Guideline

Central Administration of Pharmaceutical Care

General Administration For Drug Utilization &Pharmacy Practice

National Guidance for Antimicrobial Use in Infections with Multi-Drug Resistant Organisms (MDROs) 2024

National Rational Antimicrobial Use Committee

Code: EDREX:GL.CAP.Care.026
Version No: 1
Issue Date: May 2024

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Introduction

Antimicrobial resistance is the capability of a microorganism to resist the action of the different antimicrobials that could once be successful against them. When this resistance occurs to multiple drugs, it is known as multidrug resistance (MDR). There are different types of resistance mechanisms observed in microbes, like natural resistance in certain microbes against a particular antimicrobial, genetic mutation, or acquired resistance from other species. (1)

As per the statement of World Health Organization (WHO), MDR pathogens called 'superbugs' are one of the major public threats that yearly cause several million deaths globally. (1)

Antimicrobial resistance occurs as a direct result of antibiotic treatment, the abuse and misuse of antibiotics for the treatment, prevention, or management of diseases in people, animals, and plants. (2),(3)

Contributing factors include lack of access to clean water, sanitation, and hygiene (WASH) for both humans and animals; poor infection and disease prevention and control in homes, healthcare facilities and farms; poor access to quality and affordable vaccines, diagnostics, and medicines; lack of awareness and knowledge; and lack of enforcement of relevant legislation. (3)

Several operations, such as hip replacements, organ transplants, cesarean sections, and other surgeries, become at risk due to the introduction and spread of drug-resistant bacteria. (3)

AMR has significant costs for both health systems and national economies overall. For example, it creates need for more expensive and intensive care, affects productivity of patients or their caregivers through prolonged hospital stays, and harms agricultural productivity. (3)

AMR is a problem for all countries at all income levels. Its spread does not recognize country borders. People living in low-resource settings and vulnerable populations are especially impacted by both the drivers and consequences of AMR. (3)

The Scope of the Guidance

To describe appropriate antimicrobial chemotherapy for infections due to MDROs.

To describe best practices in antimicrobial prescribing including antimicrobial agents that are available in Egypt.

To serve as a clinical guide and not supersede the clinical judgment of physicians in the management of individual patients.

Abbreviations

A. baumannii	Acinetobacter. baumannii
AMC	Antimicrobial Consumption
AMR	Antimicrobial Resistance
CDC	Centre for Disease Prevention and Control
CFU	Colony Forming Units
CRAB	Carbapenem-Resistant Acinetobacter baumannii
CRE	Carbapenem- Resistant Enterobacterales
DTR-PA	Difficult-to-Treat P.aeruginosa
ESBL	Extended-spectrum beta-lactamases
GLASS	Global Antimicrobial Resistance and Use Surveillance System
IDSA	Infectious Diseases Society of America
KPC	Klebsiella pneumoniae carbapenemase
MBL	Metallo-beta-lactamases
MDROs	Multidrug-resistant organisms
MRGN	Multi-resistant Gram-negative bacilli
NDM	New Delhi MBL
PA	Pseudomonas aeruginosa

PDR	Pan- Drug Resistant
UTI	Urinary Tract Infection
VRE	Vancomycin-Resistant Enterococci
VAP	Ventilator Acquired Pneumoiae
VIM	Verona integron-encoded MBL
TMP-SMX	Trimethoprim- sulfamethoxazole
WHO	World Health Organization
XDR	Extensively drug-resistant

The burden of antimicrobial resistance (AMR) on the global level

The global rise in antibiotic resistance poses a significant threat, diminishing the efficacy of common antibiotics against widespread bacterial infections. (3)

The 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report highlights alarming resistance rates among prevalent bacterial pathogens. Median reported rates in 76 countries of 42% for third-generation cephalosporin-resistant *E. coli* and 35% for methicillin-resistant *Staphylococcus aureus* are a major concern. For urinary tract infections caused by *E. coli*, 1 in 5 cases exhibited reduced susceptibility to standard antibiotics like ampicillin, co-trimoxazole, and fluoroquinolones in 2020. This is making it harder to effectively treat common infections. (3)

Klebsiella pneumoniae, a common intestinal bacterium, also showed elevated resistance levels against critical antibiotics. Increased levels of resistance potentially lead to heightened utilization of last-resort drugs like carbapenems, for which resistance is in turn being observed across multiple regions. As the effectiveness of these last-resort drugs is compromised, the risks increase of infections that cannot be treated. Projections by the Organization for Economic Cooperation and Development (OECD) indicate an anticipated twofold surge in resistance to last-resort antibiotics by 2035, compared to 2005 levels, emphasize the urgent need for robust antimicrobial stewardship practices and enhanced surveillance coverage worldwide. (3)

AMR represents a global challenge, 4.95 million people who died in 2019 suffered from drug-resistant infections, AMR directly caused 1.27 million of those deaths, 1 in 5 of those deaths occurred among children under 5 years old. (4)

The Antimicrobial Consumption Data (AMC) in Egypt

The recent analysis of the national AMC data for 2022 indicates that the consumption according to the AWaRe list was as follows - Access group 55.52%, Watch group 42.86%, and Reserve group 0.96%. According to the GLASS-AMC report, penicillins make up the majority of Egypt's antimicrobial consumption; products containing a combination of penicillins and beta-lactamase inhibitors make up 29.3% of the antibacterials used, while macrolides make up 23.93%.

The Most problematic antibiotic-resistant bacteria in healthcare facilities

In 2021, WHO published the list of antibiotic-resistant pathogens (priority pathogens), especially highlighting the resistant gram-negative bacteria that pose maximum threat to human health. On the basis of urgency for new antibiotics, the list is categorized into three headings, mainly critical, high, and medium priority. (1)

The critical group of MDR bacteria includes Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae, which cause severe infections like pneumonia and blood stream infections in hospital-admitted patients. The high and medium priority group include drug-resistant bacteria like Salmonella that causes common diseases, such as gonorrhoea and food poisoning. (1)

Multi-resistant Gram-negative bacilli (MRGN)

Gram-negative bacilli are a large group of bacteria that are commonly found in the intestinal tract of humans and most animals. They form part of the normal microflora and are essential for proper digestive processes. However, these bacteria can cause infection when introduced into normally sterile body sites, such as the bladder or deep tissues, particularly via the insertion of a medical device or during surgery. (2),(5),(6)

Serious infections require the administration of antibiotics and can be associated with a high mortality rate, particularly in vulnerable patients such as those in critical care or who are immune-suppressed. (2),(6)

The term, "ESKAPE," has been proposed to express the majority of nosocomial infections due to resistant pathogens, including Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species. (7)

Resistance in Gram-negative bacilli occurs by several mechanisms and there are literally dozens of different resistance determinants. Those that pose particular problems for hospital patients can be broadly grouped into: (2)

- Transferable beta-lactam resistance, for example AMP-C, mostly found in E. coli and Salmonella species.
- Extended-spectrum beta-lactamases (ESBL)– transferable resistance to 3rd and 4th generation cephalosporins, mostly found in E. coli, Klebsiella and Enterobacter species.
- Metallo-beta-lactamases (MBL) – similar to ESBL, but can also include resistance to carbapenems, mostly found in Pseudomonas aeruginosa.
- Carbapenemase-producing Enterobacterales (formerly known as Carbapenemase-producing Enterobacteriaceae), an emerging resistance of concern.

