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Review of 2020 IDSA Treatment Guidance for Multidrug-Resistant Gram-negatives

Antimicrobial resistance among Gram-negative bacteria (GNB) remains a significant threat in 2020, and recent studies from academic and community hospitals have demonstrated antibiotic resistance among GNB is increasing.[1–3] While several new antimicrobials with novel mechanisms targeting multidrug-resistant (MDR) GNB have been developed in recent years, resistance to some of these agents has already been reported.[4] Therefore, it is critical to understand the precise application of these novel agents in comparison to existing antimicrobials in order to preserve their activity for the future. This newsletter reviews the latest treatment guidance published by the Infectious Diseases Society of America (IDSA).[5]

Methodology and Application:

This new guidance document published by the IDSA in September 2020 is not a clinical practice guideline, but rather a tool to assist clinicians in selecting appropriate therapy for treatment of infections caused by MDR GNB. In contrast to formal clinical practice guidelines, this document was prepared by a small team of experts based on a comprehensive but not necessarily systematic review of the literature and therefore does not grade each recommendation based on the quality of evidence.

This guidance document does not provide empiric treatment recommendations. Instead, these recommendations should be applied only when the causative organism has been identified and *in vitro* activity of antibiotics has been demonstrated.

Extended-Spectrum Beta-Lactamase Producing Enterobacterales (ESBL-E):

Extended-spectrum beta-lactamases inactivate most penicillins, cephalosporins, and aztreonam, but remain susceptible to carbapenems. While ESBLs do not inactivate non-beta-lactams, organisms that carry ESBL genes often harbor additional resistance genes that confer resistance to a broad-range of non-beta-lactams, such as the fluoroquinolones and sulfamethoxazole/trimethoprim (SMX/TMP). ESBLs are most prevalent among *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis,* and community-acquisition is increasingly more common.[5] Despite increasing prevalence, many clinical microbiology laboratories do not perform routine ESBL testing, but rather use ceftriaxone non-susceptibility as a proxy for ESBL production.

The carbapenems have been the preferred treatment of choice for infections caused by ESBL-E for decades; however, increasing evidence suggests some narrower-spectrum agents (e.g., nitrofurantoin) are effective treatment options for some uncomplicated infection types (e.g., cystitis with clinical symptoms). Preferential use of these narrower-spectrum agents, when appropriate, is critical to reduce selective pressure and preserve carbapenem activity for the future. **Table 1** outlines definitive treatment options for infections caused by confirmed or suspected (e.g., ceftriaxone-non-susceptible) ESBL-E and includes footnotes with select clinical information for additional guidance.

A key consideration regarding treatment of infections caused by ESBL-E is whether or not piperacillin/tazobactam or cefepime may be used if susceptibility is demonstrated. In general, piperacillin/tazobactam and/or cefepime should be avoided even if susceptibility is demonstrated, with one key exception: empiric treatment of cystitis later identified as an ESBL-E in the setting of clinical improvement. For serious infections, including bloodstream infections, piperacillin/tazobactam should be avoided on the basis of results from the MERINO Trial demonstrating inferiority versus meropenem.[6] The results and implications of the MERINO Trial are reviewed in the October 2018 DASON Newsletter.

Carbapenem-Resistant Enterobacteriaceae (CRE):

The term CRE encompasses Enterobacteriaceae that are resistant to at least one carbapenem or produce a carbapenemase enzyme. Carbapenem resistance may be conferred via a variety of resistance mechanisms (e.g., enzyme-mediated, porin modifications, efflux pumps), but carbapenemase production is responsible for approximately half of all CRE infections in the US.[7–9] Carbapenem resistance among CRE isolates varies (e.g., a single isolate may be resistant to ertapenem but susceptible to meropenem, while another isolate may be resistant to all carbapenems), and these patterns of resistance are important factors to consider when selecting an appropriate definitive treatment regimen. While newer/novel agents (e.g., ceftazidime/avibactam) are typically preferred for serious infections, some relatively narrow-spectrum oral options (e.g., nitrofurantoin, SMX/TMP) exist for uncomplicated cystitis. Table 2 outlines definitive treatment recommendations and considerations for infections caused by CRE. Of note, colistin and polymyxin B should generally be avoided, and combination therapy (e.g., beta-lactam plus an aminoglycoside, fluoroquinolone, or polymyxin B) is not routinely recommended for definitive treatment.

