MSIDC
MALAYSIAN SOCIETY OF INFECTIOUS DISEASES AND CHEMOTHERAPY

MyICID
MALAYSIAN SOCIETY OF INFECTION CONTROL AND INFECTIOUS DISEASES

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

First published 2024

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.

CONSENSUS GUIDELINES

THE TREATMENT OF MULTIDRUG RESISTANT GRAM NEGATIVES

FIRST EDITION

Expert Panel Members (in alphabetical order)

Chairman
Dato' Dr Suresh Kumar Chidambaram
Infectious Diseases Physician
Hospital Sungai Buloh

Adam Ashraf bin Ja'afer
Pharmacist
Hospital Sungai Buloh

Dr Helmi bin Sulaiman
Infectious Diseases Physician
Universiti of Malaya Medical Centre

Dr Azureen Azmel
Infectious Diseases Physician
Hospital Tengku Ampuan Rahimah

Dr Nor Anisa Md Radzi
Clinical Microbiologist
Hospital Banting

Dr David Ng Chun-Ern
Paediatric Infectious Diseases Specialist
Hospital Tuanku Ja'afar

Dr Nor Zaila Zaidan
Infectious Diseases Physician
Hospital Kajang

Dr Habib Abdul Hakim bin Esa
Clinical Microbiologist
Institute for Medical Research

Assoc. Prof.
Dr Nurul Azmawati Mohamed
Clinical Microbiologist
Universiti Sains Islam Malaysia

Assoc. Prof. Dr. Petrick Periyasamy
Infectious Diseases Physician
Hospital Canselor Tuanku Muhriz UKM

Dr Syamhanin Adnan
Pharmacist
Hospital Sungai Buloh

Dr Rahela Ambaras Khan
Pharmacist
Hospital Kuala Lumpur

Dr Tiew Wah Tin
Paediatric Infectious Diseases Specialist
Hospital Tunku Azizah

Expert Panel Members (in alphabetical order)

Dr Rosnida Mohd Noh
Infectious Diseases Physician
Universiti Teknologi MARA

Wong Jern Ni
Pharmacist
Hospital Shah Alam

Prof. Dr. Sasheela
A/P Sri La Sri Ponnampalavanar
Infectious Diseases Physician
Universiti of Malaya Medical Centre

Dr Wong Ke Juin
Paediatric Infectious Diseases Specialist
Sabah Children and Women Hospital

Dr Suhaila binti Baharuddin
Clinical Microbiologist
Hospital Tuanku Ja'afar

External Reviewers (in alphabetical order)

Dato' Dr Chow Ting Soo
Infectious Diseases Specialist
Hospital Pulau Pinang

Dr Fong Siew Moy
Paediatric Infectious Diseases Specialist
Sabah Women and Children Hospital

Dr Hafiz Abdul Aziz
Pharmacist
UQ Center for Clinical Research,
Brisbane, Australia

Lau Chee Lan
Pharmacist
Hospital Canselor Tuanku Muhriz UKM

Dr Nazedah Ain Ibrahim
Pharmacist
Hospital Tunku Azizah, Kuala Lumpur

Dr Sahlawati Mustakim
Clinical Microbiologist
Hospital Sungai Buloh

Wendy Chua
Pharmacist
Sarawak General Hospital

Dr Wong Ann Cheng
Neonatologist
Sarawak General Hospital

Dr Wong Pui Li
Infectious Diseases Specialist
University of Malaya Medical Centre

Dr Zakuan Zainy Deris
Clinical Microbiologist
Universiti Sains Malaysia

TABLE OF CONTENTS

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

SECTION 6: *Stenotrophomonas maltophilia*

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

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 Malaysia[3].

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 pressure[4].

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 days[5]

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

<table>
<tr><th>Epidemiology/ Microbiology details</th><th>Description/Recommendations</th></tr>
<tr><td>Introduction and epidemiology of Amp-C Beta-lactamase Producing Enterobacterales in Malaysia</td><td>

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>
<tr><th>Type</th><th>Features</th></tr>
<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
» Enterobacter cloacae complex
» Klebsiella aerogenes
» Citrobacter freundii
• Organisms with lower risk (<5%) of clinically significant inducible AmpC β-lactamases production
» Serratia marcescens
» Providencia spp
» Morganella morganii</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>
</table>

A study in a teaching hospital found 39.3% of cefotaxime and ceftriaxone-resistant Enterobacter spp. were positive for phenotypic AmpC[6].
Currently, there are no national surveillance programs for AmpC β-lactamase producing Enterobacterales in Malaysia.

</td></tr>
</table>

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%) • *Enterobacter cloacae complex* • *Klebsiella aerogenes* • *Citrobacter freundii*	

Infection sites	
Uncomplicated cystitis	**Confirm susceptibility before choosing antibiotic regimen** **Preferred** Nitrofurantoin PO[7] OR Trimethoprim/Sulfamethoxazole PO[8–10] OR Single dose Aminoglycoside (Gentamicin/Amikacin) IV[11] **Less preferred** Ciprofloxacin PO[12] 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 PO[8–10] OR Once Daily Aminoglycoside IV (Gentamicin/Amikacin - requires TDM monitoring)[13,14] OR Cefepime IV **Less preferred** Ciprofloxacin PO[12]
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) *Referral to an ID physician/clinical microbiologist is recommended for Cefepime Non-Susceptible isolates infection (SDD and Resistant)*
	Cefepime resistant isolates **Preferred** Carbapenem[8,15] (Ertapenem/Meropenem/Imipenem-cilastatin) IV *Referral to an ID physician/clinical microbiologist is recommended for Cefepime Non-Susceptible isolates infection (SDD and Resistant)*

Lower risk of clinically significant inducible AmpC production (<5%)

- *Serratia marcescens*
- *Providencia spp*
- *Morganella morganii*

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 PO[12] 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 PO[8–10] OR Once Daily Aminoglycoside (Gentamicin/Amikacin) IV (requires TDM monitoring)[13,14] OR Ceftriaxone/Cefotaxime IV **Less preferred** Ciprofloxacin PO[12]
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] *Referral to an ID physician/clinical microbiologist is recommended for Cefepime Non-Susceptible isolates infection (SDD and Resistant)*
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 *(Enterobacter cloacae complex, Klebsiella aerogenes, Citrobacter freundii)* 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 • Ceftazidime-avibactam • Meropenem-varbobactam • Imipenem-cilastatin-relebactam	**Avoid these agents.** These agents are reserved for the treatment of difficult to treat Carbapenem-resistant organisms.

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

2.1 Epidemiology/Microbiology

<table>
<tr><th>Epidemiology/ Microbiology details</th><th>Description/Recommendations</th></tr>
<tr><td>Introduction and Epidemiology of ESBL-producing Enterobacterales (ESBL-E) in Malaysia</td><td>

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 2022[21], almost a quarter of Escherichia coli and Klebsiella pneumoniae 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 K. pneumoniae 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%, respectively[23].

</td></tr>
<tr><td>ESBL screening test in the laboratory</td><td>

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 K. pneumoniae, K. oxytoca and E. coli
<table>
<tr><th>Antibiotic</th><th>Zone Diameter</th></tr>
<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>
</table>
ii. For Proteus mirabilis
<table>
<tr><th>Antibiotic</th><th>Zone Diameter</th></tr>
<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>
</table>
*Testing more than one antimicrobial agent improves the sensitivity of ESBL detection.
</td></tr>
</table>

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 Klebsiella pneumoniae, *Klebsiella oxytoca, Escherichia coli, and Proteus mirabilis* Other *Enterobacterales* 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] *(for E. coli only)* OR Ertapenem IV[8] *(if no other available options)*
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 *(if no other available options)*
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 *Proteus spp.*, *Morganella spp.*, and *Providencia spp.* 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 *Klebsiella pneumoniae* followed by *Enterobacter* spp., and *Escherichia coli*[21]. • Increasing trend of meropenem and imipenem resistance rate observed in *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter sp.* from 2018 to 2022. For example, the resistance rate of *Klebsiella pneumoniae* 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 enzyme[27]. • 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%) genes[28].
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.

<table>
<tr><th>Epidemiology/ Microbiology details</th><th>Description/Recommendations</th></tr>
<tr><td>Non-Carbapenemase-producing CRE (Non-CP-CRE)</td><td>

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 Proteus mirabilis isolate is intrinsically resistant to imipenem but susceptible to other carbapenem are not considered as CRE.