The increased threat from Gram-negative MDR species is widely acknowledged by global and national organizations including the WHO, European Centre for Disease Prevention and Control (CDC), Infectious Diseases Society of America (IDSA), and the United States CDC. Indeed, among the WHO's list of priority resistant bacteria for 2016–17, three are described as critical—the highest level of concern—and all three are Gram-negative, namely **Carbapenem resistant Enterobacterales**, **Carbapenem-resistant A. baumannii,** and **Carbapenem-resistant P. aeruginosa** (5)

Definitions of MDR, XDR and PDR for different MRGN

It is the general method for classifying AMR for different types of bacteria, but the treatment recommendations mentioned in the guidance are built up based on the resistance gene/ enzyme mutation.

Table 1: Definition of MDR, XDR and PDR Acinetobacter (8)

Resistance category	Criteria for defining
MDR	Non-susceptible to: ≥ 1 agent in ≥ 3 antimicrobial categories but still susceptible to agent/s in more than 2 categories from table 2. **Example: resistance to:** One or more agents of the Aminoglycoside category One or more agents of the antipseudomonal Carbapenem category One or more agents of the antipseudomonal Cephalosporins
XDR	Non-susceptible to ≥1 agent in all categories except 2 or fewer antimicrobial categories from table 2. **Example: resistance to:**

	One or more agent of the Aminoglycoside category One or more agent of the antipseudomonal Carbapenem category One or more agent of the Extended spectrum Cephalosporins One or more agent of antipseudomonal Fluoroquinolones category Piperacillin/ tazobactam of the antipseudomonal Penicillin category Fosfomycin of Phosphoric acids category, Tetracycline, Colistin, Trimethoprim-sulphamethoxazole.
PDR	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in the table 2.

Table 2: Susceptibility of Acinetobacter baumannii [8]

Antimicrobial category	**Antimicrobial agent**
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
Antipseudomonal carbapenems	Imipenem
	Meropenem
Extended spectrum cephalosporins	Cefotaxime
	Ceftriaxone
	Ceftazidime
	Cefepime
Antipseudomonal fluoroquinolones	Ciprofloxacin
	Levofloxacin
Antipseudomonal penicillin/ β- lactamase inhibitors	Piperacillin-tazobactam
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole
Monobactams	Aztreonam
Penicillins + b-lactamase inhibitors	Ampicillin-sulbactam
Phosphoric acids	Fosfomycin
Polymyxins	Colistin
	Polymyxin B
Tetracyclines	Tetracycline
	Doxycycline
	Minocycline

Table 3: Definition of MDR, XDR and PDR Enterobacteriaceae [8]

Resistance category	**Criteria for defining**
MDR	Non-susceptible to: ≥ 1 agent in ≥ 3 antimicrobial categories but still susceptible to agent/s in more than 2 categories from table 4.
XDR	Non-susceptible to ≥1 agent in all categories except 2 or fewer antimicrobial categories from table 4.
PDR	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in the table 4.

Table 4 Enterobacteriaceae; antimicrobial categories and agents used to define MDR, XDR and PDR[8]		
Antimicrobial category	**Antimicrobial agent**	**Species with intrinsic resistance to antimicrobial agents or categories**
Aminoglycosides	Gentamicin	Providencia rettgeri (P. rettgeri), Providencia stuartii (P. stuartii)
	Tobramycin	
	Amikacin	
Anti-MRSA cephalosporins	Ceftaroline (approved only for: Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca)	
Carbapenems	Ertapenem	
	Imipenem	
	Meropenem	
Non-extended spectrum cephalosporins; 1st and 2nd generation cephalosporins	Cefazolin	Citrobacter freundii (C. freundii), Enterobacter aerogenes (E. aerogenes), Enterobacter cloacae (E. cloacae), Hafnia alvei (H. alvei), Morganella morganii (M. morganii), Proteus penneri (P. penneri), Proteus vulgaris (P. vulgaris), P. rettgeri, P. stuartii, Serratia marcescens (S. marcescens)
	Cefuroxime	M. morganii, P. penneri, P. vulgaris, S. marcescens
Extended spectrum cephalosporins	Cefotaxime	
	Ceftriaxone	
	Ceftazidime	
	Cefepime	
Cephamycins	Cefoxitin	C. freundii, E. aerogenes, E. cloacae, H. alvei
Fluoroquinolones	Ciprofloxacin	
Antipseudomonal penicillin/ β- lactamase inhibitors	Piperacillin-tazobactam	Escherichia hermannii (E. hermanii)
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	
Glycylcyclines	Tigecycline	M. morganii, Proteus mirabilis (P. mirabilis), P. penneri, P. vulgaris, P. rettgeri, P. stuartii
Monobactams	Aztreonam	
Penicillins	Ampicillin	Citrobacter koseri (C. koseri), C. freundii, E. aerogenes, E. cloacae, E. hermanii, H. alvei, Klebsiellae spp., M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii, S. marcescens
Penicillins + b-lactamase inhibitors	Ampicillin-sulbactam	C. freundii, C. koseri, E. aerogenes, E. cloacae, H. alvei, P. rettgeri, S. marcescens

	Amoxicillin-clavulanic acid	C. freundii, E. aerogenes, E. cloacae, H. alvei, M. morganii, P. rettgeri, P. stuartii, S. marcescen
Phosphoric acids	Fosfomycin	
Polymyxins	Colistin	M. morganii, P. mirabilis, P. penneri, P. vulgaris, P. rettgeri, P. stuartii, S. marcescens
Tetracyclines	Tetracycline	M. morganii, P. mirabilis, P. penneri, P. vulgaris, P. rettgeri, P. stuartii
	Doxycycline	M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuartii
	Minocycline	

Table 5: Definition of MDR, XDR and PDR Pseudomonas aeruginosa [8]

Resistance category	Criteria for defining
MDR	Non susceptible to: ≥ 1 agent in ≥ 3 antimicrobial category but still susceptible to more than 2 categories from table6. Example: resistance to: One or more agents of the aminoglycoside category One or more agents of the antipseudomonal carbapenem category One or more agents of the antipseudomonal cephalosporins
XDR	Non-susceptible to ≥1 agent in all categories except 2 or fewer antimicrobial categories in table 6. Example: resistance to: One or more agents of the aminoglycoside category One or more agents of the antipseudomonal carbapenem category One or more agents of the antipseudomonal cephalosporins One or more agents of antipseudomonal fluoroquinolones category Piperacillin/ tazobactam of penicillin category Fosfomycin of Phosphoric acids category
PDR	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in the table 6

Table 6: Antimicrobial categories and agents used to define MDR, XDR and PDR Pseudomonas aeruginosa[8]

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
Antipseudomonal carbapenems	Imipenem
	Meropenem
Antipseudomonal cephalosporins	Ceftazidime
	Cefepime
Antipseudomonal fluoroquinolones	Ciprofloxacin
	Levofloxacin
Antipseudomonal penicillin/ β-lactamase inhibitors	Piperacillin-tazobactam
Monobactams	Aztreonam
Phosphoric acids	Fosfomycin
Polymyxins	Colistin- Polymyxin B

Colonization Versus True Infection

MDROs infections e.g., CRAB are most commonly recovered from respiratory specimens or wounds. Therefore, it is not always clear if an isolate is a colonizing organism in patients who are ill for reasons attributable to their underlying host status (e.g., patients requiring mechanical ventilation, patients with extensive burns), or if CRAB represents a true pathogen capable of contributing to excess mortality, leading to uncertainty about the need for antibiotic therapy. For the same reason, it is challenging to determine if poor clinical outcomes are attributable to suboptimal antibiotic therapy or underlying host factors. [9]

