)				
		Multiple Daily Dose (MDD)	2 mg/kg as loading dose followed by 1.5-2 mg/kg IV Q8H	40-60	20-40	<20	HD
				1.5-2 mg/kg IV Q12H	1.5-2 mg/kg IV Q24H	1.5-2 mg/kg IV Q48-72H	2-3 mg/kg as loading dose followed by 1-2 mg/kg IV Q48-72H Re-dose according to TDM level
	Amikacin	Uncomplicated cystitis	15 mg/kg/IV as single dose	60-80	40-60	30-40	<30
				12 mg/kg IV Q24H	7.5 mg/kg IV Q24H	4 mg/kg IV Q24H	<i>SDD is not recommended, please dose according to multiple daily dosing</i>
		Pyelonephritis or complicated urinary tract infection	15 mg/kg/IV as single daily dose (SDD)	12 mg/kg IV Q24H	7.5 mg/kg IV Q24H	4 mg/kg IV Q24H	
		Multiple Daily Dose (MDD)	7.5 mg/kg IV Q48H	10-50	<10	HD	
				7.5 mg/kg IV Q24H	7.5 mg/kg Q48H	7.5 mg/kg Q48H	



Appendix 4: Neonatal/Paediatric: Drug dosing in normal renal function^{99–102}

Name of drug	Neonates (≤28 days)	Paediatric (age > 28 days-18yo)**	Remark
*Aztreonam	Not used routinely. Consult infectious disease for advice.	90-120 mg/kg/day divided Q8H (max 8g/day)	
Amikacin	Infant (≤ 29 wk): 14 mg/kg Q48H (≤D7 OL), 12 mg/kg Q36H (D8-D28 OL), 12 mg/kg Q24H (≥D29) Infant (30-34 wk): 12 mg/kg Q36H (≤D7 OL), 12 mg/kg Q24H (≥D8 OL) Infant (≥35 wk): 12 mg/kg Q24H	15-20 mg/kg Q24H	Adjust dose based on serum concentrations Neonates - Trough: <5µg/ml, Peak: 20-30 µg/ml Paediatric - Trough: <1µg/ml, Peak: 60 µg/ml Conversion µg/ml x 1.71 = µmol/L Use with caution in patients with renal insufficiency and family history of ototoxicity.
Ampicillin-sulbactam	≤D7OL: 150 mg/kg/day (50 mg/kg/day SUL) divided Q12H >D7OL: 300 mg/kg/day (100 mg/kg/day SUL) divided Q6H	300 mg/kg/day (100mg/kg/day SUL) divided Q6H (max. 1g/dose SUL)	In treating CRAB infections, the efficacy of ampicillin/sulbactam is attributed to the sulbactam component. The formulation is available in a 2:1 ratio of ampicillin to sulbactam. Sulbactam doses of 100mg/kg/day used for treatment of CRAB infections in neonatal and paediatric population ^{101,103–105} . Prolonged infusion over 4 hours is highly recommended in less susceptible pathogen, patients with altered pharmacokinetics and severe infection.
Cefepime	100 mg/kg/day divided Q12H – 150 mg/kg/day divided Q8H	100 – 150 mg/kg/day divided Q8H (max. 2g/dose)	Use high doses for pseudomonas infections
*Cefiderocol	Safety and efficacy in children not established.		
Ceftazidime	Infant (≤ 29 wk): 50 mg/kg Q12H (≤ D28 OL), 50 mg/kg Q8H (≥D29 OL) Infant (30-36 wk): 50 mg/kg Q12H (≤ D14 OL), 50 mg/kg Q8H (≥D15 OL) Infant (≥37 wk): 50 mg/kg Q12H (≤ D7 OL), 50 mg/kg Q8H (≥D8 OL)	150-200 mg/kg/day divided Q8H (max. 6g/day)	Higher doses of 300 mg/kg/day divided Q8H (max. 12g/day) may be used for paediatric patients with cystic fibrosis.
Ceftazidime-avibactam	Safety and efficacy in neonates not established	3 months to <6 months old: 50 (40/10) mg/kg Q8H 6 months to <18 years: 62.5 (50/12.5) mg/kg Q8H	Infused over 2 hours. No safety and efficacy data in infants below 3 months old
Ceftolozane-tazobactam	Safety and efficacy in children not established		



