Antimicrobial Stewardship News

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Review of 2021 IDSA Guidance for the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

Antimicrobial resistance continues to be a significant global crisis. Infections caused by multidrug-resistant gram-negative pathogens are increasing in academic and community hospitals[1–3] and are considered urgent or serious public health threats.[4] Appropriate treatment of multidrug-resistant gram-negative infections can be challenging, especially as guidance continues to evolve with ongoing research and clinical experience. The Infectious Diseases Society of America (IDSA) released guidance in September 2020 for extended-spectrum β-lactamase-producing Enterobacterales, carbapenem-resistant Enterobacterales, and difficult-to-treat *Pseudomonas aeruginosa,*[6] which are reviewed in the September 2020 DASON newsletter. In November 2021, a second version was released. This time guidance is given for treatment of AmpC β-lactamase-producing Enterobacterales (AmpC-E), carbapenem-resistant *Acinetobacter baumanii* (CRAB), and *Stenotrophomonas maltophilia*[5] and are reviewed here.

Methodology and Application

Similar to the treatment guidance published by IDSA in September 2020,[6] this is not a formal clinical practice guideline, but instead is a document prepared by a small panel of experts based on a comprehensive, but not necessarily systematic, review of the literature as well as clinical experience and expert opinion. Due to the relative scarcity of data on the treatment of AmpC-E, CRAB, and *S. maltophilia* infections, the panel elected to provide informed suggestions rather than recommendations. This document is not intended for empiric treatment guidance, but rather treatment of an identified organism with confirmed *in vitro* antibiotic susceptibility.

AmpC β-Lactamase-Producing Enterobacterales

While there are several effective antibiotics for the treatment of AmpC-E, distinguishing which species are at highest risk for significant AmpC production remains an area of confusion. AmpC β-lactamases can be produced by several members of Enterobacterales and other gram-negative bacteria, and may occur by one of three mechanisms including inducible chromosomal resistance, stable chromosomal de-repression, or plasmid-mediated genes.[7] The guidance document focuses on the treatment of pathogens with a moderate to high likelihood of inducible *ampC* gene expression, which, in the presence of specific antibiotics, can lead to enzyme production and subsequent treatment failure. The other two mechanisms that result in AmpC production are generally always expressed, and as such isolates will appear non-susceptible during *in vitro* testing.

Inducible *ampC* gene expression has been most frequently described for *Enterobacter cloacae*, *Klebsiella aerogenes* (formerly *Enterobacter aerogenes*), and *Citrobacter freundii*.[8] Other organisms historically thought to harbor inducible AmpC production and often denoted with the acronyms "SPACE" or "SPICE," such as *Serratia marcescens*, *Morganella morganii*, and *Providencia* species, are in fact unlikely to overexpress *ampC*. For the organisms considered at moderate to high risk of clinically significant inducible AmpC production, initial *in vitro* testing may demonstrate susceptibility to ceftriaxone and ceftazidime, however, these agents can induce AmpC production and are unable to withstand enzyme hydrolysis, leading to potential treatment failure. As such, ceftriaxone and ceftazidime should be avoided for the treatment of serious infections caused by Enterobacterales at moderate to high risk of inducible AmpC production. These agents may be considered for mild infections, such as uncomplicated cystitis.

The use of piperacillin/tazobactam in the treatment of Enterobacterales at moderate to high risk of inducible AmpC production remains uncertain. Notably, tazobactam is more susceptible to degradation by AmpC than newer β-lactamase inhibitors. In fact, results of the MERINO-2 trial showed higher microbiological failure with the use of piperacillin/tazobactam over meropenem for bloodstream infections caused by AmpC-producing gram-negatives.[9] Based on these findings, the panel advised caution in using piperacillin/tazobactam for serious infections caused by AmpC-E, but similar to ceftriaxone and ceftazidime, may be an option for mild infections. A review of the MERINO-1 trial is covered in the October 2018 newsletter and the November 2020 podcast.

Cefepime can be used for those pathogens which retain a cefepime MIC ≤2 mcg/mL (current breakpoint for susceptible), but a carbapenem is preferred for strains with cefepime MIC ≥ 4mcg/mL (current breakpoint for intermediate) due to possible concomitant ESBL production. Fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX) can be considered as oral step-down therapy for those in which susceptibility to an oral agent is confirmed, source control has been achieved, the patient is hemodynamically stable and has reliable intestinal absorption. **Table 1** further outlines suggested treatment options for infections caused by AmpC-E.