Table 7: Difference between colonization and true infection

Colonization	Infection
It is the presence of bacteria on a body surface (like on the skin, mouth, intestines or airway) without causing disease for the person.[10]	It is the invasion of a host organism's bodily tissues by disease-causing organisms. Infection also results from the interplay between pathogens and the defenses of the hosts they infect.[10]
Isolates were classified as colonization when no adverse clinical signs or symptoms were documented.[11]	Infections were defined by the presence of a major bacterial load associated with clinical manifestations within the infection window period (±3 days from specimen collection). [11]
The most important factor in determining if a patient is colonized or infected with an organism is the clinical picture.[12]	
One must put together the pieces of the puzzle that constitute the clinical picture and the following factors to determine if antimicrobials should be started. [12] - Method by which sample obtained - Gram stain results - Culture results - Body temperature - Radiographic findings - Change in oxygenation or ventilation status - Underlying medical conditions - Results of white blood cell count & differential - General clinical condition	

Table 8: Diagnostic criteria for infections [11]

Infection	Site of Culture	Bacterial Load	Clinical Signs
Primary Blood Stream Infection	2 percutaneous blood samples + eventual blood from catheters		Fever/chills/hypotension + No further sign of localized infection
• If Common Commensal organisms (i.e., diphtheroids (Corynebacterium spp. not C. diphtheria), Bacillus spp. (not B. anthracis), Propionibacterium spp., coagulase-negative staphylococci			

<table>
<tr><td colspan="4">(including S. epidermidis), viridans group streptococci, Aerococcus spp. Micrococcus spp. and Rhodococcus spp.): necessary two or more blood specimens drawn on separate occasions.</td></tr>
<tr><td>Central line-associated Blood Stream Infection
(at least 48 h after catheter positioning)</td><td>percutaneous blood samples + catheter blood or catheter tip</td><td></td><td>Fever/chills/hypotension
+
No further sign of localized infection. Eventual erythema, swelling, purulent drainage from catheter insertion-site.</td></tr>
<tr><td colspan="4">• Central line colonization: positive catheter blood or catheter tip and negative percutaneous blood samples.
• If Common Commensal organisms (i.e., diphtheroids (Corynebacterium spp. not C. diphtheria), Bacillus spp. (not B. anthracis), Propionibacterium spp., coagulase-negative staphylococci (including S. epidermidis), viridans group streptococci, Aerococcus spp. Micrococcus spp. and Rhodococcus spp.): necessary two or more blood specimens drawn on separate occasions.</td></tr>
<tr><td rowspan="3">Ventilator-associated lower respiratory tract infections (at least 48 h after intubation)</td><td>Bronchoalveolar lavage</td><td>$\geq 10^4$ Colony forming units (CFU)/mL</td><td rowspan="3">1 of:
fever, leukocytosis/leucopenia.
+
1 of:
worsening oxygenation, purulent secretions
+
New/progressive radiographic infiltrate (if available)</td></tr>
<tr><td>Endotracheal Aspirate</td><td>$\geq 10^5$ CFU/mL</td></tr>
<tr><td>secondary Blood Stream Infection positive blood (specimen containing at least one matching organism to the blood specimen)</td><td></td></tr>
<tr><td colspan="4">Excluded organisms: “Normal respiratory flora,” “normal oral flora,” “mixed respiratory flora,” and, unless identified from lung tissue or pleural fluid (with specimen obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube), Candida spp, coagulase-negative staphylococci, Enterococcus spp.</td></tr>
<tr><td rowspan="2">Catheter-associated Urinary Tract Infection.
(at least 48 h after indwelling urinary catheter positioning.)</td><td>urine culture
N.B., if urinary catheter in place for more than 5 days, the catheter is removed, a new catheter is repositioned and a second specimen is collected.</td><td>$\geq 10^5$ CFU/mL</td><td></td></tr>
<tr><td>secondary Blood Stream Infection (positive blood specimen containing at least one eligible matching organism to the urine specimen)</td><td></td><td></td></tr>
<tr><td colspan="4">Excluded organisms: “mixed flora,” Candida spp, yeast, mold, dimorphic fungi, parasites</td></tr>
</table>

Acinetobacter baumannii

Table 9: Recommended treatment options for infections due to Carbapenem-Resistant Acinetobacter baumannii.(CRAB) [7],[13],[14],[15],[16],[17],[18]		
• Resistance to at least anyone carbapenem (meropenem or imipenem).[18] • Combination therapy with at least two active agents, is recommended for the treatment of CRAB infections, even if a single agent demonstrates activity, at least until clinical improvement is observed, because of the limited clinical data supporting any single antibiotic agent. [17] • In situations when prolonged durations of therapy may be needed (e.g., osteomyelitis), step-down therapy to a single active agent can be considered.[17]		
Clinical Syndrome	**Recommended Treatment**	**Alternative Treatment**
Pneumonia	• Colistin + Meropenem + Ampicillin/sulbactam (even if non-susceptible) [9],[17],[18] • Colistin + (Imipenem/cilastatin or Meropenem) • Consider concomitant administration of inhaled Colistin when it is used intravenously for VAP [5],[16], however IDSA does not suggest the use of nebulized antibiotics as adjunctive therapy for CRAB pneumonia, due to the lack of benefit observed in clinical trials.[17],[18]	Colistin + Tigecycline + Ampicillin/Sulbactam
Bloodstream Infections	• Colistin + Meropenem + Ampicillin/sulbactam. (for critically ill patients if the local rate of MDR/carbapenem resistance > 10-15%). • Colistin + (Imipenem/cilastatin or Meropenem).	Colistin + (Tigecycline OR Ampicillin/ Sulbactam)
Complicated UTI	As bloodstream infection	

Enterobacteriaceae

Resistant Enterobacterales

Table 10: ESBL & AmpC β-Lactamase		
The resistance gene/enzyme	**1-ESBL**	**2-AmpC β-Lactamase**
Definition [7],[17]	• Extended-spectrum beta-lactamases (ESBL)– transferable resistance to 3rd and 4th generation cephalosporins.	• Transferable beta-lactam resistance, AMP-C

	• ESBLs are enzymes that inactivate most Penicillins, Cephalosporins, and Aztreonam. • EBSL-E generally remains susceptible to Carbapenems. • Organisms carrying ESBL genes often harbor additional genes or mutations in genes that mediate resistance to a broad range of antibiotics.		
The most common Enterobacterales at risk for producing the resistance enzyme/gene (17)	Any gram-negative organism has the potential to harbor ESBL genes; however, <u>they are most prevalent in:</u> • Escherichia coli • Klebsiella pneumoniae • Klebsiella oxytoca • Proteus mirabilis.	(Most recovered organisms) • Enterobacter cloacae complex • Klebsiella aerogenes. • Citrobacter freundii	(less commonly recovered organisms) • S. marcescens, • M. morgannii. • Providencia spp
The antibiotics <u>avoided</u> empirically (or even if an isolate initially tests susceptible to these agents) (17)	• Piperacillin-tazobactam is not suggested for the treatment of infections outside of the urinary tract caused by ESBL-E • Ceftriaxone, cefepime, cefoxitin or cefotetan • N.B., if cefepime or piperacillin-tazobactam were initiated as empiric therapy for uncomplicated cystitis caused by an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary.	• First-generation Cephalosporins, Cefoxitin, Cefotetan • Ceftriaxone, Cefotaxime, Ceftazidime (for any infection other than uncomplicated cystitis) • Aminopenicillins (i.e., amoxicillin, ampicillin). • Piperacillin-tazobactam is not suggested for the treatment of serious infections caused by the mentioned organism. • Aztreonam	• Ceftriaxone (for infections with limited source control (e.g., endocarditis, central nervous system infections)