Name of drug	Neonates (≤ 28 days)	Paediatric (age > 28 days-18yo)**	Remark
Colistimethate sodium (Polymyxin E) 1MU/vial	200,000-300,000 units/kg/day divided Q8H	200,000-300,000 units/kg/day divided Q8H	The FDA and EMA dosage recommendations may be suboptimal in paediatric patients ^{106,107} . Higher doses have been used in infants and children ^{108,109} . Renal dose adjustment is required for AKI, according to CrCl. For obese patient, use adjusted body weight to calculate CrCl.
Ertapenem	Safety and efficacy in neonates not established	30 mg/kg/day divided Q12H (max. 500mg/dose)	Not routinely used in infants < 3 months old. Consult Infectious Disease. Ertapenem has poor activity against <i>Pseudomonas aeruginosa</i> , <i>Enterococcus</i> and <i>Acinetobacter species</i> , <i>Stenotrophomonas maltophilia</i> , Not to use for CNS infection.
Fosfomycin (oral)	Not used routinely. Consult infectious disease.	2 gm po x 1 dose	
Imipenem-cilastatin	Not a preferred carbapenem in neonates due to possible adverse effects. Should be avoided in preterm neonates. 25 mg/kg Q12H ($\leq D7$ OL), Q8H (D8 OL onwards)	4 weeks to 3 months old, wt 1.5 kg: 100 mg/kg/day divided Q6H100 ≥ 3 months old: 60-100 mg/kg/day divided Q6H (max. 1 gm/dose)	Meropenem is a better choice than imipenem-cilastatin for CNS infection as it attains a higher concentration in the CSF and has a lower incidence of seizures than imipenem-cilastatin.
Levofloxacin	Safety and efficacy in neonates not established	16-20 mg/kg/day divided Q12H (max. 750 mg/day)	Levofloxacin monotherapy is recommended per IDSA guidance document for mild infections while combination therapy with a second active agent is recommended for serious infections.
Meropenem	Infant (< 32 wk): 20 mg/kg Q12H (<D14 OL), 20 mg/kg Q8H ($\geq D14$ OL) Infant (≥ 32 wk): 20 mg/kg Q8H (< D14 OL), 30 mg/kg Q8H ($\geq D14$ OL) Meningitis: 40 mg/kg/dose at the recommended age-specific dosing interval as above	Standard dose: 60 mg/kg/day divided Q8H Serious infection (CNS & Cystic fibrosis): 120 mg/kg/day divided Q8H (max. 2g/dose)	A 4-hour infusion is recommended for improved efficacy and better clinical outcomes as it sustain drug concentrations above the pathogen's MIC for extended duration (see Appendix 4 for further details)
*Minocycline	Safety and efficacy in neonates not established	IV or oral 4 mg/kg/day divided Q12H (max. 200mg/dose)	Minocycline only for children > 8 years old. monotherapy is not recommended for bloodstream and urinary tract infections.



Name of drug	Neonates (≤28 days)	Paediatric (age > 28 days-18yo)**	Remark
Piperacillin-tazobactam	Infant (≤ 29 wk): 100 mg/kg Q12H (≤ D28 OL), 100 mg/kg Q8H (≥D29 OL) Infant (30-36 wk): 100 mg/kg Q12H (≤ D14 OL), 100 mg/kg Q8H (≥D15 OL) Infant (37-44 wk): 100 mg/kg Q12H (≤ D7 OL), 100 mg/kg Q8H (≥D8 OL)	300-400 mg/kg/day divided Q6H (Piperacillin dose, max 16g piperacillin dose/day)	Although susceptible, piperacillin/tazobactam has reduced potency in carbapenem resistant PA. If piperacillin/tazobactam is used, extended infusion over 4 hours needed to optimise exposure.
Polymyxin B (500,000 IU/50mg per vial)	15,000 – 40,000 units/kg/day divided Q12H	>28 days – 2yo: 15,000 units – 45,000 units/kg/day divided Q12H. ≥ 2yo: use adult dosing	For obese patients, use adjusted body weight. No renal dose adjustment is required for maintenance dose. Not recommended for treatment of UTIs.
Trimethoprim-sulfamethoxazole (TMP-SMX)	Generally avoided in neonates due to adverse effects. Consult infectious disease for advice.	TMP 12-15 mg/kg/day IV/PO, divided Q8H	Contraindicated in G6PD deficient children. Bactrim monotherapy may be used in mild infections, but combination therapy with a second agent is recommended for severe infections.
Tigecycline	Avoid in neonates	Avoid, but if necessary: Age 8-11yo: 1.2 mg/kg Q12H (max 50mg/dose) Age 12-17yo: 50 mg Q12H (max 50mg/dose)	Tigecycline use in children not recommended unless alternative treatment is not suitable ^{110,111}