</td></tr>
<tr><td>Phenotypic test to differentiate CP CRE and Non CP-CRE</td><td>
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>
</td></tr>
</table>

<table>
<tr><th>Epidemiology/ Microbiology details</th><th>Description/Recommendations</th></tr>
<tr><td>Phenotypic test to differentiate CP CRE and Non CP-CRE</td><td>
Combination of mCIM and EDTA carbapenem inactivation method can be used to differentiate metallo-β-lactamase and serine carbapenemases in Enterobacterales
<table>
<tr><th colspan="3">mCIM and eCIM combination test</th></tr>
<tr><th>mCIM</th><th>eCIM</th><th>Report</th></tr>
<tr><td>Negative</td><td>Do not interpret</td><td>Carbapenemase not detected</td></tr>
<tr><td>Positive</td><td>Negative</td><td>Serine carbapenemase detected</td></tr>
<tr><td>Positive</td><td>Positive</td><td>Metallo-β-lactamase carbapenemase detected</td></tr>
<tr><td>Inconclusive</td><td>Do not interpret</td><td>Inconclusive: The presence or absence of a carbapenemase cannot be confirmed.</td></tr>
</table>
</td></tr>
</table>

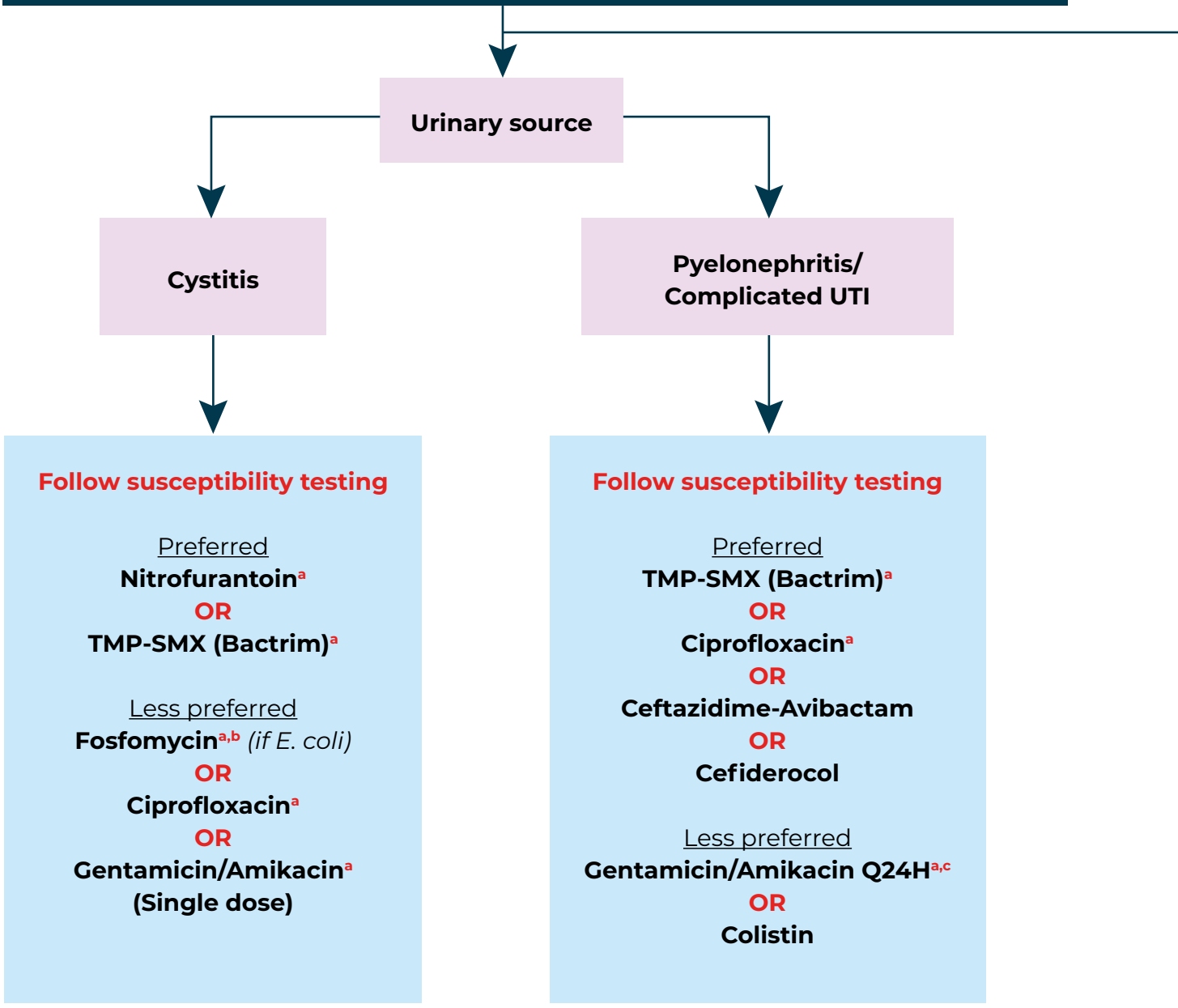
3.2 Infection Prevention and Control

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 Malaysia[24] and Responding to outbreaks of antimicrobial-resistant pathogens in health-care facilities: guidance for the Western Pacific region[25].

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)

Infection outside urinary tract / UTI with systemic involvement

Ceftazidime-Avibactam SENSITIVE

Preferred
Ceftazidime-Avibactam

**Less preferred
Cefiderocol
OR
Tigecycline (HD)
OR
Polymyxin B

****Combination therapy is highly recommended based on AST**

Ceftazidime-Avibactam RESISTANT

Presumed/Confirmed NDM Producing

Preferred
Ceftazidime-Avibactam
PLUS
Aztreonam
OR
****Cefiderocol**

**Less preferred
Tigecycline (HD)
OR
Polymyxin B

****Combination therapy is highly recommended based on AST**

Unknown mechanism of resistance

Preferred
****Cefiderocol**

**Less preferred
Tigecycline (HD)
OR
Polymyxin B

****Combination therapy is highly recommended based on AST**

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

Adopt & adapt with permission from: Hospital Sungai Buloh's Treatment Algorithm for Resistant Gram Negative (GNR) Infection 2024

3.3 Treatment

Infection details/ challenges	Recommendations Refer here for suggested duration of treatment
Non-CP CRE susceptible to Meropenem/Imipenem[8]	
CRE susceptible to Meropenem and Imipenem (MICs ≤1 µg/mL) and non-susceptible to Ertapenem (MICs ≥1 µg/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 *E.coli 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** ***Susceptible to Ceftazidime/Avibactam:*** **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	
	Non-Susceptible to Ceftazidime/Avibactam**: **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 ≤ 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.
	Non-Susceptible to Ceftazidime/Avibactam (Presumed/ Confirmed NDM-producing): **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 ≤ 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 BNF 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 available[31]. 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 producers[32]
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/Avibactam[8]. 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 guidelines[33] 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 ≤ 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. coli[34]. • Polymyxin B in combination with Fosfomycin IV that resulted in rapid bacterial killing in KPC-producing CRE[35].
What is the recommended combination therapy for Tigecycline?	• Combination with Polymyxin B has been shown to assist in rapid and sustained bacterial killing[35].

SECTION 4: Carbapenem-Resistant *Acinetobacter baumannii*

4.1 Epidemiology/Microbiology

Epidemiology/ Microbiology details	Description/Recommendations
Introduction & Epidemiology of *A. baumannii* in Malaysia	• *Acinetobacter baumannii* is a ubiquitous, Gram-negative coccobacillus and a significant cause of nosocomial infection[36]. • *Acinetobacter* contains fimbriae that enable it to attach to surfaces and form biofilms in both biotic and abiotic environments[127]. Under dry conditions, *A. baumannii* develops thicker cell walls, allowing it to survive long in the environment and making it difficult to eradicate[128-129]. • A study conducted at the University Malaya Medical Centre found that identical resistance patterns and PFGE profiles of *A. baumannii* from environmental samples, healthcare workers' hands, and patient isolates indicate a possible transmission route in the ICU[134]. • *A. baumannii* isolated from clinical specimens are mostly colonisers. Clinical correlation is important to avoid unnecessary antibiotic therapy[38]. • When isolated, it tends to be multidrug-resistant (MDR) due to many intrinsic resistant mechanisms and can acquire resistance through mobile genetic elements[37]. • A study conducted at Sungai Buloh Hospital from August 2017 to April 2018 revealed that *A. baumannii* 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 *A. baumannii* isolated from this study were also MDR[39]. • From 2009 to 2022, the nationwide carbapenem resistance rate of *A. baumannii* steadily ranges around 50-60%[21]. This resistance is mainly caused by the OXA-23 carbapenemase[43–46]. • Individual hospitals may have higher antibiotic resistance rates depending on the infection control practices and antibiotic use[40]. A surveillance study in Kuala Lumpur Hospital from 2018 - 2020 revealed positive correlation of MDR *A. baumannii* to increasing carbapenem consumption[41]. • In a study done by Rao et al in 2020 using whole genome sequencing, 11 isolates of carbapenem-resistant *A. baumannii* (CRAB) belong to international clone II[42].