The active antimicrobial agents [17]	• Carbapenems • Ciprofloxacin • Levofloxacin • Trimethoprim-sulfamethoxazole [TMP-SMX] • Gentamicin • Piperacillin/tazobactam (only for UTI)	• TMP-SMX, Fluoroquinolones, Aminoglycosides, Tetracyclines • Ceftriaxone, Ceftazidime & Piperacillin-tazobactam (used only if the mentioned organisms are recovered in clinical urine cultures in uncomplicated cystitis.)	• Cefepime (for infections with limited source control (e.g., endocarditis, central nervous system infections)

Table 11: CRE

The resistance gene/ enzyme	**CRE**
Definition	• CREs are members of the Enterobacterales resistant to at least one Carbapenem antibiotic or producing a carbapenemase enzyme. [17] • Carbapenemase-producing Enterobacterales (formerly known as Carbapenemase producing Enterobacteriaceae), an emerging resistance of concern (7) • Carbapenamases enzymes, belong to Ambler class A, B or D beta-lactamases. (19) • Carbapenem resistant Enterobacterales: These include the serine b-lactamases Klebsiella pneumoniae carbapenemase (KPC) (Ambler class A), metallo-b-lactamase (MBL) including New Delhi MBL (NDM) or Verona integron-encoded MBL (VIM), imipenemase (IMP) (Ambler class B) and OXA-48-like carbapenemases (Ambler class D). (5), (19) • KPCs hydrolyse penicillins, cephalosporins, monobactams and carbapenems. • KPC, NDM and OXA-48 enzymes are among the carbapenem resistance mechanisms of greatest concern. [5],[19]
Notes	• The drugs of choice for treatment of CRE: Tigecycline, Aminoglycosides and Colistin however, IDSA guidelines don`t suggest Colistin for the treatment of infections caused by CRE but consider it as an alternative agent for uncomplicated CRE cystitis. [1],[17] • Infections caused by Enterobacterales isolates without carbapenemase production that remain susceptible to Meropenem and Imipenem (i.e., MICs ≤1 µg/mL) but are not susceptible to Ertapenem (i.e., MICs ≥1 µg/mL) → the use of extended-infusion Meropenem (or Imipenem - cilastatin) is suggested. [17] • Standard-infusion Meropenem or Imipenem-cilastatin may be reasonable for uncomplicated cystitis. [17] • For isolates susceptible to Meropenem but not susceptible to Imipenem (and vice versa), in the absence of data to inform the optimal treatment approach, the treatment decision will depend on the severity of illness of the patient and site of infection. For example, in this scenario, Meropenem may be a reasonable treatment for a urinary tract infection but not for a complex intra-abdominal infection. [17] • For patients with CRE infections who within the previous 12 months have received medical care in countries with a relatively high prevalence of metallo-β-lactamase-producing organisms or who have previously had a clinical or surveillance culture where a metallo-

<table>
<tr><td></td><td colspan="4">β-lactamase producing isolate was identified, preferred treatment options include the combination of Ceftazidime-avibactam plus Aztreonam. [17]
• Since these organisms are mainly found in the intestine, any environmental surfaces that come into contact with faecal material can become contaminated and serve as a reservoir for cross-infection. In addition, these organisms generally prefer a wet environment, and can quickly colonise sink drains and taps. They have also been known to contaminate diluted disinfectants and detergent solutions used for cleaning. (17)
• The primary mode of cross-transmission is via the unwashed hands of clinical staff. (13) Patients may also spread infection by touching their own urinary catheter or wound drainage tube. (17)</td></tr>
<tr><td rowspan="4"></td><td colspan="4">Carbapenemases/ β-Lactamases [20]</td></tr>
<tr><td colspan="2">Serine- β-Lactamases</td><td colspan="2">Metallo- β-Lactamases</td></tr>
<tr><td colspan="2">Class A: KPC, IMI, SME, CTX-M
Class C: AmpC, ACT, CMY, DHA
Class D: OXA-48</td><td colspan="2">Class B: NDM, VIM, IMP</td></tr>
<tr><td>KPC</td><td>OXA-48</td><td>NDM</td><td>Other Metallo</td></tr>
<tr><td>Definition</td><td></td><td></td><td>New Delhi metallob-lactamase</td><td>Metallo-beta-lactamases (MBL) – similar to ESBL, but can also include resistance to carbapenems, mostly found in Pseudomonas aeruginosa [2]</td></tr>
<tr><td>The active antibiotics against CRE [17]</td><td colspan="2">One of the following
• Ceftazidime-avibactam
• Tigecycline (only for infections not involving the bloodstream or urinary tract)</td><td>• Tigecycline (only for infections not involving the bloodstream or urinary tract)
• Although aztreonam is active against NDMs, it can be hydrolyzed by ESBLs, AmpC β-lactamases, KPCs, or OXA-48-like carbapenemases which are frequently co-produced by NDM-producing isolate.</td><td>• Combination of ceftazidime-avibactam plus aztreonam</td></tr>
</table>

Table 12: Recommended treatment options for Carbapenem-Resistant Enterobacterales (CRE) when Carbapenemase testing result is not available [7],[13],[17],[18],[20],[21]
(Treatment based on clinical syndrome plus risk factors for infection by MDR strains)

Empiric treatment is recommended when there are signs of infections with strong or multiple risk factors for infection by MDR strains producing KPC or OXA-48 as follows: [21]

If there is one of the following:

- Known colonization or prior infection (or roommate infected) by Enterobacteriaceae strain producing KPC or OXA-48
- Local epidemiology (or recent hospitalization in settings) with more than 20-25% prevalence of carbapenem producing and ESBL- producing Enterobacteriaceae.

Plus, any of the following:

- Prior use of carbapenems and/or colistin.
- ICU admission or long admission in hospital wards.
- Severe hospital acquired infection.
- Immunosuppression, multiple comorbidities.

Clinical Syndrome	Recommended Treatment	Alternative Treatment	Notes
Bloodstream Infections (BSI)	• Colistin+ (Tigecycline or Meropenem) N.B., For complicated infections or hemodynamically unstable patients, it is recommended to use Colistin Plus another agent to which organism has demonstrated susceptible MIC (like tigecycline, aminoglycosides) or high dose carbapenems if MIC < 16).[18]		• Monotherapy with ceftazidime/ avibactam should be reserved in non-life-threatening infections. [21] • Colistin as a single agent (for uncomplicated infections like UTI, any other infection for which source reduction has been done and patient is hemodynamically stable). [18] • Aminoglycosides (for uncomplicated infections like UTI, any other infection for which source reduction has been done). [18] • The term **complicated urinary tract infection (cUTI)** refers to UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in an adolescent or adult male.
Uncomplicated Cystitis	• Nitrofurantoin, • Trimethoprim-sulfamethoxazole (TMP-SMX) • Ciprofloxacin, or Levofloxacin (their use for uncomplicated cystitis is discouraged when other safe and effective options are available) [17]	• A single dose of an Aminoglycoside • Oral Fosfomycin (for E. coli only) • Colistin, • Ceftazidime-avibactam	