Footnote:

*This product is not registered in Malaysia and not listed in MOH drug formulary.

**If paediatric doses exceed the recommended adult doses, cap the doses at the adult dose.



Appendix 5: Prolonged Infusion Guide

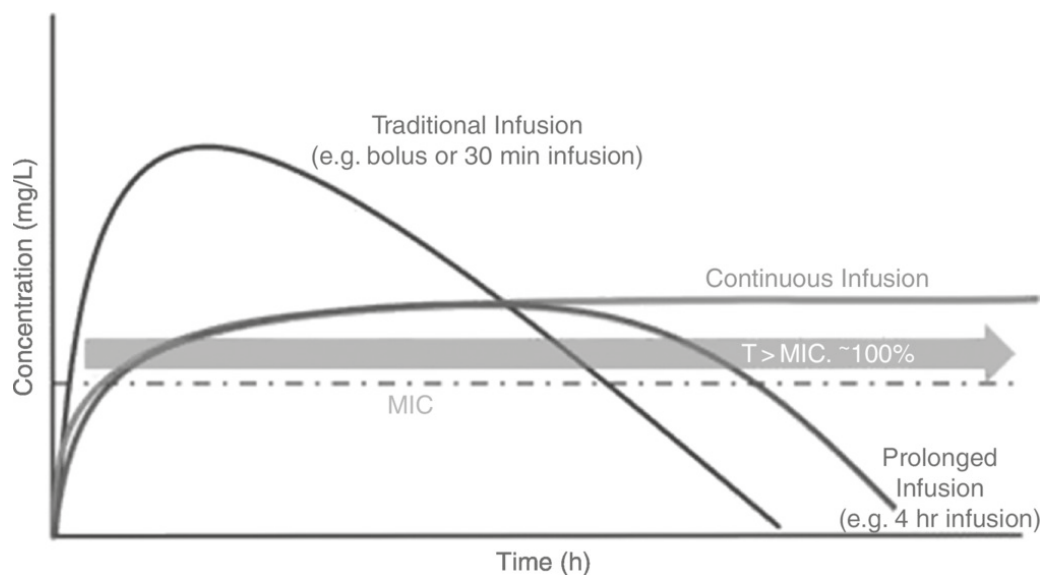
General principles:

What is defined as an extended/prolonged infusion?

The administration of drugs through prolonged infusion can be achieved using either the extended method which involves infusion over 3-4 hours during a dosing interval or through continuous infusion (constant intravenous infusion over 24 hours or sequential infusions over 6, 8, or 12 hours)¹¹². This dosing strategy is particularly important for time-dependent antibiotics, such as beta-lactam antibiotics.

Why do we need extended/prolonged infusion?

Prolonged infusion improves the efficacy of time-dependent antibiotics by increasing the fraction of time that the free drug concentrations remain above the minimum inhibitory concentration, MIC. This effect was demonstrated in preclinical PK/PD models of infection¹¹³ as well as clinical PK/PD and dosing simulation studies. The percentage of time above MIC is typically lower with standard intermittent infusion (infusion lasting ≤ 120 minutes). The concentration-time differences between the three dosing administration methods are illustrated in the graph below¹¹⁴.





Which patients would benefit from the prolonged infusion of beta-lactam antibiotics?

