Chapter 100
Approach to Gram-Negative Multidrug-Resistant Organisms (MDROs) in the ICU

100.1 Introduction

Gram-negative multidrug-resistant organisms (MDROs) pose a significant challenge in intensive care units (ICUs) due to their capacity to resist multiple classes of antibiotics. Organisms such as extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E), carbapenem-resistant *Enterobacterales* (CRE), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are associated with increased morbidity, mortality, and healthcare costs. The emergence of extensively drug-resistant (XDR) pathogens necessitates a comprehensive approach that includes updated susceptibility testing, optimized antimicrobial therapy, and preventive strategies. Prompt identification and individualized management are critical to improving patient outcomes [1, 2] [Ref: Algorithm 100.1].

Step 1: Confirm Diagnosis

1. Objective: Suspect MDRO infections based on clinical, epidemiological, and laboratory factors.

    - Clinical Clues: Previous healthcare exposure, recurrent infections, invasive devices, or inadequate response to conventional antibiotics.
    - Diagnostic Tools:
    - Cultures: Obtain specimens from blood, urine, respiratory secretions, or wound swabs based on the suspected source.
    - Rapid Diagnostic Testing: Utilize PCR-based assays or matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry for early identification.
    - Susceptibility Testing: Refer to the latest Infectious Diseases Society of America (IDSA) guidelines and joint Clinical and Laboratory Standards Institute (CLSI)/European Committee on Antimicrobial Susceptibility

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Testing (EUCAST) recommendations for specific testing methods and breakpoints, especially for agents like colistin and polymyxin B.
- Early and accurate pathogen identification directs targeted therapy, improves outcomes, and reduces unnecessary broad-spectrum antibiotic use.

Step 2: Determine Infection Type

1. Key Considerations:

- Site of Infection: Identify whether the infection involves the urinary tract, bloodstream, respiratory tract, central nervous system (CNS), or is of polymicrobial origin.
- Severity Assessment: Distinguish between complicated infections (e.g., complicated urinary tract infections [cUTIs] with obstruction, bacteremia, or ventilator-associated pneumonia) and uncomplicated cases.
- The type and location of infection influence the choice of empiric antibiotics, the need for adjunctive therapies like inhalation or intrathecal administration, and the urgency of interventions (e.g., source control).

Step 3: Initiate Empiric Therapy (Ref: Tables 100.1 and 100.2)

1. Factors Influencing Empiric Therapy:

- Severity of Illness: Critically ill patients require broader coverage until pathogen susceptibility is known.
- Local Resistance Patterns: Utilize local antibiograms and molecular epidemiology data to guide empiric therapy decisions, acknowledging regional variations in MDRO prevalence.
- Recent Antibiotic Exposure: Adjust empiric coverage based on prior treatments to minimize resistance selection.
- Patient-Specific Factors: Consider immune status, comorbidities, organ function, and pharmacokinetics/pharmacodynamics when selecting agents.

Step 4: Evaluate Pathogen and Susceptibility

1. Interpretation of Susceptibility Results:

- Updated Guidelines: Follow the latest IDSA and CLSI/EUCAST recommendations for susceptibility testing and breakpoint interpretations.
- If ESBL-E: Carbapenems (e.g., meropenem) are preferred. Alternatives may include ertapenem, trimethoprim-sulfamethoxazole (TMP-SMX), or fluoroquinolones if susceptible. (Refer Table 100.1).
- If CRE: Utilize novel beta-lactam/beta-lactamase inhibitor combinations like ceftazidime-avibactam or meropenem-vaborbactam. Cefiderocol may be considered based on susceptibility. (Refer Table 100.1).
- If difficult-to-treat *Pseudomonas aeruginosa*: Consider ceftolozane-tazobactam, cefiderocol, or imipenem-relebactam.
- If carbapenem-resistant *Acinetobacter baumannii* (CRAB): High-dose sulbactam-durlobactam is preferred. Polymyxins (colistin or polymyxin B) may be used as alternatives.
- If *Stenotrophomonas maltophilia*: TMP-SMX is the drug of choice; levofloxacin is an alternative.