Difficult-to-Treat Resistant (DTR) *Pseudomonas*:

In 2017, MDR *P. aeruginosa* was responsible for 32,600 infections and 2,700 deaths, according to the CDC.[1] For the purposes of this guidance document, difficult-to-treat resistant (DTR) *Pseudomonas aeruginosa* is defined as non-susceptibility to all of the following: piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem/cilastatin, ciprofloxacin, and levofloxacin. These DTR *P. aeruginosa* isolates are generally isolated from patients with cystic fibrosis or from patients with a history of extensive broad-spectrum antibiotic use, and treatment was historically limited to combination therapy with particularly toxic antibiotics (e.g., colistin plus an aminoglycoside). However, several new antimicrobials with enhanced activity are now available and offer a more attractive safety profile. Table 3 outlines definitive treatment recommendations and considerations for infections caused by DTR *P. aeruginosa*. Of note, combination therapy (e.g., the addition of an aminoglycoside to ceftolozane/tazobactam) is not routinely recommended if the isolate demonstrates *in vitro* susceptibility to a preferred treatment option.

Durations of Therapy:

A common clinical question related to treatment of infections caused by MDR GNB is whether or not antibiotic therapy should be extended for longer durations solely on the basis of resistance. In general, prolonged treatment courses are not necessary for MDR infections as compared with infections caused by the same bacteria with a more favorable susceptibility profile. However, the duration of therapy might be impacted if susceptibility results indicate that the antibiotic used initially was not active against the isolate being treated. In this setting, the decision to "restart the clock" should be made in the context of the patient's clinical status and infection type (e.g., no need to restart the clock for a patient that improved clinically on an "non-susceptible" empiric regimen with cystitis; but restart the clock in a patient with a bloodstream infection or pneumonia). Durations of therapy for common infection types are reviewed in our November 2016 and December 2019 newsletters.

Take Home Points:

- Historically, treatment of infections caused by MDR GNB was complex and required combination therapy with antimicrobials with unfavorable safety profiles
- The antimicrobial armamentarium is now larger than ever, and several monotherapy treatment options exist for most infections caused by ESBL-E, CRE, and DTR *P. aeruginosa*
- Despite recent advances in antimicrobial development, many non-severe infections (e.g., cystitis) caused by these organisms can be successfully treated with familiar antimicrobials (e.g., nitrofurantoin)
- Emphasis should be placed on preserving the activity of newly-developed antimicrobials for the future

Table 1. Definitive Treatment Options for ESBL-producing Enterobacteriaceae

Source of Infection	Preferred Treatment	Alternative Treatment
Cystitis	• nitrofurantoin • SMX/TMP	• amox/clav[1a] • single-dose AG[1b] • fosfomycin (*E. coli* only)[1c]
Pyelonephritis or cUTI	• carbapenem[1d] • SMX/TMP • ciprofloxacin, levofloxacin	

Infections outside of the urinary tract	• carbapenem
	• oral step-down:[1e]
	  • ciprofloxacin
	  • levofloxacin
	  • SMX/TMP	

cUTI, complicated urinary tract infection, defined as UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.
SMX/TMP, sulfamethoxazole/trimethoprim

[1a] amoxicillin/clavulanate. This option is reserved as an alternative treatment on the basis of a single randomized controlled trial comparing a 3-day course of amox/clav vs ciprofloxacin that demonstrated amox/clav was associated with a higher clinical failure rate, presumably due to persistent vaginal bacterial colonization. Of note, this trial evaluated amox/clav 500/125mg dosed twice-daily and did not specifically evaluate ESBLs[10]

[1b] AG, aminoglycoside; robust clinical trial data are lacking

[1c] fosfomycin should be used only for treatment of ESBL-producing *E. coli*, because *K. pneumoniae* and other Gram-negative organisms frequently harbor the *fosA* gene that hydrolyzes fosfomycin and renders it inactive

[1d] if a carbapenem is initiated and susceptibility to SMX/TMP, ciprofloxacin, or levofloxacin is demonstrated, transitioning to these agents is preferred over completing the treatment course with a carbapenem

