Guidance for Empiric Treatment of Multidrug-Resistant Gram-Negative Infections

Not all treatment options may be immediately available at all NM facilities. Contact the pharmacy department or local antimicrobial stewardship pharmacist to discuss options and follow local policy as necessary.

References:

1. Tamma PD, Aitken SL, Bonomo RA, et al. IDSA Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. IDSA 2022; Version 1.1. Available at https://www.idsociety.org/practice-guideline/amr-guidance/.
2. Tamma PD, Aitken SL, Bonomo RA, et al. IDSA Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections. IDSA 2022; Version 2.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance-2.0/.
3. NM Antibiogram 2021.

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I. AmpC β-lactamase-producing Enterobacterales

- ***Enterobacter cloacae, Klebsiella aerogenes,* and *Citrobacter freundii*** are considered to be moderate to high risk for clinically significant AmpC production.
- Other organisms (e.g., *Serratia* spp., *Morganella* spp., *Providencia* spp.) are unlikely to overexpress *ampC* so **no need to treat these organisms empirically as AmpC producers.**
- **Empiric therapy:** Follow guidance outlined in **Table 1** for patients with *Enterobacter cloacae, Klebsiella aerogenes,* or *Citrobacter freundii* in culture pending susceptibilities or in critically ill patients with recent (past 6 months) cultures with those organisms.
- **Directed therapy:** Since *ampC* can be induced during antibiotic treatment, β-lactams other than cefepime and meropenem should be avoided regardless of culture susceptibilities. Non-β-lactam agents such as TMP-SMX, ciprofloxacin, and levofloxacin should be considered first-line or oral step-down when susceptible, the patient is hemodynamically stable, source control has been achieved, and no patient-specific contraindications exist.

Table 1: Empiric Recommendations for *Enterobacter cloacae, Klebsiella aerogenes,* & *Citrobacter freundii*

Infection	1st Line	2nd Line
Uncomplicated Cystitis	Nitrofurantoin, TMP-SMX, ciprofloxacin, levofloxacin or single-dose aminoglycoside[1]	Ceftriaxone
All Other Infections	Cefepime[2] or meropenem	

[1]Amikacin 15 mg/kg IV once or gentamicin 5 mg/kg IV once or tobramycin 5 mg/kg IV once
[2]Meropenem preferred if history of elevated cefepime MIC > 2 in a culture within the previous 6 months

II. Carbapenem-resistant *Acinetobacter baumannii* (CRAB)

- **Assess for colonization vs. true infection**
- **Empiric therapy:** Follow guidance outlined in **Table 2** for patients with recent (past 6 months) cultures with CRAB. ID consult is required for use of cefiderocol.
- **Directed therapy:** High-dose ampicillin-sulbactam is preferred therapy for CRAB infections and should still be utilized as combination therapy even if it appears to be non-susceptible in the susceptibility report.

Table 2: Empiric Recommendations for CRAB

Infection	1st Line	2nd Line	Salvage Therapy
Colonization	No antibiotics indicated		
Mild Infections: Uncomplicated Cystitis, SSTI, Tracheitis	High-dose ampicillin-sulbactam[1] (Add minocycline[2] if history of ampicillin-sulbactam resistance)	Minocycline[2]	
Moderate to Severe Infections	High-dose ampicillin-sulbactam[1] + minocycline[2] (Consider adding meropenem[3] if hemodynamically unstable)		High-dose ampicillin-sulbactam[1] + meropenem[3] + (polymyxin B or cefiderocol)

[1] 9 g IV q8h over 4h (See renal dose adjustments)
[2] 200 mg q12h
[3] 2 g IV q8h over 3h (See renal dose adjustments); use as part of combination therapy

III. Carbapenem-resistant Enterobacterales (CRE)

- **ID consult is required** for use of ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, & cefiderocol.
- **Empiric therapy:** Follow guidance outlined in **Table 3** for patients with positive carbapenemase molecular test results (e.g., BioFire with positive NDM, VIM, IMP, KPC, OXA-48-like) or in critically ill patients with recent (past 6 months) CRE in cultures. The primary team must consult ID within 24 hours for recommendations on continuation therapy.
- **Directed therapy:** Non-β-lactam agents such as TMP-SMX, ciprofloxacin, and levofloxacin should be considered first-line or oral step-down when susceptible, the patient is hemodynamically stable, source control has been achieved, and no patient-specific contraindications exist.