Epidemiology/ Microbiology details	Description/Recommendations
Multidrug-resistant (MDR) *Acinetobacter baumannii*	Any *Acinetobacter baumannii* 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) • ß-lactam/ ß-lactam ß-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 Malaysia[24] and Responding to outbreaks of antimicrobial-resistant pathogens in health-care facilities: guidance for the Western Pacific region[25]

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 *A. baumannii* 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 AIDA[52] and OVERCOME[53] 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 *P. aeruginosa* in Malaysia	• An aerobic, Gram-negative bacillus found ubiquitously in soil, plants and hospital water reservoirs, including showers, sinks, and toilet water. • *P. aeruginosa* 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, *P. aeruginosa* 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 *Pseudomonas aeruginosa* 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% respectively[54]. • 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 *P. aeruginosa* 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 enzymese[55].

Epidemiology/ Microbiology details	Description/Recommendations
MDR *P. aeruginosa*	**NON**-susceptibility to at **least one** antibiotic in at **least three** antibiotic classes of the following[47]: • 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 *P. aeruginosa*	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 fluoroquinolones[56]. **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 Malaysia[24] and Responding to outbreaks of antimicrobial-resistant pathogens in health-care facilities: guidance for the Western Pacific region[25].

5.3 Treatment

Infection details/ challenges	Recommendations Refer here for suggested duration of treatment
Infections by MDR *P. aeruginosa*	
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-P. aeruginosa?	Newer BLBLI should be reserved for DTR-*P.aeruginosa*. 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-*P. aeruginosa*?	Nebulised antibiotics are not recommended[8,51]

Clinical pearls	
Can we use IV gentamicin for *P. aeruginosa* infection?	The use of gentamicin to treat infections by *P. aeruginosa* is **no longer** recommended as there are no CLSI breakpoints available.
Is there a role of combination therapy for the treatment of DTR- *P. aeruginosa* infection?	Most support for combination therapy comes from observational data[135,136], while a recent subanalysis from a randomized controlled trial does not support it[130]. 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.**

6.1 Epidemiology/Microbiology

Epidemiology/ Microbiology details	Description/Recommendations
Introduction and epidemiology of *S. maltophilia* in Malaysia	• A ubiquitous, non-fermenting Gram-negative rod closely related to *Pseudomonas* spp[59]. • It can be isolated from the environment, such as sinks, water, fomites, plants and hospital equipment[60]. • An emerging cause of healthcare-associated infection[61]. • Most *S. maltophilia* 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 *S. maltophilia* in the Malaysian tertiary centre is 6.9%[64]. • *S. maltophilia* prevalence and antibiotic resistance rate are currently not included in the national surveillance program. • *S. maltophilia* is intrinsically resistant to many antibiotics, including penicillin group, cephalosporin (excluding ceftazidime), aztreonam, and carbapenem[63]. • The ceftazidime breakpoints against *S. maltophilia* were removed from the M100 CLSI document, due to lack of supporting data and poor reproducibility in susceptibility testing[65].

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
Stenotrophomonas maltophilia 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 polymyxins[8].
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 serum[66]. 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.

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.

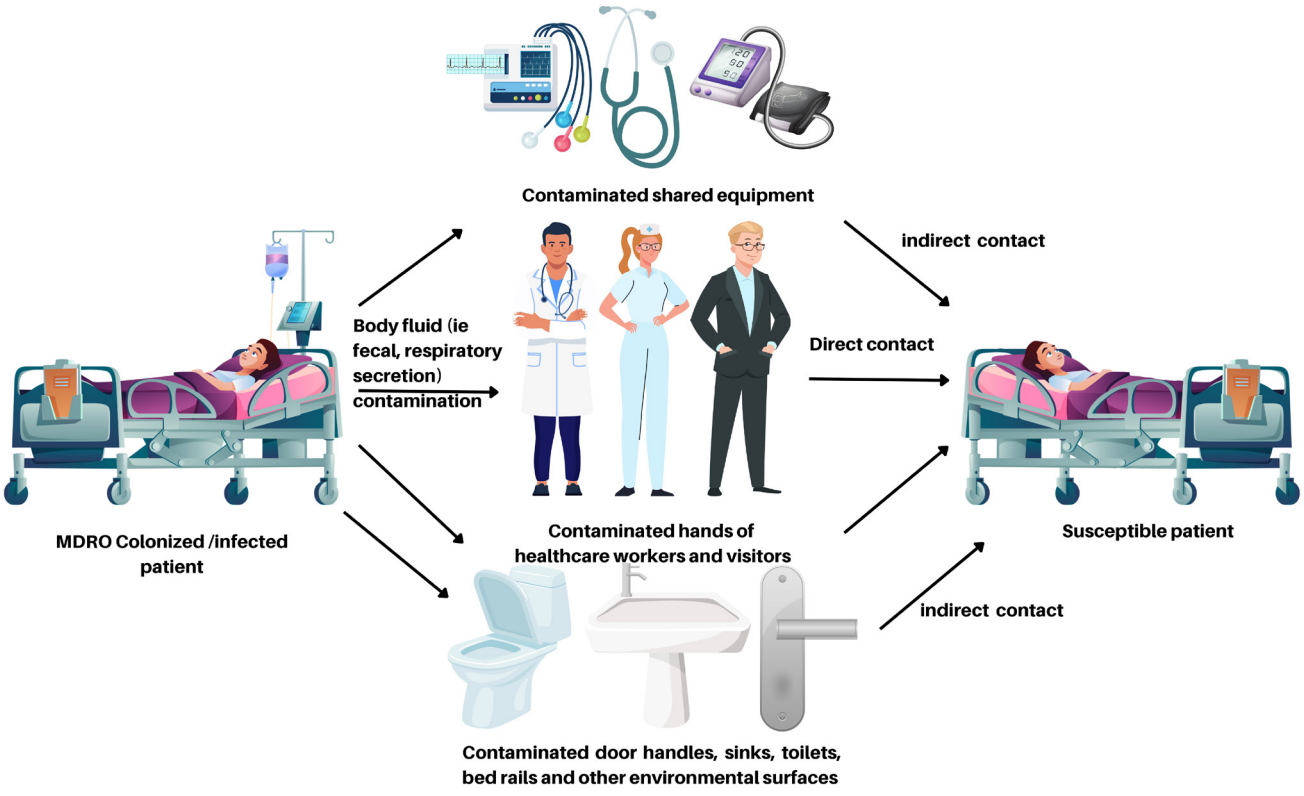


Figure 1: Potential transmission routes of hospital-acquired MDR GN infections. Image courtesy of Infection Control Dept, University Malaya Medical Centre

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 transmission[70].
  - » 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 outbreaks[71].
  - » 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

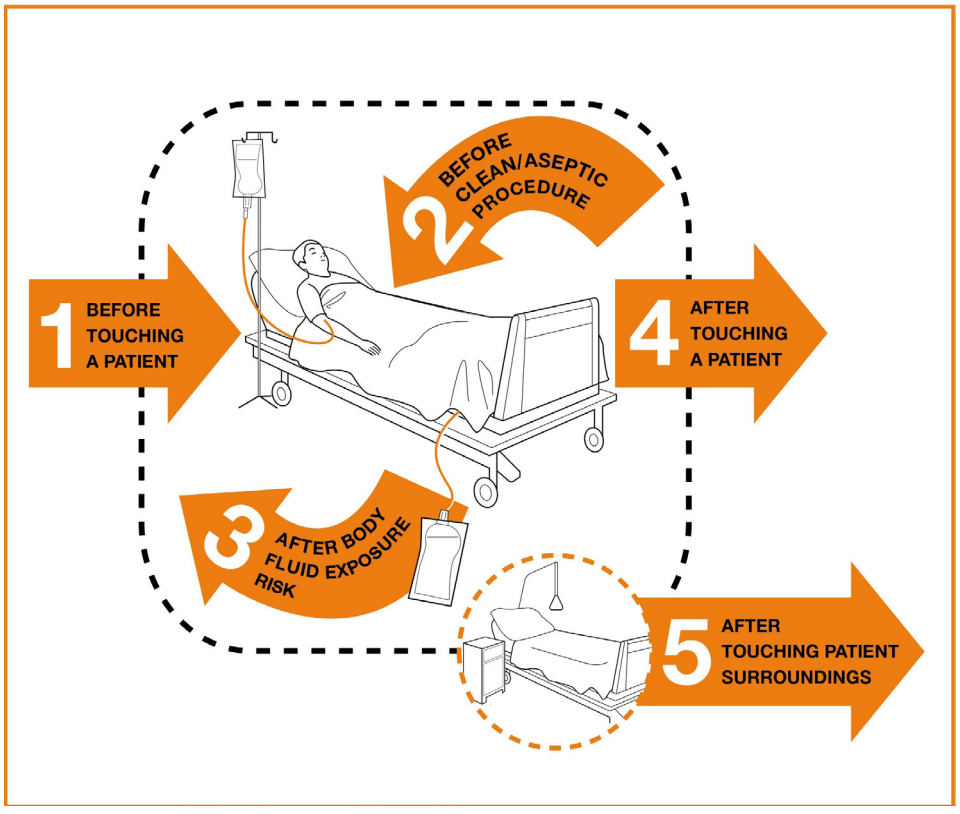


Figure 2: "My five moments for hand hygiene"
(Image source: WHO guidelines on hand hygiene in health care)