Table 100.1 GNB organism and the preferred treatment

S. no.	Organism	Condition/scenario	Treatment
1a.	ESBL-E	Uncomplicated cystitis	**Preferred**—TMP-SMX **Alternative**—ciprofloxacin, levofloxacin, carbapenems, aminoglycoside (single dose), and oral fosfomycin (*E. coli* only)
b.		Pyelonephritis or complicated UTI	**Preferred**—TMP-SMX, ciprofloxacin, or levofloxacin **Alternative**—ertapenem, meropenem, and imipenem-cilastatin, and aminoglycosides
c.		Outside urinary tract	**Preferred**—meropenem, imipenem-cilastatin, or ertapenem **Transition**—oral TMP-SMX, ciprofloxacin, or levofloxacin if susceptible and good clinical response
2 a.	*Enterobacterales* with AmpC, e.g., *E. cloacae* complex, *K. aerogenes*, and *C. freundii*	Uncomplicated cystitis	**Preferred**—nitrofurantoin and TMP-SMX **Alternative**—ciprofloxacin, levofloxacin, or an aminoglycoside (as a single dose)
b.		Pyelonephritis or complicated UTI	**Preferred**—TMP-SMX, ciprofloxacin, or levofloxacin **Alternative**—aminoglycosides
c.		Outside urinary tract	**Preferred**—cefepime **Transition**—oral TMP-SMX, ciprofloxacin, or levofloxacin
3 a.	Carbapenem resistant *Enterobacterales* (CRE)	Uncomplicated cystitis	**Preferred**—nitrofurantoin, TMP-SMX, ciprofloxacin, or levofloxacin **Alternative**—aminoglycoside (as a single dose), oral fosfomycin (for *E. coli* only), colistin, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, cefiderocol, or colistin
b.		Pyelonephritis or complicated UTI	**Preferred—**TMP-SMX, ciprofloxacin, or levofloxacin if susceptible. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol **Alternative**—aminoglycosides

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Table 100.1 (continued)

S. no.	Organism	Condition/scenario	Treatment
c.		Outside urinary tract not producing carbapenemase (susceptible to meropenem and imipenem (i.e., MICs ≤1 μg/mL), but are not susceptible to ertapenem (i.e., MICs ≥1 μg/mL))	**Preferred**—extended-infusion meropenem (or imipenem-cilastatin)
d.		Outside urinary tract **not producing carbapenemase** with resistance to all carbapenems	**Preferred—**ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam
e.		Outside urinary tract with **KPC** production	**Preferred**—meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatin- relebactam **Alternative—**cefiderocol
f.		Outside urinary tract with **NDM** or other **MBL** production	**Preferred**—ceftazidime-avibactam in combination with aztreonam or cefiderocol
g.		Outside urinary tract with **OXA-48** like production	**Preferred**—Ceftazidime-avibactam **Alternative—**cefiderocol
4 a.	*Pseudomonas aeruginosa* difficult-to-treat resistance (DTR)	Susceptible to both traditional non-carbapenem β-lactam agents and carbapenems	**Preferred**—piperacillin-tazobactam, ceftazidime, cefepime, and aztreonam
		Not susceptible to any carbapenem agent but susceptible to traditional β-lactams	**Preferred**—piperacillin-tazobactam, ceftazidime, cefepime, and aztreonam—*high-dose extended-infusion therapy*
b.		Poor source control with *P. aeruginosa* isolates resistant to carbapenems but susceptible to traditional β-lactams	**Preferred—**ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam
c.		Uncomplicated cystitis	**Preferred—**ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol **Alternative**—tobramycin or amikacin (as a single dose

(continued)

Table 100.1 (continued)

S. no.	Organism	Condition/scenario	Treatment
d.		Pyelonephritis or cUTI	**Preferred—**ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol **Alternative**—tobramycin or amikacin once daily
e.		Outside of the urinary tract	**Preferred—**ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam **Alternative—**cefiderocol
f.		Produce **MBL** enzymes	**Preferred—**cefiderocol
5.	*Acinetobacter baumannii*	Carbapenem resistant	**Preferred—**sulbactam-durlobactam in combination with a carbapenem (i.e., imipenem-cilastatin or meropenem) **Alternative—**high-dose ampicillin-sulbactam (9 gm sulbactam) + 1 of polymyxin B, minocycline > tigecycline, or cefiderocol Polymyxin B + another agent High-dose Minocycline or Tigecycline + another agent Cefiderocol—refractory cases only
6.	*Stenotrophomonas maltophilia*		**Preferred** (a) Two of the following agents: cefiderocol, minocycline, TMP-SMX, or levofloxacin. oor (b) Ceftazidime-avibactam and aztreonam **Alternative—**cefiderocol as a component of combination therapy

Note:
TMP-SMX—trimethoprim-sulfamethoxazole
Tigecycline and eravacycline are alternative options when β-lactam agents are either not active or unable to be tolerated for the treatment of CRE urinary tract infections or bloodstream infections.
Ceftazidime-avibactam and aztreonam have to be given simultaneously using a three-way cannula
Refer Appendix 1 for dosing of each drug
MBL—metallo-beta-lactamase
NDM—New Delhi metallo-beta-lactamase
KPC—*Klebsiella pneumoniae* carbapenemase
OXA—oxacillinase
UTI—urinary tract infection