Complicated Urinary Tract Infections	<u>According to susceptibility</u>: • Levofloxacin [17] • Ciprofloxacin [17] • Ceftazidime/avibactam • Gentamicin or Amikacin		• cUTI is treated with similar agents and for similar treatment durations as pyelonephritis. • For cUTI where the source has been controlled (e.g., removal of a Foley catheter) and ongoing concerns for urinary stasis or indwelling urinary hardware are no longer present, it is reasonable to select antibiotic agents and treatment durations similar to those that would be selected for uncomplicated cystitis. [17] • If an antibiotic not active against the causative organism was administered empirically for uncomplicated cystitis, but clinical improvement occurred, it is generally not necessary to repeat a urine culture, change the antibiotic regimen, or extend the planned treatment course. [17]
Complicated Intraabdominal Infections	• Ceftazidime/avibactam + Metronidazole • Colistin + Tigecycline or Meropenem		• Tigecycline (approved for intra-abdominal infection and skin–soft tissue infection)- DO NOT use for blood stream infection or pneumonia as a monotherapy. [18]

Table 13: Recommended treatment options for Carbapenem-Resistant Enterobacterales (CRE) (7), (13),(16),(17)

If Carbapenemase testing result is *<u>unavailable</u>* (treatment based on Lab report and clinical syndrome)

It is suspected when there is resistance to at least anyone carbapenem (ertapenem, imipenem or meropenem). [18]

Lab reports/Clinical Syndrome	Recommended Treatment	Alternative Treatment

The following types of bacteria have higher risk to harbor **AmpC β-Lactamase:** • Enterobacter cloacae complex • Klebsiella aerogenes. • Citrobacter freundii • S. marcescens, • M. morgannii. • Providencia spp **Uncomplicated AmpC-E cystitis** [17]	• Nitrofurantoin • TMP-SMX	• Aminoglycosides a single IV dose • Ciprofloxacin or Levofloxacin
The following types of bacteria have higher risk to harbor **AmpC β-Lactamase:** • Enterobacter cloacae complex • Klebsiella aerogenes. • Citrobacter freundii • S. marcescens, • M. morgannii. • Providencia spp **Invasive infections** [17]	• Fluoroquinolones • Oral step-down therapy with TMP-SMX or fluoroquinolones have been shown to be reasonable treatment considerations for Enterobacterales bloodstream infections.	
If resistance to aztreonam, ceftriaxone, cefotaxime, cefepime but susceptible to carbapenems, so it is likely to be Extended-Spectrum B-lactamase-producing Enterobacterales (ESBL-E) ESBL producer Causing infections outside the urinary tract [5], [13],[15],[17]	• Meropenem • Imipenem cilastatin • Ertapenem ➢ N.B., it is suggested that the use of Meropenem or Imipenem-cilastatin, rather than Ertapenem, is preferred as initial therapy in critically ill patients with ESBL-E infections. [17] Oral step-down therapy to ciprofloxacin, levofloxacin, or trimethoprim/sulfamethoxazole can be considered after: [5],[15],[17] 1. Susceptibility to the oral agent is demonstrated. 2. Patients are afebrile and haemodynamically stable. 3. Appropriate source control is achieved. 4. There are no issues with intestinal absorption.	• Ceftazidime- avibactam • Ceftolozane-tazobactam

• Uncomplicated cystitis due to extended-spectrum b-lactamase-producing Enterobacterales (ESBL-E) [5],[13] N.B., ESBL-E lab report interpretation was mentioned before.	• Nitrofurantoin • Trimethoprim/ sulfamethoxazole • Piperacillin/tazobactam	• Amoxicillin/clavulanate (if current isolates, or if using empirically, recent isolates, are fully susceptible.) [22] Ciprofloxacin, levofloxacin, and Carbapenems [17]
• Pyelonephritis or Complicated urinary tract infection UTI due to extended-spectrum b-lactamase-producing Enterobacterales (ESBL-E) [5],[13] N.B., ESBL-E lab report interpretation was mentioned before.	• Ciprofloxacin • Levofloxacin • Trimethoprim/sulfamethoxazole	• Ertapenem • Meropenem • Imipenem/Cilastatin • Aminoglycosides for a full treatment course
• If resistance to Aztreonam, Ceftriaxone, Cefotaxime, Cefepime, Meropenem or Imipenem or both but susceptible to Ceftazidime avibactam, so it is likely Carbapenemase-Resistant Enterobacterales (CRE) Klebsiella pneumoniae carbapenemase (KPC) producer [5],[13]	• Ceftazidime- avibactam [13],[18] • Combination of Colistin, Tigecycline, Aminoglycosides. • (Colistin or Aminoglycoside) + (Carbapenem and/or tigecycline) • Consider concomitant administration of inhaled Colistin /Aminoglycoside when they are used intravenously for VAP	
• If resistance to Aztreonam, Ceftriaxone, Cefotaxime, Cefepime, Meropenem or Imipenem or both, Ceftazidime- avibactam, Flouroquinolones, Aminoglycosides and Sulfamethoxazole trimethoprim, it is likely metallo-carbapenemase producer (ie. (NDM), (VIM) or, (IMP)) [5],[13]	• Ceftazidime- avibactam + Aztreonam (The two drugs should be infused concomitantly) N.B., if a patient is infected with a CRE strain with an unknown carbapenemase status and the patient has recently travelled from an area where metallo-b-lactamases are endemic (e.g. Middle East, South Asia, Mediterranean), treatment with ceftazidime/avibactam plus aztreonam is recommended.	• Colistin plus other agent to which organism has demonstrated susceptible MIC (like tigecycline, aminoglycosides) or high dose carbapenems if MIC < 16. [18] • Tigecycline (approved for intra-abdominal infection and skin –soft tissue infection)- DO-NOT use for blood stream infection or pneumonia as a single agent. [18] • Aminoglycosides (for uncomplicated infections like UTI, any other infection for which source reduction has been done). [18]

• Carbapenem-resistant Enterobacterales with: [5],[13]
  • Resistant to Avibactam
  OR
  • Absence of new options
	• Colistin + high dose carbapenem ± Tigecyclin
	• Aminoglycoside + high dose carbapenem ± Tigecyclin.	

Table 14: Recommended treatment options for Carbapenem-Resistant Enterobacterales (CRE) [7],[13],[16],[17]

If Carbapenemase testing result is *available*

Lab reports/Clinical Syndrome	Recommended Treatment	Alternative Treatment
Uncomplicated AmpC-E cystitis [17]	• Nitrofurantoin • TMP-SMX	• Aminoglycosides A single IV dose • Ciprofloxacin or Levofloxacin
AmpC β-Lactamase Invasive infections [17]	• Fluoroquinolones • Oral step-down therapy with TMP-SMX or fluoroquinolones have been shown to be reasonable treatment considerations for Enterobacterales bloodstream infections	
Extended-Spectrum B-lactamase-producing Enterobacterales (ESBL-E) ESBL producer Causing infections outside the urinary tract [5],[13],[15],[17]	• Meropenem • Imipenem cilastatin • Ertapenem ➢ N.B., it is suggested that the use of Meropenem or Imipenem-cilastatin, rather than Ertapenem, is preferred as initial therapy in critically ill patients with ESBL-E infections. [17] Oral step-down therapy to ciprofloxacin, levofloxacin, or trimethoprim/sulfamethoxazole can be considered after: [15],[17] • Susceptibility to the oral agent is demonstrated. • Patients are afebrile and haemodynamically stable.	• Ceftazidime- avibactam • Ceftolozane-tazobactam