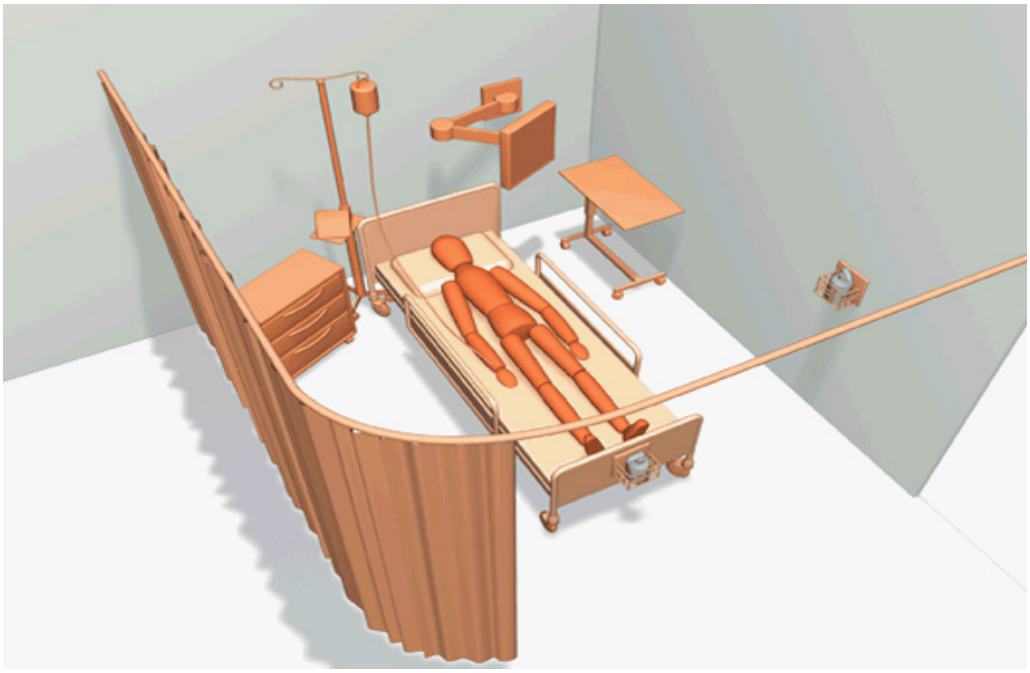


Figure 3: Patient environmnt includes the curtain and areas behind it.
(Image source: Public Health Ontario. Just Clean Your Hands – Hospitals)

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 recommended[69]
- Risk assessment for onward transmission to prioritise patient placement in a single isolation room[70]:
    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 beds[75]
- 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 transmission[88].
- 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 plumbing[79–83]. 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 areas[84]. Refer to Policies & Procedures on Infection Prevention & Control (3rd ed.) MOH Malaysia[24] 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 properly[131].
- Monitoring adherence to recommended environmental cleaning practices is essential in controlling the transmission of MDROs[89]. 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 linen[24].

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 considered[73]:

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 CRE[72]

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 months[71].
  - » 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 resources[90].

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 Malaysia[24].
- 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 2019[24].

- 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 Malaysia[24] and Responding to outbreaks of antimicrobial-resistant pathogens in health-care facilities: guidance for the Western Pacific region[25].
- 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 trolly. 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 infections[82]. 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 biofilm[133]. 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 sinks[83]. Discuss with engineers.
- Refer to Facility Guideline Documents (FGI) Guideline for Hospitals A2.1-8.4.3.2 (1) a. for recommended sink designs[92]

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-*Pseudomonas*. 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	*Steno. maltophilia* & 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)	
Polypeptide[98]	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) Cystitis (CRE)	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.
		CNS infection (AmpC/ESBL) All other infections (CRE)	2 gm IV Q8H			
	Imipenem	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 IVQ8H	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
		All other infections	2 gm IVQ8H, 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)
	Cefiderocol	CRE, DTR-PA, CRAB	2 gm IV Q8H	**>120**	**30-59**	**15-29**	**<15**
				2 g IV Q6H	1.5 gm IV Q8H	1 gm IV Q8H	0.75 gm Q12H
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	
			50 0mg -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) Uncomplicated cystitis (CRE)	1 gm IV Q8H	**30-50**	**10-29**	**<10 or HD**	
				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	*SDD is not recommended, please dose according to multiple daily dosing*
		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	*SDD is not recommended, please dose according to multiple daily dosing*
		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 IVQ24H	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 Pseudomonas aeruginosa, Enterococcus and *Acinetobacter species, Stenotrophomonas maltophilia,* 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 (≤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 (≥D14 OL) Infant (≥32 wk): 20 mg/kg Q8H (< D14 OL), 30 mg/kg Q8H (≥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

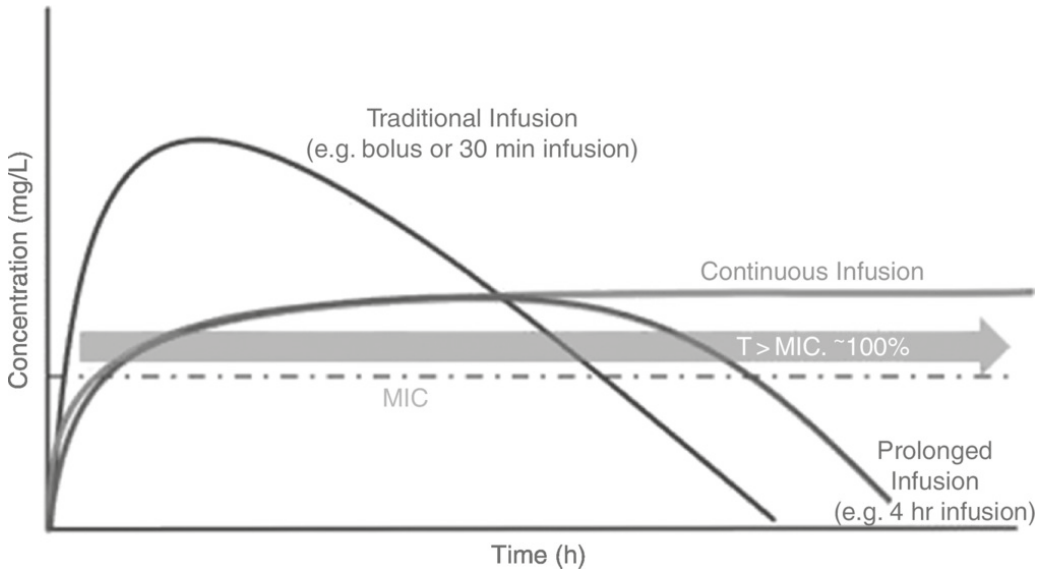
General principles:

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 infection[113] 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 below[114].



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 strategies[112]:

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 CrCL ≥ 120 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 infusions. 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:

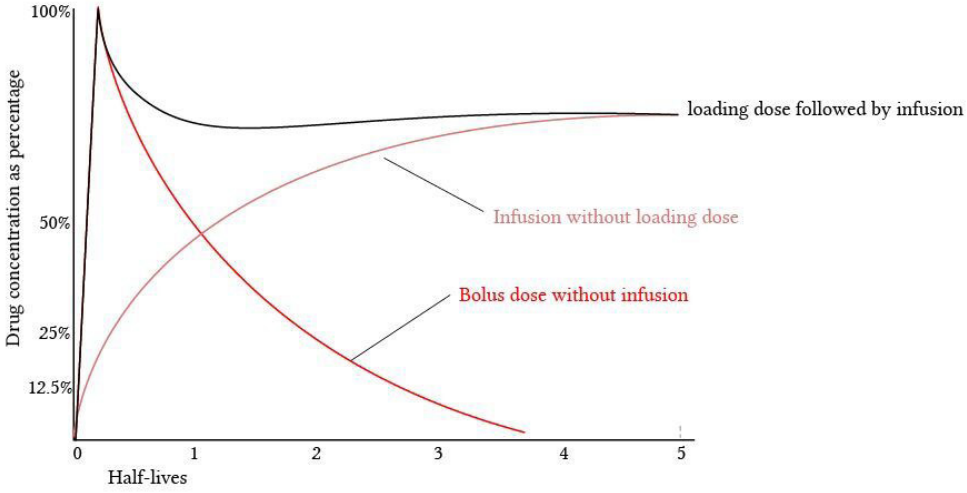


Table 1: Drug Stability for Prolonged Infusion

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/m[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.