Table 100.2 Antibiotics and their dose

S. No.	Drug/antibiotic	Dose
1	TMP-SMX—trimethoprim-sulfamethoxazole	10–15 mg of trimethoprim/kg/day—in 2 or 3 divided doses (160 mg for uncomplicated cystitis on 2 divided dose)
2	Ciprofloxacin	IV—400 mg 3 times daily PO—750 mg twice daily In uncomplicated cystitis IV 400 mg twice daily or PO 500 mg twice daily
3	Levofloxacin	750 mg once daily
4	Amikacin (aminoglycoside)	15 mg/kg
5	Tobramycin (aminoglycoside)	7 mg/kg 5 mg/kg (uncomplicated cystitis)
6	Ertapenem	1 gm once daily over 30 min
7	Imipenem cilastatin	500 mg 4 times daily over 3 h infusion Over half an hour in uncomplicated cystitis
8	Meropenem	2 gm 3 times daily over 3 h infusion 1 gm 3 times daily over half hour in uncomplicated cystitis
9	Imipenem-cilastatin-relebactam	1.25 gm 4 times daily over 30 min
10	Meropenem vaborbactam	4 gm thrice daily over 3 h infusion
11	Ceftazidime avibactam	2.5 gm 3 times daily over 3 h infusion
12	Aztreonam	2 gm 3 times daily over 3 h infusion
13	Nitrofurantoin	100 mg twice daily
14	Cefepime	2 gm 3 times daily over 3 h infusion 1 gm in uncomplicated cystitis
15	Cefiderocol	2 gm 3 times daily over 3 h infusion
16	Fosfomycin	3 gm PO single dose for uncomplicated cystitis
17	Polymyxin B	See text
18	Colistin	See text
19	Ceftolozane tazobactam	3 gm 3 times daily over 3 h infusion 1.5 gm over 1 h in uncomplicated cystitis
20	Eravacycline	1 mg/kg per dose twice daily
21	Tigecycline	200 mg loading dose then 100 mg twice daily
22	Minocycline	200 mg twice daily
23	Ampicillin sulbactam	9 gm of sulbactam daily: 6 gm ampicillin +3 gm sulbactam 3 times daily over 4 h infusion or 27 gm ampicillin + sulbactam over 24 h infusion
24	Sulbactam durlobactam	1 gm each 4 times daily over 3 h infusion

2. Polymyxin Use and Dosing Guidelines:

- Optimal Use: Reserve polymyxins for infections caused by XDR organisms when no safer, effective alternatives are available.
- Dosing regimens:
- Colistin (Polymyxin E):
- Loading Dose: A loading dose is essential due to colistin's pharmacokinetics and to rapidly achieve therapeutic plasma concentrations. The recommended loading dose is nine million international units (MIU), which is approximately 300 mg of colistin base activity (CBA), administered intravenously over 30–60 min.
- Maintenance Dose: The maintenance dosing depends on the patient's renal function. For patients with normal renal function (creatinine clearance [CrCl] $\geq$ 80 mL/min), the recommended maintenance dose is 4.5 MIU (150 mg CBA) every 12 h.
- Renal Dosing Adjustments: Adjust maintenance doses for patients with impaired renal function:
- CrCl 50–79 mL/min: 3 MIU (100 mg CBA) every 12 h.
- CrCl 30–49 mL/min: 2.25 MIU (75 mg CBA) every 12 h.
- CrCl 10–29 mL/min: 2.25 MIU (75 mg CBA) every 24 h.
- CrCl<10 mL/min or on intermittent hemodialysis: 1.5 MIU (50 mg CBA) every 24 h, administered after dialysis, on dialysis days.
- Continuous Renal Replacement Therapy (CRRT): May require dosing similar to patients with normal renal function; consult a specialist.
- Critically Ill Patients: Due to altered pharmacokinetics in critically ill patients, they may require higher maintenance doses or more frequent dosing. Therapeutic drug monitoring (TDM) is recommended to adjust dosing based on plasma concentrations.
- Polymyxin B:
- Loading Dose: A loading dose is recommended to achieve effective plasma levels quickly. The suggested loading dose is 2.0–2.5 mg/kg (based on total body weight), administered intravenously over 1 h.
- Maintenance Dose: The maintenance dose is 1.25–1.5 mg/kg every 12 h (based on total body weight).
- Renal Dosing Adjustments: Polymyxin B is less affected by renal function because it is not significantly eliminated by the kidneys. Therefore, no dosage adjustment is generally necessary for patients with renal impairment, including those on dialysis.
- Critically Ill Patients: Similar to colistin, critically ill patients may have altered drug clearance. TDM is advisable to ensure therapeutic levels without reaching toxicity.