	• Appropriate source control is achieved. • There are no issues with intestinal absorption.	
Uncomplicated cystitis due to extended-spectrum b-lactamase-producing Enterobacterales (ESBL-E) (5), (13)	• Nitrofurantoin • Trimethoprim/ sulfamethoxazole • Piperacillin/tazobactam	• Amoxicillin/clavulanate • (if current isolates, or if using empirically, recent isolates, are fully susceptible.) (22) • Ciprofloxacin, levofloxacin, and Carbapenems (17)
Pyelonephritis or Complicated urinary tract infection UTI due to extended-spectrum b-lactamase-producing Enterobacterales (ESBL-E) (5),(13)	• Ciprofloxacin • Levofloxacin • Trimethoprim/ sulfamethoxazole	• Ertapenem. • Meropenem. • Imipenem/Cilastatin. • Aminoglycosides for a full treatment course.
Carbapenemase-Resistant Enterobacterales (CRE) Klebsiella pneumoniae carbapenemase (KPC) producer (5),(13)	• Ceftazidime- avibactam (13),(18) • Combination of Colistin, Tigecycline, Aminoglycosides. • (Colistin or Aminoglycoside) + (Carbapenem and/or tigecycline) • Consider concomitant administration of inhaled Colistin /Aminoglycoside when they are used intravenously for VAP	• Meropenem+Ertapenem (25) use ertapenem infusion prior to a high-dose meropenem infusion as a salvage therapy for critically ill patients with CRE infections. • Meropenem+ Ertapenem+ (Colistin/Tigecycline) (25) It might be a reasonable strategy for severe CRE infections.
Metallo-carbapenemase producer (ie. (NDM), (VIM) or, (IMP)) (5),(13)	• Ceftazidime- avibactam + Aztreonam (The two drugs should be infused concomitantly) N.B., if a patient is infected with a CRE strain with an unknown carbapenemase status and the patient has recently travelled from an area where metallo-b-lactamases are endemic (e.g. Middle East, South Asia, Mediterranean), treatment with ceftazidime/avibactam plus aztreonam is recommended.	• Colistin Plus other agent to which organism has demonstrated susceptible MIC (like tigecycline, aminoglycosides) or high dose carbapenems if MIC < 16. (18) • Tigecycline (approved for intra-abdominal infection and skin –soft tissue infection)- DO-NOT use for blood stream infection or pneumonia as a single agent. (18) • Aminoglycosides (for uncomplicated infections

		like UTI, any other infection for which source reduction has been done). (18) • Meropenem+ Ertapenem (26) N.B., the synergistic activity of meropenem plus ertapenem combination suggests this combination can be a possible way to treat the infection caused by the carbapenem-resistant organisms, especially for IMP or NDM producer with a lesser minimum inhibitory concentration (MIC) and the infected individual who was not recommended to use colistin or tigecycline.

Pseudomonas aeruginosa	
Table 15: Recommended treatment options for infections due to Pseudomonas aeruginosa (PA) and Difficult-to-Treat P.aeruginosa (DTR-PA).	
Definitions	• *Pseudomonas aeruginosa* is a key gram-negative aerobic bacillus in the differential diagnosis of several infections. This organism is important because it is often antibiotic resistant and can cause severe hospital-acquired infections associated with a high mortality rate, especially in immunocompromised hosts. [23] *P. aeruginosa* is intrinsically resistant to numerous antibiotics and can acquire resistance to other agents during therapy. Some strains are multidrug resistant (i.e, they are resistant to three or more classes of antibiotics). [23] • MDR- P. aeruginosa is defined as P. aeruginosa not susceptible to at least one antibiotic in at least three antibiotic classes for which P. aeruginosa susceptibility is generally expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems. [17] • In 2018, the concept of "difficult-to-treat" resistance was proposed which is defined as P. aeruginosa exhibiting non-susceptibility to all the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin. [17] • Carbapenem resistant PA (CRPA): Resistance to at least anyone carbapenem (meropenem or imipenem). [18]
Clinical Syndrome	**Recommended Treatment**
Any clinical syndrome due Pseudomonas aeruginosa [17]	• When P. aeruginosa isolates test susceptible to both no carbapenem β-lactam agents (i.e., piperacillin tazobactam, ceftazidime, cefepime, aztreonam) and carbapenems, the no carbapenem β-lactam agents are preferred over carbapenem therapy. [17] • If the isolate remains susceptible to a traditional non-carbapenem β-lactam (e.g., cefepime) on repeat testing, it is recommended to administer the non-carbapenem agent as high-dose extended infusion therapy (e.g., cefepime 2 g IV every 8 hours, infused over at least 3 hours) [17]
Any clinical syndrome due to CRPA susceptible to other antimicrobial agents [7], [13], [17], [20], [22]	Use one of the following antibiotics: • Piperacillin/tazobactam • Ceftazidime • Cefepime • Ciprofloxacin • Levofloxacin • Amikacin (only if urinary tract infection) • When P. aeruginosa isolates not susceptible to any carbapenem agent but susceptible to traditional βlactams, the administration of a traditional agent as high-dose extended-infusion therapy is suggested, and repeat AST is encouraged. [17] • For critically ill patients or those with poor source control with P. aeruginosa isolates resistant to carbapenems but susceptible to traditional βlactams, use of a novel β-lactam agent that tests susceptible (e.g., ceftolozane-tazobactam & ceftazidime-avibactam) is a reasonable treatment approach.

	• Combination of two agents from different classes with in vitro activity against P. aeruginosa for empiric treatment of serious infections known or suspected to be caused by P. aeruginosa in the following conditions: (22), (23) 1. When signs of severe sepsis or septic shock are present 2. Neutropenic patients with bacteremia 3. Burn patients (who have a high incidence of multidrug-resistant P. aeruginosa infections) with serious infections. 4. In other settings where the incidence of resistance to the chosen antibiotic class is high (e.g., >10 to 15 %) For patients with severe infections caused by CRPA susceptible in vitro only to Colistin or aminoglycosides a combination therapy is suggested. Colistin plus other agent to which organism has demonstrated susceptible MIC or in intermediate range or SDD (susceptible dose dependent) can be used. (18)
Any clinical syndrome due to DTR-PA (5), (13), (15),(16), (17),(22)	• Ceftolozane/tazobactam (preferred empirical choice in absence of concomitant risk of CRE) • Ceftazidime/avibactam • Colistin + (Imipenem/cilastatin OR Meropenem) • Combination of Colistin, Tigecycline, Aminoglycosides. (16) • (Colistin or Aminoglycoside) + (Carbapenem and/or tigecycline) (16) • If resistant to Ceftazidime/avibactam: o Ceftazidime/ avibactam + Aztreonam (5) o Colistin + (Imipenem/cilastatin OR Meropenem) o Aminoglycosides + carbapenems • Consider concomitant administration of inhaled Colistin /Aminoglycoside when they are used intravenously for VAP (7), however IDSA guidelines does not suggest the use of nebulized antibiotics for the treatment of respiratory infections caused by DTR-P. aeruginosa. (17) • Combination antibiotic therapy is not suggested if susceptibility to ceftolozane-tazobactam, ceftazidime-avibactam, has been confirmed (17) N.B. oral Fosfomycin for DTR-P. aeruginosa cystitis is not recommended as it is associated with a high likelihood of clinical failure (17)