Table 3. Recommendations for Confirmed CRE Infections Based on Prior Culture Results or Molecular Tests

Infection	1st Line	2nd Line	3rd Line
CRE in Prior Culture but no Resistance Genes Detected			
Uncomplicated Cystitis	Nitrofurantoin, TMP-SMX, ciprofloxacin, levofloxacin, or single-dose aminoglycoside[1]	Ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-cilastatin-relebactam	Cefiderocol
All Other Infections	Ceftazidime-avibactam	Meropenem-vaborbactam or imipenem-cilastatin-relebactam	Cefiderocol
Resistance Genes Detected on Molecular Tests			
KPC	Meropenem-vaborbactam[2] or ceftazidime-avibactam	Imipenem-cilastatin-relebactam or cefiderocol	
NDM, VIM, or IMP	Ceftazidime-avibactam + aztreonam	Cefiderocol	
OXA-48-like	Ceftazidime-avibactam	Cefiderocol	

[1]Amikacin 15 mg/kg IV once or gentamicin 5 mg/kg IV once or tobramycin 5 mg/kg IV once

[2]Possibly offers a higher threshold of resistance for KPC; however, susceptibilities may be delayed from the microbiology lab

IV. Extended-spectrum β-lactamase-producing Enterobacterales (ESBL)

- **Empiric therapy:** Follow guidance outlined in **Table 4** for patients with **CTX-M** detected on molecular test results (e.g., BioFire) or in critically ill patients with recent (past 6 months) ESBL in cultures.
- **Directed therapy:** Non-β-lactam agents such as TMP-SMX, ciprofloxacin, and levofloxacin should be considered first-line or oral step-down when susceptible, the patient is hemodynamically stable, source control has been achieved and no patient-specific contraindications exist

Table 4. Empiric Recommendations for Suspected ESBL Infections Based on Prior Culture Results or Molecular Tests

Infection	1st Line	2nd Line	3rd Line
Uncomplicated Cystitis	Nitrofurantoin, TMP-SMX, ciprofloxacin or levofloxacin	Single-dose aminoglycoside[1] or fosfomycin (*E. coli* only)	Meropenem
Pyelonephritis or complicated UTI	Meropenem[2]		
CTX-M and All Other Infections	Meropenem[2]		

[1]Amikacin 15 mg/kg IV once or gentamicin 5 mg/kg IV once or tobramycin 5 mg/kg IV once
[2]Consult ADSP or ID if contraindication to meropenem

V. Multidrug-resistant (MDR) *Pseudomonas aeruginosa*

- **ID consult is required** for use of ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, & cefiderocol.
- **MDR**= Non-susceptibility to at least 3 of the following: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, & carbapenems.
- **Empiric therapy:** Follow guidance outlined in **Table 5** for critically ill patients with history of MDR *P. aeruginosa* isolates within the past 6 months.
- **Directed therapy**: Susceptibilities should be reviewed when available.

Table 5: Empiric Recommendations for MDR *P. aeruginosa* Infections

Infection	1st Line	2nd Line	3rd Line
Uncomplicated Cystitis	Ceftolozane-tazobactam or single-dose aminoglycoside[1]	Ceftazidime-avibactam	Imipenem-cilastatin-relebactam or cefiderocol
All Other Infections	Ceftolozane-tazobactam	Ceftazidime-avibactam	Imipenem-cilastatin-relebactam or cefiderocol

[1]Amikacin 15 mg/kg IV once or gentamicin 5 mg/kg IV once or tobramycin 5 mg/kg IV once

VI. *Stenotrophomonas maltophilia*

- **Assess for colonization vs. true infection**
- Ceftazidime is not recommended regardless of infection severity due to presence of intrinsic β-lactamases rendering it ineffective even if reported as susceptible.
- **Empiric therapy:** Follow guidance outlined in **Table 6** for patients with *Stenotrophomonas* in culture pending susceptibilities or recent (past 6 months) cultures with *Stenotrophomonas*.
- **Directed therapy:** Susceptibilities should be reviewed when available. TMP-SMX is preferred when susceptible and no allergies.

Table 6: Empiric Recommendations for *Stenotrophomonas maltophilia*

Infection	1st Line	2nd Line	3rd Line
Colonization	No antibiotics indicated		
Mild Infections	TMP-SMX[1]	Minocycline[2]	
Moderate to Severe Infections	TMP-SMX[1] (Add minocycline[2] if delay in clinical improvement with TMP-SMX alone)	TMP-SMX[1] + minocycline[2]	TMP-SMX[1] + levofloxacin OR Ceftazidime-avibactam + aztreonam

[1]8-12 mg/kg/day TMP divided q8-12h (See renal dose adjustments)
[2]200 mg q12h