Key Considerations

- Therapeutic Drug Monitoring (TDM):
- Purpose: TDM helps in optimizing dosing by measuring plasma drug concentrations, ensuring efficacy while minimizing toxicity.
- Recommendations: Regularly monitor colistin plasma levels, especially in critically ill patients or those with fluctuating renal function.
- Target Concentrations: Aim for a steady-state plasma concentration of colistin (as the active formed colistin base) between 2 and 4 mg/L for efficacy, while keeping below levels associated with increased toxicity.
- Toxicity Management:
- Nephrotoxicity:
- Risk Factors: High doses, prolonged therapy, concomitant use of other nephrotoxic agents (e.g., aminoglycosides, vancomycin), and preexisting renal impairment.
- Monitoring: Check serum creatinine and urine output at baseline and at least every 2–3 days during therapy.
- Management: If nephrotoxicity develops, consider dose adjustment, increased monitoring, or alternative therapies if possible.
- Neurotoxicity:
- Symptoms: Paresthesias, dizziness, ataxia, visual disturbances, and, rarely, neuromuscular blockade leading to respiratory failure.
- Monitoring: Assess for neurological symptoms regularly, especially in patients with risk factors such as high doses or concomitant neuromuscular blockers.
- Management: Discontinue or adjust dosing if significant neurotoxicity occurs.
- Administration tips:
- Infusion Rates: Administer colistin over 30–60 min and polymyxin B over 1 h to reduce the risk of infusion-related reactions.
- Compatibility: Ensure compatibility with other intravenous medications to prevent precipitation or inactivation.
- Preparation: Reconstitute according to manufacturer instructions, and use prepared solutions promptly to maintain stability.
- Pharmacokinetics and Pharmacodynamics:
- Colistin: It is administered as colistin methanesulfonate (CMS), an inactive prodrug converted to active colistin in the body. The conversion is slow and variable, necessitating a loading dose and careful maintenance dosing.
- Polymyxin B: Administered in its active form, leading to more predictable plasma concentrations and not requiring adjustment in renal impairment.
- Achieving adequate plasma concentrations is crucial for bactericidal activity against MDROs.
- Suboptimal dosing can promote the development of resistance.

Step 5: Consider Adjunctive Therapies

1. Combination Therapy Strategies:

   - Rationale for Combination Therapy: Combining polymyxins with other agents (e.g., rifampin, carbapenems, or tigecycline) may enhance efficacy against XDR pathogens like *Pseudomonas aeruginosa* and *Acinetobacter baumannii* and minimize resistance development.
   - Select combinations based on in vitro synergy studies and clinical evidence.

   Combination antibiotic therapy (i.e., the use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, tetracycline, or polymyxin) is not suggested for the treatment of infections caused by CRE. Combination antibiotic therapy is not suggested for infections caused by DTR *P. aeruginosa* if susceptibility to ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin- relebactam, or cefiderocol has been confirmed.
2. Alternative Delivery Methods:

   - Inhalation Therapy: Consider aerosolized antibiotics (e.g., colistin) for respiratory infections to achieve high local concentrations while reducing systemic toxicity.
   - Intrathecal or Intraventricular Therapy: Utilize for CNS infections caused by MDROs when systemic therapy is inadequate.

3. Source Control:

   - Interventions: Drain abscesses, remove or replace infected devices, and debride infected tissues promptly.

4. Rationale: Adjunctive therapies address the infection comprehensively, enhancing antimicrobial effectiveness and improving patient outcomes.

Step 6: Transition to Oral Therapy

1. Criteria for Transition:

   - Clinical Stability: Improvement in hemodynamics and resolution of systemic signs of infection.
   - Effective Oral Options: Ensure availability of effective oral agents based on susceptibility, such as Fluoroquinolones or TMP-SMX.
   - Gastrointestinal Function: Confirm adequate absorption capability.
   - Patient Factors: Consider comorbidities and potential drug interactions.

2. Transitioning to oral therapy reduces the risks associated with prolonged intravenous access, lowers healthcare costs, and facilitates earlier discharge when appropriate.