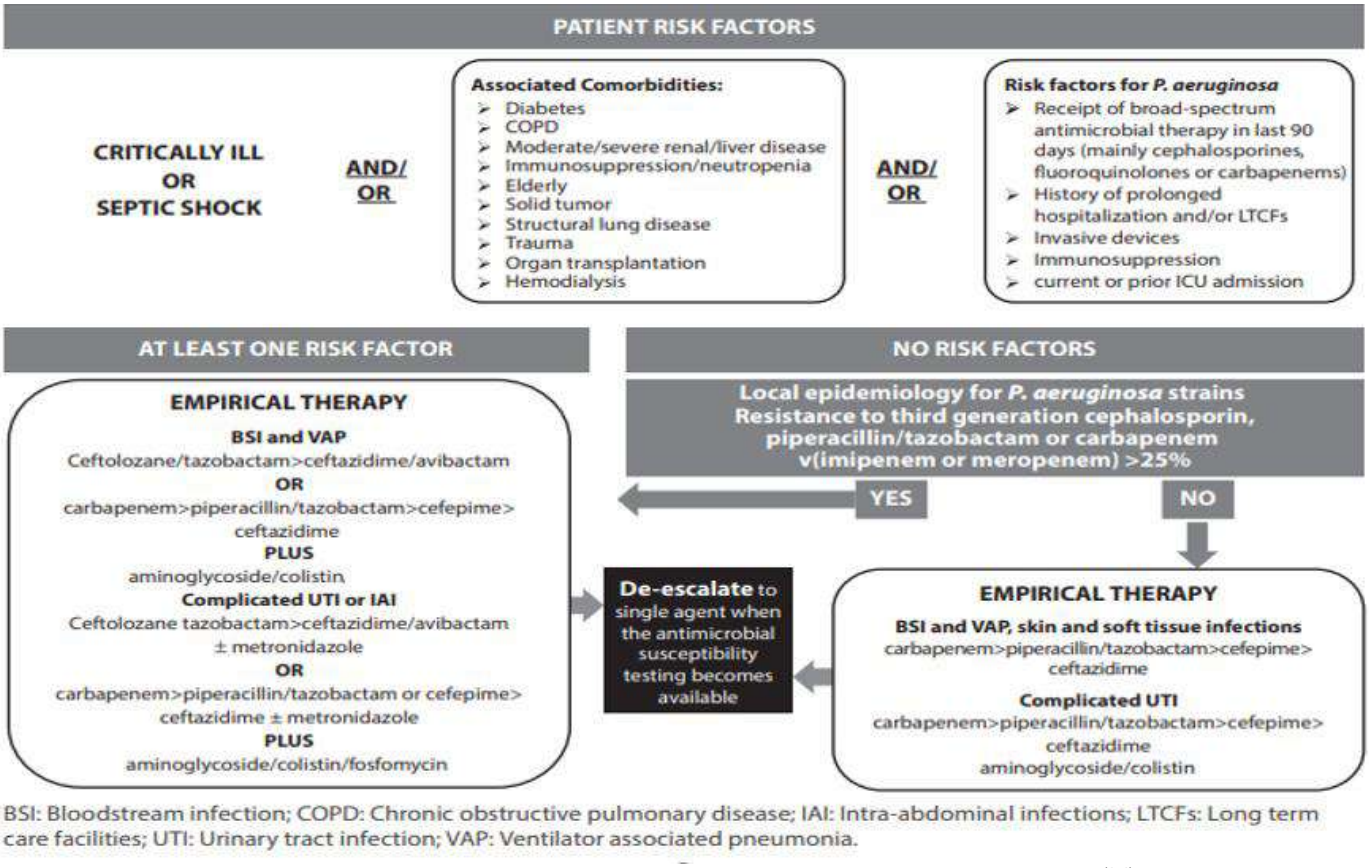

Figure 1: Clinical approach to patients with suspected P. aeruginosa infection [24]

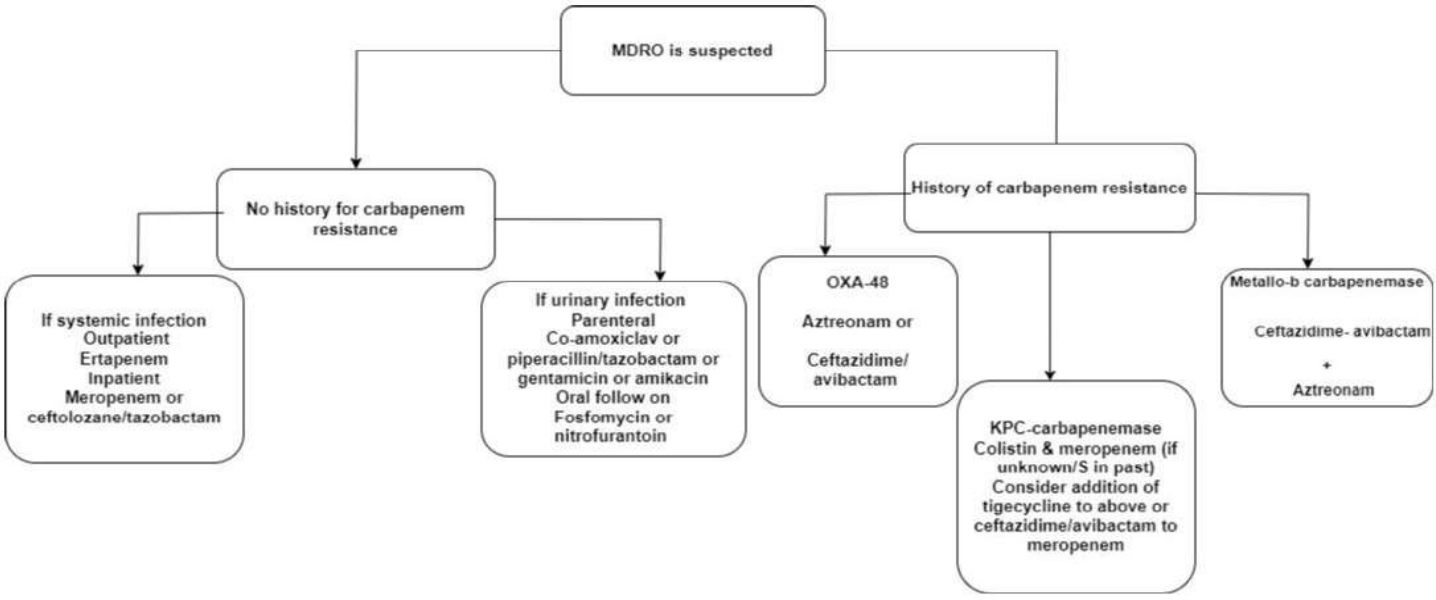

Figure 2: Suggested algorithm for the treatment of MDR Gram-negative bacterial infections admitted to hospitals. [22]

Stenotrophomonas maltophilia

Table 16: Recommended treatment options for infections due to Stenotrophomonas maltophilia [13], [17]

- Stenotrophomonas maltophilia is an aerobic, glucose non-fermenting, gram-negative bacillus that is ubiquitous in water environments.
- The organism has a long history of changing nomenclatures and a complicated phylogeny.
- Although generally believed to be less pathogenic than many other nosocomial organisms, S. maltophilia produces biofilm and virulence factors that can enable colonization or infection in vulnerable hosts, such as those with underlying lung disease and hematological malignancies.
- S. maltophilia is often recovered as a component of a polymicrobial infection further challenging the need for targeted S. maltophilia therapy.
- It is not recommended to use Polymyxins for the treatment of S. maltophilia infections.