References

1. Ministry of Health Malaysia. National Antimicrobial Guideline, 3rd Edition. 3rd ed. Pharmaceutical Services Programme, MOH Malaysia; 2019. Accessed May 17, 2024. www.pharmacy.gov.my
2. World Health Organization (WHO). The WHO AWaRe (Access, Watch, Reserve) Antibiotic Book. World Health Organization; 2022. Accessed March 11, 2024. https://www.who.int/publications/i/item/9789240062382
3. Ministry of Health Malaysia. Protocol on Antimicrobial Stewardship (AMS) Programme in Healthcare Facilities. Second. Pharmaceutical Service Programme, MOH; 2022.
4. Spellberg B. Shorter Is Better. Published 2024. Accessed May 30, 2024. https://www.bradspellberg.com/shorter-is-better
5. Soto CL, Hsu AJ, Lee JH, et al. Identifying Effective Durations of Antibiotic Therapy for the Treatment of Carbapenem-resistant Enterobacterales Bloodstream Infections: A Multicenter Observational Study. Clinical Infectious Diseases. 2024;78(1):27-30. doi:10.1093/CID/CIAD476
6. Khari FIM, Karunakaran R, Rosli R, Tay ST. Genotypic and Phenotypic Detection of AmpC β-lactamases in Enterobacter spp. Isolated from a Teaching Hospital in Malaysia. PLoS One. 2016;11(3):150643. doi:10.1371/JOURNAL.PONE.0150643
7. Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. JAMA. 2018;319(17):1781-1789. doi:10.1001/JAMA.2018.3627
8. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Clinical Infectious Diseases. Published online July 18, 2023. doi:10.1093/CID/CIAD428
9. Fox MT, Melia MT, Same RG, Conley AT, Tamma PD. A Seven-Day Course of TMP-SMX May Be as Effective as a Seven-Day Course of Ciprofloxacin for the Treatment of Pyelonephritis. Am J Med. 2017;130(7):842-845. doi:10.1016/J.AMJMED.2017.01.025
10. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. JAMA. 2000;283(12):1583-1590. doi:10.1001/JAMA.283.12.1583
11. Goodlet KJ, Benhalima FZ, Nailor MD. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? Antimicrob Agents Chemother. 2018;63(1). doi:10.1128/AAC.02165-18
12. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet. 2012;380(9840):484-490. doi:10.1016/S0140-6736(12)60608-4
13. Elbaz M, Zadka H, Weiss-Meilik A, Ben-Ami R. Effectiveness and safety of an institutional aminoglycoside-based regimen as empirical treatment of patients with pyelonephritis. J Antimicrob Chemother. 2020;75(8):2307-2313. doi:10.1093/JAC/DKAA148

14. Wagenlehner FME, Cloutier DJ, Komirenko AS, et al. Once-Daily Plazomicin for Complicated Urinary Tract Infections. New England Journal of Medicine. 2019;380(8):729-740. doi:10.1056/NEJMoa1801467
15. Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ. A Primer on AmpC β-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. Clin Infect Dis. 2019;69(8):1446-1455. doi:10.1093/CID/CIZ173
16. Kunz Coyne AJ, Ghali A El, Lucas K, et al. High-dose Cefepime vs Carbapenems for Bacteremia Caused by Enterobacterales With Moderate to High Risk of Clinically Significant AmpC β-lactamase Production. Open Forum Infect Dis. 2023;10(3). doi:10.1093/OFID/OFAD034
17. Lee NY, Lee CC, Li CW, et al. Cefepime Therapy for Monomicrobial Enterobacter cloacae Bacteremia: Unfavorable Outcomes in Patients Infected by Cefepime-Susceptible Dose-Dependent Isolates. Antimicrob Agents Chemother. 2015;59(12):7558-7563. doi:10.1128/AAC.01477-15
18. Chaubey VP, Pitout JDD, Dalton B, Gregson DB, Ross T, Laupland KB. Clinical and microbiological characteristics of bloodstream infections due to AmpC β-lactamase producing Enterobacteriaceae: an active surveillance cohort in a large centralized Canadian region. BMC Infect Dis. 2014;14(1). doi:10.1186/S12879-014-0647-4
19. Drozdinsky G, Neuberger A, Rakedzon S, et al. Treatment of Bacteremia Caused by Enterobacter spp.: Should the Potential for AmpC Induction Dictate Therapy? A Retrospective Study. Microb Drug Resist. 2021;27(3):410-414. doi:10.1089/MDR.2020.0234
20. Cheng L, Nelson BC, Mehta M, et al. Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC β-Lactamase-Producing Enterobacteriaceae. Antimicrob Agents Chemother. 2017;61(6). doi:10.1128/AAC.00276-17
21. Institute for Medical Research (IMR) NIH Malaysia. NATIONAL ANTIBIOTIC RESISTANCE SURVEILLANCE REPORT 2022.; 2023.
22. Mahdi Yahya Mohsen S, Hamzah HA, Muhammad Imad Al-Deen M, Baharudin R. Antimicrobial Susceptibility of Klebsiella pneumoniae and Escherichia coli with Extended-Spectrum β-lactamase associated Genes in Hospital Tengku Ampuan Afzan, Kuantan, Pahang. Malays J Med Sci. 2016;23(2):14. Accessed May 17, 2024. /pmc/articles/PMC4976709/
23. Mohd Helmi U, Mohd Desa MN, Taib NM, Tengku Jamaluddin TZM, Masri SN. Multiple ambler class A ESBL genes among Klebsiella pneumoniae isolates in a Malaysian district hospital. Trop Biomed. 2016;33(1):109-119. Accessed May 17, 2024. https://europepmc.org/article/med/33579148
24. Ministry of Health Malaysia. POLICIES & PROCEDURES on Infection Prevention and Control. 3rd ed. Infection Control Unit, Medical Care Quality Section, Medical Development Division, MOH; 2019.
25. World Health Organization Regional Office for the Western Pacific. Responding to Outbreaks of Antimicrobial-Resistant Pathogens in Health-Care Facilities: Guidance for the Western Pacific Region.; 2022. Accessed May 30, 2024. https://www.who.int/publications-detail-redirect/9789290619970

26. Zusman O, Farbman L, Tredler Z, et al. Association between hypoalbuminemia and mortality among subjects treated with ertapenem versus other carbapenems: prospective cohort study. Clin Microbiol Infect. 2015;21(1):54-58. doi:10.1016/J.CMI.2014.08.003
27. Yakubu A, Marwanis Anua S, Suraiya S, Mazlan N. A Current Review on Prevalence and Molecular Charaterisation of Carbapenem Resistant Klebsiella Pneumoniae in Malaysia. Malaysian Journal of Medicine and Health Sciences. 2021;17(SUPP8):2636-9346.
28. Ngoo SKMH, Sakudat K, Yamid SA, Hashim R. THE CARBAPENEMASE PRODUCING CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CP-CRE) GENE DISTRIBUTION IN MALAYSIA (2016 – 2021): A REPORT. International Journal of Infectious Diseases. 2023;130:S133. doi:10.1016/j.ijid.2023.04.329
29. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. Vol CLSI Supplement M100. 28th Ed. (Wayne P, ed.). Clinical and Laboratory Standards Institute, 2024; 2024. Accessed May 17, 2024. www.clsi.org.
30. Paediatric Formulary Committee. BNF for Children : 2022-2023.; 2022.
31. EMA. Tigecycline - Summary of Product Characteristics. Published 2022. Accessed May 31, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/tygacil
32. Viale P, Sandrock CE, Ramirez P, Rossolini GM, Lodise TP. Treatment of critically ill patients with cefiderocol for infections caused by multidrug-resistant pathogens: review of the evidence. Ann Intensive Care. 2023;13(1). doi:10.1186/S13613-023-01146-5
33. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clinical Microbiology and Infection. 2022;28(4):521-547. doi:10.1016/j.cmi.2021.11.025
34. Cai Y, Lim TP, Teo JQM, et al. Evaluating Polymyxin B-Based Combinations against Carbapenem-Resistant Escherichia coli in Time-Kill Studies and in a Hollow-Fiber Infection Model. Antimicrob Agents Chemother. 2017;61(1). doi:10.1128/AAC.01509-16
35. Bulman ZP, Zhao M, Satlin MJ, et al. Polymyxin B and fosfomycin thwart KPC-producing Klebsiella pneumoniae in the hollow-fibre infection model. Int J Antimicrob Agents. 2018;52(1):114-118. doi:10.1016/J.IJANTIMICAG.2018.02.010
36. Mehrad B, Clark NM, Zhanel GG, Lynch JP. Antimicrobial resistance in hospital-acquired gram-negative bacterial infections. Chest. 2015;147(5):1413-1421. doi:10.1378/CHEST.14-2171
37. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global Challenge of Multidrug-Resistant Acinetobacter baumannii. Antimicrob Agents Chemother. 2007;51(10):3471. doi:10.1128/AAC.01464-06
38. Martín-Aspas A, Guerrero-Sánchez FM, García-Colchero F, Rodríguez-Roca S, Girón-González JA. Differential characteristics of Acinetobacter baumannii colonization and infection: risk factors, clinical picture, and mortality. Infect Drug Resist. 2018;11:861. doi:10.2147/IDR.S163944
39. Nor FM, Shahari AS, Palaniasamy NK, et al. Multidrug resistant (MDR) Acinetobacter baumannii: rate of occurrence from a tertiary hospital, Malaysia. International Journal of Infectious Diseases. 2019;79(S1):46-47. doi:10.1016/j.ijid.2018.11.126