Extended or continuous infusions of certain medications are often considered advantageous in critically ill patients compared to traditional intermittent infusion methods. This approach can offer several benefits and the following are some of the clinical scenarios that may benefit from these strategies¹¹²:

1. Infections caused by less susceptible pathogens, characterised by higher baseline MIC or a propensity to develop resistance during antibiotic therapy. Examples of such pathogens include *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Carbapenem-resistant Enterobacterales*.
2. Patients who are at risk of altered pharmacokinetics:
 - i. Critically ill patients
 - ii. Patients with augmented renal clearance (ARC) defined as $\text{CrCL} \geq 120 \text{ mL/min}$. Risk factors for ARC include: young patients and/or patients with traumatic brain injury (TBI)
 - iii. Obese patients
 - iv. Hypoalbuminemia patients (for highly protein bound drugs)
3. Sites of infections that pose challenges for antibiotic penetration, e.g.: central nervous system (CNS) infection, bone and joint infections, pneumonia

However, the choice between continuous or intermittent infusion ultimately depends on several factors including the specific medication, patient characteristics, clinical scenario, and institutional capabilities. While continuous infusions offer these potential advantages, they are not universally superior and must be tailored to individual patient needs and clinical contexts.

How best to give extended/prolonged infusion?

An initial loading dose (LD) is essential to rapidly attain therapeutic concentration, and this can typically be given over 30-60 minutes. These loading doses are often higher than standard doses and are not affected by the patient's renal function. Subsequent doses should be administered through extended or continuous infusion, commencing after the loading dose, rather than waiting for the next scheduled dose.

The basis of this is as illustrated in the graph on the next page:

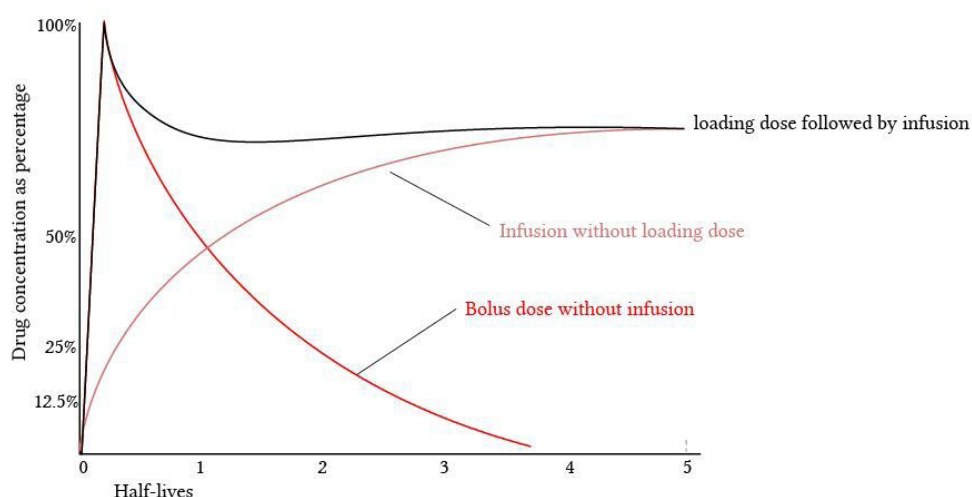


Table 1: Drug Stability for Prolonged Infusion

Drug	Diluent	Stability	Remarks
Ampicillin-sulbactam	NS D5	8 hours 2 hours	Conc: 45 mg/ml ¹¹⁵ Conc: 30 mg/ml ¹¹⁵
Piperacillin-tazobactam	NS D5	24 hours	1 vial (20 ml) in 50 ml diluent ¹¹⁶
Ceftazidime	NS D5	12 hours	Conc: ≤ 40 mg/ml ¹¹⁷
Cefepime	NS D5	24 hours	Conc: ≤ 40 mg/ml ¹¹⁷
Ceftolozane-tazobactam	NS D5	24 hours	In 100 ml diluent ¹¹⁹
Ceftazidime-avibactam	NS D5	12 hours	Conc: ≤ 40 mg/ml ¹²⁰
Cefiderocol	NS D5	12 hours ¹²¹	In 100 ml diluent ¹²² OR 62.5 mg/ml ¹²¹
Imipenem-cilastatin	NS D5	4 hours	Conc: 5 mg/ml ¹²³
Meropenem	NS D5	8 hours 1 hour	Conc: ≤ 20 mg/ml ^{124,125}
Aztreonam	NS D5	48 hours	Conc: ≤ 20 mg/ml ¹²⁶

Stability and maximum concentration allowed might differ from one brand to another brand. Please refer to your pharmacy for clarification.



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