Newer agents, such as cefiderocol, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and meropenem-vaborbactam, likely retain efficacy against AmpC-E, but should be reserved for carbapenem-resistant infections. Due to the relative ineffectiveness of tazobactam against AmpC hydrolysis and the uncertain independent activity of ceftolozane against AmpC-E, ceftolozane-tazobactam should be avoided.

Carbapenem-Resistant *Acinetobacter baumanii* (CRAB)
Contrary to AmpC-E, there are relatively limited well-studied options for the treatment of CRAB. *Acinetobacter baumanii* is most often recovered from respiratory or wound cultures, and differentiation between colonization and infection can be difficult. Once carbapenem resistance is acquired, *A. baumanii* is also typically resistant to multiple other antibiotics. As such, differentiation between colonization and infection is even more crucial as unnecessary antibiotic exposure can further select for multidrug-resistant strains.

Use of a single active agent may be effective for mild infections, however for moderate to severe CRAB infections combination therapy with at least two active agents is generally recommended.

Ampicillin-sulbactam is the preferred treatment, and although there is insufficient data to determine the ideal dose, the panel favored high-dose ampicillin-sulbactam (9g of ampicillin component) over standard dosing. Even in ampicillin-sulbactam resistant strains, the panel suggests the use of high-dose ampicillin-sulbactam in combination with active agents due to the potential for sulbactam to saturate penicillin-binding proteins and work synergistically with other agents.[10] **Table 2** details the treatment options of mild and moderate to severe infections caused by CRAB.

Notably, extended-infusion meropenem should not be used in combination with a polymyxin without a third agent. Similarly, cefiderocol should be used in a combination regimen and reserved for CRAB infections refractory to other antibiotic options. Due to lack of clinical benefit demonstrated in several clinical trials,[11–13] nebulized antibiotics are not recommended for the treatment of respiratory infections due to CRAB.

***Stenotrophomonas maltophilia* Infections**
Similar to Acinetobacter, *Stenotrophomonas maltophilia* has the potential to cause severe infections but is also a common respiratory commensal in those with cystic fibrosis, ventilator dependency, or other underlying pulmonary condition, making the differentiation between infection and colonization problematic. As with CRAB, *S. maltophilia* can harbor numerous antimicrobial resistance genes, gene mutations, and efflux pumps. Further complicating treatment selection is the relatively limited number of agents with established MIC interpretative criteria.

Based on extensive clinical experience and relatively high proportion of strains that retain susceptibility, TMP-SMX remains the preferred treatment option for *S. maltophilia*. For mild infections, the panel suggests the preferential use of TMP-SMX or minocycline monotherapy. For moderate to severe infections, three general approaches are proposed, including (1) combination therapy, preferably with TMP-SMX and minocycline, (2) TMP-SMX monotherapy with the subsequent addition of a second agent if there is delay in clinical improvement, (3) combination therapy with ceftazidime-avibactam and aztreonam in cases of resistance or intolerance to other agents. Notably, ceftazidime (without avibactam) is not recommended regardless of the severity of the infection due to intrinsic β-lactamase production. **Table 3** displays the suggested treatment of mild and moderate to severe infections caused by *S. maltophilia*.

Antimicrobial Dosing Regimens

The guidance document promotes many drug dosing regimens designed to optimize pharmacodynamic properties of available agents to maximize outcomes. These include a preference for extended interval dosing for many beta-lactam agents and higher doses than traditionally used for some agents (i.e. ampicillin-sulbactam). Stewards play an invaluable role in ensuring the correct agent(s) at the appropriate doses are being used in patients with presumed or documented infections due to these resistant gram-negative pathogens.

Duration of Therapy

Recent studies have supported shorter treatment durations for gram-negative infections, including those caused by cephalosporin-resistant Enterobacterales[14]. Although recommendations for the duration of therapy are not included in the guidance document, in general, prolonged treatment courses are not necessary based solely on the presence of an antimicrobial-resistant pathogen. Treatment duration should be tailored to each clinical situation with consideration of host factors, source control, and response to treatment. Durations of therapy are reviewed in our December 2019 newsletter and February 2021 webinar.