40. Rani FM, Rahman NIA, Ismail S, et al. Acinetobacter spp. infections in Malaysia: A review of antimicrobial resistance trends, mechanisms and epidemiology. Front Microbiol. 2017;8(DEC):301069. doi:10.3389/FMICB.2017.02479/BIBTEX
41. Tan SY, Khan RA, Khalid KE, Chong CW, Bakhtiar A. Correlation between antibiotic consumption and the occurrence of multidrug-resistant organisms in a Malaysian tertiary hospital: a 3-year observational study. Scientific Reports 2022 12:1. 2022;12(1):1-9. doi:10.1038/s41598-022-07142-2
42. Rao M, Rashid FA, Shukor S, Hashim R, Ahmad N. Detection of Antimicrobial Resistance Genes Associated with Carbapenem Resistance from the Whole-Genome Sequence of Acinetobacter baumannii Isolates from Malaysia. Can J Infect Dis Med Microbiol. 2020;2020. doi:10.1155/2020/5021064
43. Hwa WE, Subramaniam G, Navaratnam P, Sekaran SD. Detection and characterization of class 1 integrons among carbapenem-resistant isolates of Acinetobacter spp. in Malaysia. J Microbiol Immunol Infect. 2009;42(1):54-62. Accessed May 17, 2024. https://europepmc.org/article/med/19424559
44. Lean SS, Suhaili Z, Ismail S, et al. Prevalence and Genetic Characterization of Carbapenem- and Polymyxin-Resistant Acinetobacter baumannii Isolated from a Tertiary Hospital in Terengganu, Malaysia . ISRN Microbiol. 2014;2014:1-9. doi:10.1155/2014/953417
45. Biglari S, Alfizah H, Ramliza R, Rahman MM. Molecular characterization of carbapenemase and cephalosporinase genes among clinical isolates of acinetobacter baumannii in a tertiary medical centre in Malaysia. J Med Microbiol. 2015;64(1):53-58. doi:10.1099/JMM.0.082263-0/CITE/REFWORKS
46. Kamolvit W, Sidjabat HE, Paterson DL. Molecular Epidemiology and Mechanisms of Carbapenem Resistance of Acinetobacter spp. in Asia and Oceania. https://home.liebertpub.com/mdr. 2015;21(4):424-434. doi:10.1089/MDR.2014.0234
47. CDC, NCEZID, DHQP. Antimicrobial-Resistant Phenotype Definitions. Published online January 2022. Accessed May 17, 2024. https://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/phenotype_definitions.pdf
48. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant Acinetobacter baumannii. Scand J Infect Dis. 2007;39(1):38-43. doi:10.1080/00365540600951184
49. Jaruratanasirikul S, Nitchot W, Wongpoowarak W, Samaeng M, Nawakitrangsan M. Population pharmacokinetics and Monte Carlo simulations of sulbactam to optimize dosage regimens in patients with ventilator-associated pneumonia caused by Acinetobacter baumannii. Eur J Pharm Sci. 2019;136. doi:10.1016/J.EJPS.2019.05.018
50. Nation RL, Velkov T, Li J. Colistin and Polymyxin B: Peas in a Pod, or Chalk and Cheese? Clin Infect Dis. 2014;59(1):88. doi:10.1093/CID/CIU213
51. Rello J, Solé-Lleonart C, Rouby JJ, et al. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Clinical Microbiology and Infection. 2017;23(9):629-639. doi:10.1016/j.cmi.2017.04.011
52. Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis. 2018;18(4):391-400. doi:10.1016/S1473-3099(18)30099-9

53. Kaye KS, Marchaim D, Thamlikitkul V, et al. Colistin Monotherapy versus Combination Therapy for Carbapenem-Resistant Organisms. NEJM Evidence. 2022;2(1). doi:10.1056/EVIDOA2200131
54. Suhaila Tuan Soh T, Singh S, Chen Shin Ying V. In Vitro Activity of Ceftazidime-Avibactam against Clinical Isolates of Enterobacterales and Pseudomonas Aeruginosa Collected in Malaysia: Results from the ATLAS Programme, 2013 to 2019. www.atlas-surveillance.com.
55. Karlowsky JA, Kazmierczak KM, Bouchillon SK, De Jonge BLM, Stone GG, Sahm DF. In Vitro Activity of Ceftazidime-Avibactam against Clinical Isolates of Enterobacteriaceae and Pseudomonas aeruginosa Collected in Asia-Pacific Countries: Results from the INFORM Global Surveillance Program, 2012 to 2015. Antimicrob Agents Chemother. 2018;62(7). doi:10.1128/AAC.02569-17
56. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin Infect Dis. 2018;67(12):1803. doi:10.1093/CID/CIY378
57. Almangour TA, Ghonem L, Alassiri D, et al. Ceftolozane-Tazobactam Versus Ceftazidime-Avibactam for the Treatment of Infections Caused by Multidrug-Resistant Pseudomonas aeruginosa: a Multicenter Cohort Study. Antimicrob Agents Chemother. 2023;67(8). doi:10.1128/AAC.00405-23
58. Shields RK, Abbo LM, Ackley R, Aitken SL. A multicenter, observational study to compare the effectiveness of Ceftazidime-Avibactam versus Ceftolozane-Tazobactam for multidrug-resistant Pseudomonas aeruginosa infections in the United States (CACTUS). In: ESCMID GLOBAL. ; 2024.
59. Huang C, Lin L, Kuo S. Risk factors for mortality in Stenotrophomonas maltophilia bacteremia – a meta-analysis. Infect Dis. 2024;56(5):335-347. doi:10.1080/23744235.2024.2324365
60. Said MS, Tirthani E, Lesho E. Stenotrophomonas Maltophilia. StatPearls. Published online June 12, 2023. Accessed May 17, 2024. https://www.ncbi.nlm.nih.gov/books/NBK572123/
61. Neela V, Rankouhi SZR, van Belkum A, Goering R V., Awang R. Stenotrophomonas maltophilia in Malaysia: Molecular epidemiology and trimethoprim-sulfamethoxazole resistance. International Journal of Infectious Diseases. 2012;16(8):e603-e607. doi:10.1016/j.ijid.2012.04.004
62. Baidya A, Kodan P, Fazal F, et al. Stenotrophomonas maltophilia: More than Just a Colonizer! Indian J Crit Care Med. 2019;23(9):434. doi:10.5005/JP-JOURNALS-10071-23241
63. Mojica MF, Humphries R, Lipuma JJ, et al. Clinical challenges treating Stenotrophomonas maltophilia infections: an update. JAC Antimicrob Resist. 2022;4(3). doi:10.1093/jacamr/dlac040
64. Ismaeil R, Nahas ARF, Kamarudin NB, Abubakar U, Mat-Nor MB, Mohamed MHN. Evaluation of the impact of COVID-19 pandemic on hospital-acquired infections in a tertiary hospital in Malaysia. BMC Infect Dis. 2023;23(1):1-8. doi:10.1186/S12879-023-08770-3/TABLES/4