Clinical Syndrome	Recommended Treatment	Notes
Any clinical syndrome cause by S. maltophilia	• Two of the following agents: TMP-SMX (The preferred agent), Tigecycline, or Levofloxacin. N.B., A general concern with tetracycline derivatives is that they achieve rapid tissue distribution following administration, resulting in limited concentrations in the urine and poor serum concentrations. • When significant clinical instability is evident or intolerance to or inactivity of other agents: Ceftazidime-avibactam + Aztreonam, • For mild and polymicrobial infection where the role of S. maltophilia is unclear, use monotherapy of monotherapy of TMP-SMX, Levofloxacin, Tigecycline. [13]	Tigecycline: FDA cites higher risk of death among patients given tigecycline compared to other antibacterials and recommends use only in situations where alternative therapy is not suitable. [13]

Multi-resistant Gram-positive cocci

Vancomycin-resistant Enterococci (VRE)

Table 17: Recommended treatment options for Vancomycin-resistant Enterococci (VRE). [7]

Clinical Syndrome	Recommended Treatment
Pneumonia	Linezolid
Bloodstream infections	Linezolid OR (Daptomycin +/- Carbapenem)
Complicated intraabdominal infections	Linezolid OR Tigecycline
Complicated urinary tract infections	Linezolid OR Daptomycin

Suggested dosing of antibiotics for the treatment of infections caused by antimicrobial resistant organism

Table18: Suggested dosing of antibiotics for the treatment of infections caused by antimicrobial resistant organism [13], [17],[18],[20])

Agent	Adult dose (Assuming normal renal and liver function)	Target Organism
Amikacin	**Uncomplicated cystitis:** 15 mg/kg IV as a single dose Any clinical syndrome due to CRPA susceptible to other antimicrobial agents: 15mg/kg **All other infections:** 20 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation. **N.B.,** Use adjusted body weight for patients .120% of ideal body weight for aminoglycoside dosing.	ESBL-E, AmpC-E, CRE, DTR-P. aeruginosa
Ampicillin/sulbactam	Total daily dose of 6-9 grams of sulbactam N.B., (high dose of ampicillin/ sulbactam used but no agreed consensus on the right dose) **Potential infusion strategies include the following:** - 9 grams of ampicillin-sulbactam (6 grams' ampicillin, 3 grams sulbactam) IV every 8 hours, infused over 4 hours - 27 grams of ampicillin-sulbactam (18 grams' ampicillin, 9 grams sulbactam) IV as a continuous infusion **For mild infections** caused by CRAB isolates susceptible to ampicillin-sulbactam, particularly if intolerance or toxicities preclude the use of higher dosages. - 3 grams of ampicillin-sulbactam (2 grams ampicillin, 1-gram sulbactam) IV every 4 hours, infused over 30 minutes	CRAB
Aztreonam	2g IV over 3 h /6h	DTR-PA
Cefepime	**Uncomplicated cystitis**: 1gram IV every 8 hours, infused over 30 minutes **All other infections**: 2 grams IV every 8 hours, infused over 3 hours (if possible)	AmpC-E, CRPA
Ceftazidime	Any clinical syndrome due to CRPA susceptible to other antimicrobial agents: 2 g IV q8h	CRPA
Ceftazidime/avibactam	2.5 grams IV every 8 hours, infused over 3 hours	CRE, DTR-P. aeruginosa
Ceftazidime/avibactam PLUS Aztreonam	**Ceftazidime-avibactam:** 2.5 grams IV every 8 hours, infused over 3 hours.	Metallo-β-lactamase-producing CRE, S. maltophilia

	PLUS **Aztreonam:** 2 grams IV every 6-8 hours (every 6-hour dosing preferred if possible), infused over 3 hours. Administered at the same time as ceftazidime-avibactam	
Ceftolozane/tazobactam	**Cystitis:** 1.5 grams IV every 8 hours, infused over 1 hour **All other infections:** 3 grams IV every 8 hours, infused over 3 hours	DTR-P. aeruginosa ESBL-E (outside theUTI)
Ciprofloxacin	**Cystitis:** 400 mg IV every 12 hours or 500 mg PO every 12 hours **All other infections:** 400 mg IV every 8 hours OR 750 mg PO every 12 hours	ESBL-E, AmpC-E, CRPA
Colistin (14)	Colistin IV 2.5 mg Colistin Base Activity (CBA)/kg IV loading dose, then 1.5 mg CBA over 1 hour IV /12 h	CRE, DTR-P. aeruginosa, CRAB
Colistin inhalation (14)	Colistin inhalation 75 to 150 mg CBA twice daily.	
Daptomycin	IV 8-12mg/kg/day	VRE
Ertapenem	1 gram IV every 24 hours, infused over 30 minutes	ESBL-E, AmpC-E
		CRE
Fosfomycin	**Uncomplicated cystitis:** 3 grams PO as a single dose	ESBL-E. coli cystitis
Gentamicin	**Uncomplicated cystitis:** 5 mg/kg/dose IV as a single dose **All other infections:** 7 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation. **N.B.,** Use adjusted body weight for patients (120% of ideal body weight for aminoglycoside dosing).	ESBL-E, AmpC-E, CRE, DTR-P.aeruginosa
Imipenem-cilastatin	**Uncomplicated cystitis (standard infusion):** 500 mg IV every 6 hours, infused over 30 minutes. All other ESBL-E or AmpC-E infections: 500 mg IV every 6 hours, infused over 30 minutes. All other CRE and CRAB infections: 500 mg IV every 6 hours, infused over 3 hours	ESBL-E, AmpC-E, CRE, CRAB, DTR-PA
Levofloxacin	750 mg IV/PO every 24 hours.	ESBL-E, AmpC-E, S. maltophilia, CRPA

Linezolid	600 mg IV every 12 hours.	VRE
Metronidazole	Complicated intraabdominal infections: 500 mg / 6h	
Meropenem	**Uncomplicated cystitis (standard infusion):** 1 grams IV every 8 hours, infused over 30 minutes. All other ESBL-E or AmpC-E infections: 1–2 g IV q8h, infused over 30 minutes. All other CRE and CRAB infections: 2 g IV every 8 hours, infused over 3 hours	ESBL-E, AmpC-E, CRE, CRAB, DTR-PA
Nitrofurantoin	**Macrocrystal/monohydrate:** 100 mg PO every 12 hours.	ESBL-E cystitis, AmpC-E cystitis
Piperacillin-tazobactam	Any clinical syndrome due to CRPA susceptible to other antimicrobial agents: 4.5 g IV loading over 30 minutes then, 4 hrs later, start 4.5gmIV over 4 hours and then repeat every 8 hours over 4 hours.	
Tigecycline	200 mg IV as a single dose, then 100 mg IV every 12 hours	CRE, CRAB, S. maltophilia
Trimethoprim - sulfamethoxazole	**Cystitis:** 160 mg (trimethoprim component) PO q12h**Other infections:** 8–12 mg/kg/day (trimethoprim component) PO divided every 8–12 hours (consider maximum dose of 960 mg trimethoprim component per day).	ESBL-E, AmpC-E, S. maltophilia

Duration of therapy for common clinical syndromes

Table 19: Duration of therapy for common clinical syndromes

Clinical syndrome	Duration of therapy [7],[18]
Ventilator associated pneumonia or hospital acquired pneumonia	7- 10 days
Complicated urinary tract infections	10 days
Catheter associated UTI	5-7 days Removal of catheter is strongly recommended if infection with an MDR organism is confirmed
Intra-abdominal infections	5- 7 days
Central line associated blood stream Infections	10-14 days Removal of central line is strongly recommended if infection with an MDR organism is confirmed
BSI due to CRE	7-14 days [7]
Complicated Intraabdominal Infections	5- 7 days [7]
Any clinical syndrome due to CRPA susceptible to other antimicrobial agents	• 5-14 days [7] • 5-10 days for complicated urinary tract infection and complicated intra-abdominal infection. [7] • A treatment course of 10-14 days is suggested for hospital-acquired or ventilator-associated pneumonia and bloodstream infection. [7]

Any clinical syndrome due to DTR-PA	• 10-14 days [7]

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