Take Home Points

- *Enterobacter cloacae*, *Klebsiella aerogenes,* and *Citrobacter freundii* are considered moderate to high risk for inducible AmpC production.
- In general, mild infections caused by CRAB and *Stenotrophomonas* may be treated with a single active agent, however combination therapy should be considered for moderate to severe infections.
- Appropriate treatment of multidrug-resistant infections can be challenging. Consultation with an infectious diseases specialist and pharmacist is recommended in the management of difficult-to-treat infections.
- Newer agents, such as cefiderocol, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and meropenem-vaboractam, should be reserved for the future.

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Table 1. Treatment Options for Enterobacterales at Moderate to High Risk of Inducible AmpC Production

Type of Infection		Preferred Treatment	Other Considerations
Uncomplicated cystitis		nitrofurantoin trimethoprim-sulfamethoxazole aminoglycoside[1a]	ceftriaxone, ceftazidime, piperacillin/tazobactam[1b]
All other infections	Cefepime MIC ≤ 2	cefepime	Fluoroquinolone, TMP-SMX[1c]
	Cefepime MIC ≥ 4	carbapenem	

[1a] Single dose of an intravenous aminoglycoside can be administered for uncomplicated cystitis.

[1b] Ceftriaxone, ceftazidime, or piperacillin/tazobactam may be considered for uncomplicated cystitis in select situations, such as when susceptibility results demonstrate inactivity of the antibiotic selected empirically but clinical improvement nonetheless occurred.

[1c] Fluoroquinolones and trimethoprim-sulfamethoxazole can be administered intravenously or as oral step-down therapy in the appropriate clinical context.

Table 2. Treatment Options for Carbapenem-Resistant *Acinetobacter baumanii*

Type of Infection	Preferred Treatment	Alternative Treatments
Mild infection[2a]	ampicillin-sulbactam[2b]	Tetracycline derivates,[2c] polymyxins,[2d] cefiderocol
Moderate to severe infection	Combination therapy with at least two active agents: ampicillin-sulbactam,[2b] tetracycline derivative,[2c] polymyxin B, extended-infusion meropenem,[2e] cefiderocol	

[2a] Mild infections may include, but are not limited to, infections of the urinary tract, skin/soft tissue, or tracheitis. Treatment with a single active agent may be considered.

[2b] High-dose ampicillin-sulbactam is favored, however lower dosing may be considered for mild infections. High-dose ampicillin-sulbactam may be used for non-susceptible strains when combined with other active agents.

[2c] Minocycline or tigecycline are preferred therapies. Due to insufficient clinical data, the panel suggested limiting the use of eravacycline to cases in which other tetracyclines are inactive or not tolerated. Omadacycline is not recommended for use against CRAB infections.

[2d] Panel preferentially suggested polymyxin B due to its more favorable pharmacokinetics. However, colistin should be used for CRAB urinary tract infections. Although there are no CLSI breakpoints for polymyxin B against *A. baumannii*, evidence suggests limited benefit for polymyxin MIC >2 mcg/mL.[15]

[2e] Meropenem should never be used alone or in combination with a polymyxin without a third agent. Imipenem-cilastatin can be used as an alternative to meropenem.

Table 3. Treatment Options for *Stenotrophomonas maltophilia*

Type of Infection	Preferred Treatment	Alternative Treatments
Mild infection	TMP-SMX	Tetracycline derivative, [3a] levofloxacin,[3b] cefiderocol
Moderate to severe infection	1. Combination therapy with TMP-SMX + second agent[3c] 2. Sequential therapy with TMP-SMX, + second agent if no clinical response observed 3. Combination therapy with ceftazidime-avibactam and aztreonam[3d]	

[3a] Due to availability of established CLSI breakpoints, improved tolerability, and slightly more favorable *in vitro* data, minocycline is preferred over tigecycline. Tetracyclines are not recommended for *S. maltophilia* urinary tract infections and only as a part of combination therapy for bloodstream infections due to rapid tissue distribution and limited urine and serum concentrations, respectively.

[3b] Use with caution due to observed emergence of resistance while on fluoroquinolone therapy.

[3c] Minocycline, tigecycline, levofloxacin, or cefiderocol.

[3d] Reserved for cases of resistance or intolerance to other agents.

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