65. Bixby ML, Zheng D. What's New in 2023 From the CLSI Subcommittee on Antimicrobial Susceptibility Testing. Contagion Live. https://www.contagionlive.com/view/what-s-new-in-2023-from-the-clsi-subcommittee-on-antimicrobial-susceptibility-testing. Published October 23, 2023. Accessed May 17, 2024.
66. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. Journal of Antimicrobial Chemotherapy. 2006;58(2):256-265. doi:10.1093/JAC/DKL224
67. World Health Organization. Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, Acinetobacter Baumannii, and Pseudomonas Aeruginosa in Health Care Facilities.
68. Jane D. Siegel, Emily Rhinehart, Marguerite Jackson, Linda Chiarello, the Healthcare Infection Control Practices Advisory Committee. Guideline for Isolation: Preventing Transmission of Infectious Agents in Healthcare Settings.; 2007. Accessed May 17, 2024. https://www.cdc.gov/infection-control/hcp/isolation-precautions/index.html
69. Ontario. Provincial Infectious Diseases Advisory Committee., Public Health Ontario. Routine Practices and Additional Precautions in All Health Care Settings. Public Health Ontario; 2012.
70. Department of Health Victoria. Australia. Patient-centred risk management strategy for multi-resistant organisms. Published 2023. Accessed May 17, 2024. https://www.health.vic.gov.au/infectious-diseases/patient-centred-risk-management-strategy-for-multi-resistant-organisms
71. Hooper DavidC. Extended-spectrum beta-lactamases. In: Connor RF, ed. UpToDate. Wolters Kluwer; 2024. Accessed May 17, 2024. https://www.uptodate.com/contents/extended-spectrum-beta-lactamases
72. US Centers for Disease Control and Prevention. Carbapenem-resistant Enterobacterales (CRE) Infection Control. CDC Explore Topics. Accessed May 17, 2024. https://www.cdc.gov/cre/hcp/infection-control/?CDC_AAref_Val=https://www.cdc.gov/hai/organisms/cre/technical-info.html
73. Department of Health Victoria. Australia. Victorian guideline on CPO for health services. Published November 22, 2023. Accessed May 17, 2024. https://www.health.vic.gov.au/infectious-diseases/victorian-guideline-on-cpo-for-health-services
74. Hayden MK, Program for the C for DC and PE, Lin MY, et al. Prevention of Colonization and Infection by Klebsiella pneumoniae Carbapenemase–Producing Enterobacteriaceae in Long-term Acute-Care Hospitals. Clinical Infectious Diseases. 2015;60(8):1153-1161. doi:10.1093/CID/CIU1173
75. Cawangan Kawalan Amalan Perubatan Swasta KKM. Handbook on Setting up of Private Hospitals in Malaysia. (MOH, ed.).; 2019. Accessed June 20, 2024. https://hq.moh.gov.my/medicalprac/wp-content/uploads/2021/09/ Requirements-and-Prosedures-under-Act-5863.pdf
76. Ohl M, Schweizer M, Graham M, Heilmann K, Boyken L, Diekema D. Hospital privacy curtains are frequently and rapidly contaminated with potentially pathogenic bacteria. Am J Infect Control. 2012;40(10):904-906. doi:10.1016/j.ajic.2011.12.017
77. Gall E, Long A, Hall KK. Chlorhexidine Bathing Strategies for Multidrug-Resistant Organisms: A Summary of Recent Evidence. J Patient Saf. 2020;16(3S Suppl 1):S16-S22. doi:10.1097/PTS.0000000000000743

78. Lin MY, Lolans K, Blom DW, et al. The effectiveness of routine daily chlorhexidine gluconate bathing in reducing Klebsiella pneumoniae carbapenemase-producing Enterobacteriaceae skin burden among long-term acute care hospital patients. Infect Control Hosp Epidemiol. 2014;35(4):440-442. doi:10.1086/675613
79. Cahill ME, Jaworski M, Harcy V, et al. Cluster of Carbapenemase-Producing Carbapenem-Resistant Pseudomonas aeruginosa Among Patients in an Adult Intensive Care Unit — Idaho, 2021–2022. MMWR Morb Mortal Wkly Rep. 2023;72(31):844-846. doi:10.15585/MMWR.MM7231A2
80. Parkes LO, Hota SS. Sink-Related Outbreaks and Mitigation Strategies in Healthcare Facilities. Curr Infect Dis Rep. 2018;20(10):1-14. doi:10.1007/S11908-018-0648-3/METRICS
81. Kotay S, Chai W, Guilford W, Barry K, Mathers AJ. Spread from the sink to the patient: In situ study using green fluorescent protein (GFP)-expressing Escherichia coli to model bacterial dispersion from hand-washing sink-trap reservoirs. Appl Environ Microbiol. 2017;83(8):3327-3343. doi:10.1128/AEM.03327-16
82. Feller S. Sink drains, plumbing pose risk for MDRO spread in hospitals. Healio Infectious Disease News. Published August 4, 2023. Accessed May 17, 2024. https://www.healio.com/news/infectious-disease/20230804/sink-drains-plumbing-pose-risk-for-mdro-spread-in-hospitals
83. US Centre for Disease Control and Prevention. Considerations for Reducing Risk: Water in Healthcare Facilities - CDC HAI. Published April 2024. Accessed May 17, 2024. https://www.cdc.gov/hai/prevent/environment/water.html
84. US Center for Disease Control and Prevention. Environmental Cleaning Procedures. HAI. Published March 2024. Accessed May 31, 2024. https://www.cdc.gov/healthcare-associated-infections/hcp/cleaning-global/procedures.html?CDC_AAref_Val=https://www.cdc.gov/hai/prevent/resource-limited/cleaning-procedures.html
85. Tanner WD, Leecaster MK, Zhang Y, et al. Environmental Contamination of Contact Precaution and Non-Contact Precaution Patient Rooms in Six Acute Care Facilities. Clin Infect Dis. 2021;72(Suppl 1):S8. doi:10.1093/CID/CIAA1602
86. Trivedi PP, Mirza S, Gandham NR, et al. Environmental colonization and transmission of carbapenem-resistant enterobacteriaceae and carbapenem-resistant Acinetobacter baumannii in intensive care unit. Medical Journal of Dr DY Patil Vidyapeeth. 2023;16(5):761-766. doi:10.4103/MJDRDYPU.MJDRDYPU_210_21
87. García-Arenzana N, Redondo-Bravo L, Espinel-Ruiz MA, et al. Carbapenem-Resistant Enterobacteriaceae Outbreak in a Medical Ward in Spain: Epidemiology, Control Strategy, and Importance of Environmental Disinfection. Microb Drug Resist. 2020;26(1):54-59. doi:10.1089/MDR.2018.0390
88. Aygün G, Demirkiran O, Utku T, et al. Environmental contamination during a carbapenem-resistant Acinetobacter baumannii outbreak in an intensive care unit. Journal of Hospital Infection. 2002;52(4):259-262. doi:10.1053/jhin.2002.1300
89. US Center for Disease Control and Prevention. Considerations for Reducing Risk: Surfaces in Healthcare Facilities. HAIs. Published April 2024. Accessed May 31, 2024. https://www.cdc.gov/healthcare-associated-infections/hcp/infection-control/index.html

90. Banach DB, Bearman G, Barnden M, et al. Duration of Contact Precautions for Acute-Care Settings. Infect Control Hosp Epidemiol. 2018;39(2):127-144. doi:10.1017/ice.2017.245
91. Ministry of Health Malaysia. Management of Carbapenem-Resistant Enterobacteriaceae (CRE) in Healthcare Setting. 4th ed. INFECTION CONTROL UNIT, ; 2019. Accessed May 6, 2024. https://myohar.moh.gov.my/publications-human-health/
92. Facility Guideline Documents (FGI). Guideline Documents. Published 2022. Accessed May 31, 2024. https://www.fgiguidelines.org/guidelines/editions/
93. Lenhard JR, Smith NM, Bulman ZP, et al. High-Dose Ampicillin-Sulbactam Combinations Combat Polymyxin-Resistant Acinetobacter baumannii in a Hollow-Fiber Infection Model. Antimicrob Agents Chemother. 2017;61(3). doi:10.1128/AAC.01268-16
94. Abdul-Mutakabbir JC, Griffith NC, Shields RK, Tverdek FP, Escobar ZK. Contemporary Perspective on the Treatment of Acinetobacter baumannii Infections: Insights from the Society of Infectious Diseases Pharmacists. Infect Dis Ther. 2021;10(4):2177-2202. doi:10.1007/S40121-021-00541-4
95. Shields RK, Paterson DL, Tamma PD. Navigating Available Treatment Options for Carbapenem-Resistant Acinetobacter baumannii-calcoaceticus Complex Infections. Clin Infect Dis. 2023;76(Suppl 2):S179-S193. doi:10.1093/CID/CIAD094
96. Biagi M, Tan X, Wu T, et al. Activity of Potential Alternative Treatment Agents for Stenotrophomonas maltophilia Isolates Nonsusceptible to Levofloxacin and/or Trimethoprim-Sulfamethoxazole. J Clin Microbiol. 2020;58(2). doi:10.1128/JCM.01603-19
97. Xie J, Roberts JA, Alobaid AS, et al. Population Pharmacokinetics of Tigecycline in Critically Ill Patients with Severe Infections. Antimicrob Agents Chemother. 2017;61(8). doi:10.1128/AAC.00345-17
98. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2019;39(1):10-39. doi:10.1002/PHAR.2209
99. Gilbert DN, Chambers HF, Saag MS, Pavia A, Boucher HW. The Sanford Guide to Antimicrobial Therapy.; 2023.
100. Micromedex. Micromedex Neofax. In: IBM Corporation; 2024.
101. Sydney Local Health District. RPA Newborn Care Drug Database. Published 2024. Accessed May 31, 2024. https://www.slhd.nsw.gov.au/rpa/neonatal/html/finddrug.html
102. Lexi-Comp Online. Pediatric & Neonatal Lexi-Drugs Online. In: Lexi-Comp, Inc; 2024.
103. Azimi PH, Barson WJ, Janner D, Swanson R. Efficacy and safety of ampicillin/sulbactam and cefuroxime in the treatment of serious skin and skin structure infections in pediatric patients. UNASYN Pediatric Study Group. Pediatr Infect Dis J. 1999;18(7):609-613. doi:10.1097/00006454-199907000-00008
104. Gkentzi D, Tsintoni A, Christopoulou I, et al. Extensively-drug resistant Acinetobacter baumannii bacteremia in neonates: effective treatment with the combination of colistin and ampicillin/sulbactam. J Chemother. 2020;32(2):103-106. doi:10.1080/1120009X.2020.1716478