Step 7: Duration of Therapy

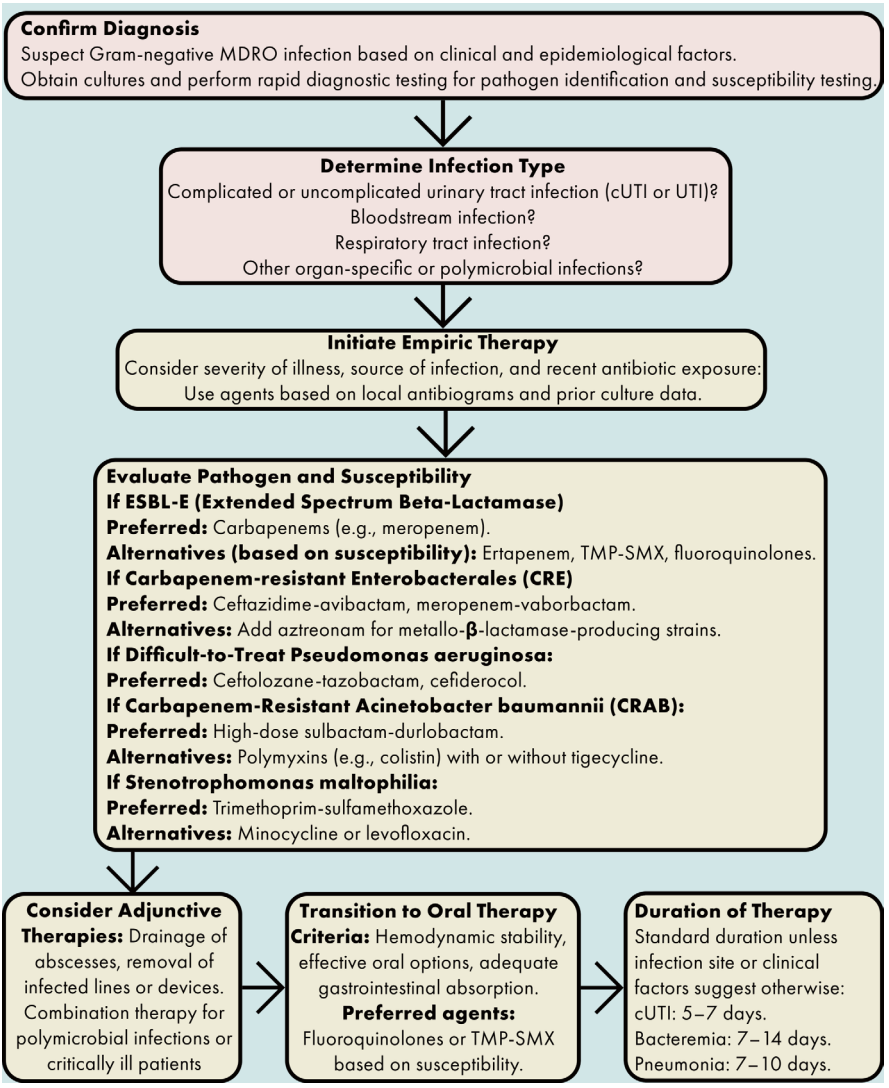
1. Tailored duration based on infection type and patient response:

- cUTI: Typically 5–7 days.
- Bacteremia: Usually 7–14 days, depending on the source and patient factors.
- Pneumonia: Generally 7–10 days.
- MDRO Considerations: Evidence suggests that MDRO-associated infections may not always require extended durations compared to nonresistant infections.
- TDM and Monitoring: Use TDM and clinical markers to guide therapy duration.

100.2 Conclusion

Managing Gram-negative MDROs in the ICU requires a multidisciplinary and patient-centered approach. Utilizing updated susceptibility testing methods and adhering to the latest guidelines ensures accurate pathogen identification and effective therapy selection. Empiric therapy should be guided by local resistance patterns, patient-specific factors, and a thorough understanding of pharmacokinetics and pharmacodynamics. Adjunctive strategies, including combination therapies and alternative delivery methods, play a crucial role in treating XDR pathogens. Therapeutic drug monitoring, especially for nephrotoxic agents like polymyxins, optimizes therapeutic outcomes while mitigating toxicity. Preventive strategies are equally important. Infection prevention measures such as antimicrobial stewardship programs, strict hand hygiene, and decolonization protocols help curb the transmission and emergence of MDROs. By emphasizing individualized therapy adjustments, source control, and judicious use of antibiotics, healthcare professionals can optimize patient outcomes while combating the growing threat of antimicrobial resistance in the ICU setting.

Algorithm 100.1: Approach to gram-negative multidrug-resistant organisms (MDROs) in the ICU



Bibliography

1. Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, 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. 2019;39(1):10–39.
2. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. Clin Infect Dis. 2024;