[1e] based on oral bioavailability, these agents are reasonable step-down options if: 1) susceptibility to the oral agent is demonstrated; 2) patients are afebrile and hemodynamically stable; 3) appropriate source control is achieved; and 4) there are no issues with intestinal absorption

Table 2. Definitive Treatment Options for Carbapenem-resistant Enterobacteriaceae (CRE)

Source of Infection	Preferred Treatment	Alternative Treatment
Cystitis	• nitrofurantoin • SMX/TMP • ciprofloxacin, levofloxacin • single-dose AG[2a] • standard-infusion meropenem[2b]	• ceftazidime/avibactam • meropenem/vaborbactam • imipenem/cilastatin/relebactam • cefiderocol • colistin (only when no alternative options are available)[2c]
Pyelonephritis or cUTI	• ceftazidime/avibactam • meropenem/vaborbactam • imipenem/cilastatin/relebactam • cefiderocol • extended-infusion meropenem[2b]	• once-daily AG[2d]
Infections outside of the urinary tract, if:[2f] • ertapenem - R • meropenem - S • carbapenemase testing neg or N/A	• extended-infusion meropenem[2b]	• ceftazidime/avibactam
Infections outside of the urinary tract, if: • meropenem - R • carbapenemase + • KPC identified	• ceftazidime/avibactam • meropenem/vaborbactam • imipenem/cilastatin/relebactam	• cefiderocol[2e] • tigecycline, eravacycline (uncomplicated intra-abdominal infections only)
Metallo-beta-lactamase (e.g., NDM, VIM, or IMP) carbapenemase identified	• ceftazidime/avibactam + aztreonam • cefiderocol	• tigecycline, eravacycline (uncomplicated intra-abdominal infections only)
OXA-48-like carbapenemase identified	• ceftazidime/avibactam	• cefiderocol • tigecycline, eravacycline (uncomplicated intra-abdominal infections only)

N/A, not available

[2a] almost exclusively eliminated by the renal route, and a single dose is generally effective for cystitis with minimal toxicity[11]

[2b] avoid if carbapenemase testing is positive, even if susceptibility is demonstrated

[2c] not interchangeable with polymyxin B due to predominant non-renal clearance

[2d] once-daily plazomicin was noninferior to meropenem in a randomized trial including patients with pyelonephritis[12]

[2e] cefiderocol has been associated with higher 28-day mortality in patients with CRE, especially patients with pneumonia and bloodstream infections; avoid cefiderocol unless clear contraindications or resistance to preferred agents - this increased risk in mortality does not appear to extend to urinary tract infections[13]

[2f] the majority of infections caused by CRE that are resistant to ertapenem but susceptible to meropenem are caused by organisms that do not produce a carbapenemase enzyme

Table 3. Definitive Treatment Options for Difficult-to-treat (DTR) *Pseudomonas aeruginosa*

Source of Infection	Preferred Treatment	Alternative Treatment
Cystitis	• ceftolozane/tazobactam • ceftazidime/avibactam • imipenem/cilastatin/relebactam • cefiderocol • single-dose AG[3a]	• colistin[3b]
Pyelonephritis or cUTI	• ceftolozane/tazobactam • ceftazidime/avibactam • imipenem/cilastatin/relebactam • cefiderocol	• once-daily AG[3c]
Infections outside of the urinary tract	• ceftolozane/tazobactam • ceftazidime/avibactam • imipenem/cilastatin/relebactam	• cefiderocol[3d] • monotherapy AG (limited to uncomplicated BSI with complete source control)

BSI, bloodstream infection

[3a] if resistant to amikacin, gentamicin, and tobramycin, the isolate is also likely resistant to plazomicin

[3b] not interchangeable with polymyxin B due to predominant non-renal clearance

[3c] avoid use unless benefit outweighs increased risk for potential nephrotoxicity

[3d] cefiderocol has been associated with higher 28-day mortality than the comparator (best available therapy) in patients with CRE, especially patients with pneumonia and bloodstream infections; avoid cefiderocol unless clear contraindications or resistance to preferred agents - this increased risk in mortality does not appear to extend to urinary tract infections[13]

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