105. Kanra G, Secmeer G, Akalin E, et al. Sulbactam/ampicillin in the treatment of pediatric infections. Diagn Microbiol Infect Dis. 1989;12(4 Suppl):185-187. doi:10.1016/0732-8893(89)90134-X
106. Sutton AM, Turner TL, Cockburn F, McAllister TA. Pharmacokinetic study of sulbactam and ampicillin administered concomitantly by intraarterial or intravenous infusion in the newborn. Rev Infect Dis. 1986;8 Suppl 5:518-522. doi:10.1093/CLINIDS/8.SUPPLEMENT_5.S518
107. Ooi MH, Ngu SJ, Chor YK, Li J, Landersdorfer CB, Nation RL. Population Pharmacokinetics of Intravenous Colistin in Pediatric Patients: Implications for the Selection of Dosage Regimens. Clin Infect Dis. 2019;69(11):1962-1968. doi:10.1093/CID/CIZ067
108. Antachopoulos C, Karvanen M, Iosifidis E, et al. Serum and Cerebrospinal Fluid Levels of Colistin in Pediatric Patients. Antimicrob Agents Chemother. 2010;54(9):3985. doi:10.1128/AAC.01799-09
109. Antachopoulos C, Geladari A, Landersdorfer CB, et al. Population Pharmacokinetics and Outcomes of Critically Ill Pediatric Patients Treated with Intravenous Colistin at Higher Than Recommended Doses. Antimicrob Agents Chemother. 2021;65(6). doi:10.1128/AAC.00002-21
110. Tsiatsiou O, Iosifidis β, Katragkou A, et al. Successful management of an outbreak due to carbapenem-resistant Acinetobacter baumannii in a neonatal intensive care unit. Eur J Pediatr. 2015;174(1):65-74. doi:10.1007/S00431-014-2365-8
111. FDA. FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning | FDA. Published 2017. Accessed May 31, 2024. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-increased-risk-death-iv-antibacterial-tygacil-tigecycline
112. Hong LT, Downes KJ, FakhriRavari A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: Endorsed by the American College of Clinical Pharmacy, British Society for Antimicrobial Chemotherapy, Cystic Fibrosis Foundation, European Society of Clinical Microbiology and Infectious Diseases, Infectious Diseases Society of America, Society of Critical Care Medicine, and Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2023;43(8):740-777. doi:10.1002/PHAR.2842
113. Mouton JW, Den Hollander JG. Killing of Pseudomonas aeruginosa during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother. 1994;38(5):931-936. doi:10.1128/AAC.38.5.931
114. Grupper M, Kuti JL, Nicolau DP. Continuous and Prolonged Intravenous β-Lactam Dosing: Implications for the Clinical Laboratory. Clin Microbiol Rev. 2016;29(4):759-772. doi:10.1128/CMR.00022-16
115. Ampicillin/Sulbactam 1.5g Inj - Product Information Leaflet. Published online 2023.
116. Piperacillin-Tazobactam 4.5g Inj - Product Information Leaflet. Published online November 2023.
117. NPRA. Ceftazidime 2g Inj - Product Information Leaflet. Published online 2020.
118. NPRA. Cefepime 1g Inj - Product Information Leaflet. Published online 2022.
119. EMA. Ceftolozane-Tazobactam - Summary of Product Characteristics. Published online 2020.

120. EMA. Ceftazidime-Avibactam - SUMMARY OF PRODUCT CHARACTERISTICS. European Medicines Agency; 2021.
121. Loeuille G, Vigneron J, D'Huart E, Charmillon A, Demoré B. Physicochemical stability of cefiderocol, a novel siderophore cephalosporin, in syringes at 62.5 mg/mL for continuous administration in intensive care units. Eur J Hosp Pharm. 2023;30(e1):E29-E34. doi:10.1136/EJHPHARM-2021-002935
122. FDA. FETROJA (Cefiderocol) for injection, for intravenous use - Prescribing Information. Published online 2019. Accessed May 31, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209445s002lbl.pdf
123. NPRA. Imipenem/Cilastatin 500mg Inj - Product Information Leaflet. Published online 2020.
124. Carlier M, Stove V, Verstraete AG, De Waele JJ. Stability of generic brands of meropenem reconstituted in isotonic saline. Minerva Anestesiol. 2015;81(3):283-287.
125. NPRA. Meropenem 1g Inj - Product Information Leaflet. Published online 2022.
126. ASHP. Aztreonam. In: ASHP® Injectable Drug InformationTM. ASHP; 2021:179-187. doi:10.37573/9781585286850.046
127. Moubareck CA, Halat DH. Insights into Acinetobacter baumannii: A Review of Microbiological, Virulence, and Resistance Traits in a Threatening Nosocomial Pathogen. Antibiotics 2020, Vol 9, Page 119. 2020;9(3):119. doi:10.3390/ANTIBIOTICS9030119
128. Fournier PE, Richet H. The epidemiology and control of Acinetobacter baumannii in health care facilities. Clinical Infectious Diseases. 2006;42(5):692-699. doi:10.1086/500202/2/42-5-692-TBL003.GIF
129. Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. Clinical and pathophysiological overview of Acinetobacter infections: A century of challenges. Clin Microbiol Rev. 2017;30(1):409-447. doi:10.1128/CMR.00058-16/
130. Foucrier A, Dessalle T, Tuffet S, et al. Association between combination antibiotic therapy as opposed as monotherapy and outcomes of ICU patients with Pseudomonas aeruginosa ventilator-associated pneumonia: an ancillary study of the iDIAPASON trial. Crit Care. 2023;27(1):1-9. doi:10.1186/S13054-023-04457-Y
131. The Health Research & Educational Trust of the American Hospital Association (HRET), American Society for Health Care Engineering (ASHE), Association for Professionals in Infection Control and Epidemiology, Society of Hospital Medicine, University of Michigan. Using the Health Care Physical Environment to Prevent and Control Infection. A Best Practice Guide to Help Health Care Organizations Create Safe, Healing Environments. Vol 1. (ASHE, ed.).; 2018. Accessed June 19, 2024. https://www.ashe.org/sites/default/files/ashe/CDCfullbookDIGITAL.pdf
132. WHO Infection Prevention and Control (IPC) and Integrated Health Service. Implementation Manual to Prevent and Control the Spread of Carbapenem-Resistant Organisms at the National and Health Care Facility Level. (World Health Organization, ed.).; 2019. Accessed June 19, 2024. https://www.who.int/publications/i/item/ WHO-UHC-SDS-2019-6
133. Lv Y, Xiang Q, Jin YZ, et al. Faucet aerators as a reservoir for Carbapenem-resistant Acinetobacter baumannii: a healthcare-associated infection outbreak in a neurosurgical intensive care unit. Antimicrob Resist Infect Control. 2019;8(1):205. doi:10.1186/s13756-019-0635-y

134. Kong, B. H., Hanifah, Y. A., Yusof, M. Y., & Thong, K. L. (2011). Antimicrobial susceptibility profiling and genomic diversity of multidrug-resistant Acinetobacter baumannii isolates from a teaching hospital in Malaysia. Japanese journal of infectious diseases, 64(4), 337–340.
135. Khawcharoenporn T, Chuncharunee A, Maluangnon C, Taweesakulvashra T, Tiamsak P. Active monotherapy and combination therapy for extensively drug-resistant Pseudomonas aeruginosa pneumonia. Int J Antimicrob Agents. 2018;52(6):828-834. doi:10.1016/J.IJANTIMICAG.2018.09.008
136. Apisarnthanarak A, Mundy LM. Carbapenem-resistant Pseudomonas aeruginosa pneumonia with intermediate minimum inhibitory concentrations to doripenem: combination therapy with high-dose, 4-h infusion of doripenem plus fosfomycin versus intravenous colistin plus fosfomycin. Int J Antimicrob Agents. 2012;39(3):271-272. doi:10.1016/J.IJANTIMICAG.2011.11.012