Clinical Infectious Diseases

IDSA FEATURES

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

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Background. Antimicrobial-resistant infections are commonly encountered in US hospitals and result in significant morbidity and mortality. This guidance document provides recommendations for the treatment of infections caused by extended-spectrum β-lactamase–producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*).

Methods. A panel of 6 infectious diseases specialists with expertise in managing antimicrobial-resistant infections formulated common questions regarding the treatment of ESBL-E, CRE, and DTR-*P. aeruginosa* infections. Based on review of the published literature and clinical experience, the panel provide recommendations and associated rationale for each recommendation. Because of significant differences in the molecular epidemiology of resistance and the availability of specific anti-infective agents globally, this document focuses on treatment of antimicrobial-resistant infections in the United States.

Results. Approaches to empiric treatment selection, duration of therapy, and other management considerations are briefly discussed. The majority of guidance focuses on preferred and alternative treatment recommendations for antimicrobial-resistant infections, assuming that the causative organism has been identified and antibiotic susceptibility testing results are known. Treatment recommendations apply to both adults and children.

Conclusions. The field of antimicrobial resistance is dynamic and rapidly evolving, and the treatment of antimicrobial-resistant infections will continue to challenge clinicians. This guidance document is current as of 17 September 2020. Updates to this guidance document will occur periodically as new data emerge. Furthermore, the panel will expand recommendations to include other problematic gram-negative pathogens in future versions. The most current version of the guidance including the date of publication can be found at www.idsociety.org/practice-guideline/amr-guidance/.

Keywords. ESBL; CRE; *Pseudomonas aeruginosa*; MDRGN; antimicrobial resistance.

The rise in antimicrobial resistance (AMR) continues to be a global crisis [1, 2]. Collectively, antimicrobial-resistant pathogens cause more than 2.8 million infections and more than 35 000 deaths annually in the United States, according to the 2019 Centers for Disease Control and Prevention (CDC) Antibiotic Resistant Threats Report [2]. Although there has been an increase in the availability of novel antibiotics to combat resistant infections in recent years [3], resistance to a number of these agents has been observed [4]. Three groups of antimicrobial-resistant gram-negative bacteria pose particular therapeutic challenges: extended-spectrum β-lactamase–producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa)* [5]. The CDC has designated these pathogens as urgent or serious threats [2]. They are encountered in US hospitals of all sizes and cause a wide range of serious infections that carry significant morbidity and mortality. Treatment options against ESBL-E, CRE, and

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DTR-*P. aeruginosa* infections remain limited despite approval of new antibiotics. There is often uncertainty about the precise role(s) of new agents in clinical practice [6–8].

The Infectious Diseases Society of America (IDSA) identified the development and dissemination of clinical practice guidelines and guidance documents for clinicians as a top initiative in its 2019 Strategic Plan [9]. IDSA acknowledged that the ability to address rapidly evolving topics such as AMR was limited by prolonged timelines needed to generate new or updated clinical practice guidelines. As an alternative and complement to comprehensive clinical practice guidelines, IDSA endorsed the development of more narrowly focused guidance documents for the treatment of specific infectious processes. Guidance documents address specific clinical questions for difficult-to-manage infections that are not covered by present guidelines. The documents are prepared by a small team of experts based on a comprehensive (but not necessarily systematic) review of the literature. Additionally, such guidance documents do not include a formal grading of the evidence, unlike IDSA guidelines that use the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework. This guidance document is current as of 17 September 2020. Updates to this document will occur periodically as new data emerge. Future iterations will also address other resistant pathogens. The most current version of the guidance including the date of publication can be found at www.idsociety.org/practice-guideline/amr-guidance/.

The overarching goal of this document is to assist clinicians, including those with and without infectious diseases expertise, in selecting antibiotic therapy for infections caused by ESBL-E, CRE, and DTR-*P. aeruginosa*. Although brief descriptions of notable clinical trials, resistance mechanisms, and susceptibility testing methods are included, this guidance is not meant to provide a comprehensive review of these topics. This document is framed as answers to a series of clinical questions, each of which can stand on its own. Because of significant differences in the molecular epidemiology of resistance and availability of specific anti-infectives globally, this document focuses on treatment recommendations for antimicrobial-resistant infections in the United States.

METHODOLOGY

This IDSA guidance document was developed by a panel of 6 actively practicing infectious diseases specialists with clinical and research expertise in the treatment of resistant bacterial infections. Through a series of web-based meetings, the panel developed several commonly encountered treatment questions and corresponding answers for each pathogen group. They reached consensus on the recommendations for each question based on extensive review of the published literature, coupled with clinical experience. Answers include a brief discussion of the rationale that supports the recommendations. For each pathogen group, a table is provided with preferred and alternative treatment recommendations, after antimicrobial susceptibility data are known. Treatment recommendations apply to both adult and pediatric populations. Suggested antibiotic dosing for adult patients with antimicrobial-resistant infections, assuming normal renal and hepatic function, is provided in Table 1.

GENERAL MANAGEMENT RECOMMENDATIONS

Preferred and alternative treatment recommendations in this guidance document assume that the causative organism has been identified and in vitro activity of antibiotics has been demonstrated. The panel did not consider the cost of agents. Assuming 2 antibiotics are equally effective and safe, cost, convenience, and local formulary availability are important considerations in selecting a specific agent. The panel recommends that infectious diseases specialists be involved in the management of patients with antimicrobial-resistant infections, if feasible.

Empiric Therapy

Empiric treatment recommendations are not provided in this guidance document since a given host at risk for infection by 1 of the pathogen groups is usually at risk of infection by other antimicrobial-resistant pathogens. Empiric treatment decisions should be guided by local susceptibility patterns for the most likely pathogens. When determining empiric treatment for a given patient, clinicians should consider previous organisms and associated antibiotic susceptibility data in the past 6 months and antibiotic exposures in the past 30 days (eg, if a treatment course of piperacillin-tazobactam was recently completed, consider empiric coverage with a gram-negative agent from a different class that offers a comparable spectrum of activity, such as meropenem). Empiric decisions should be refined based on the severity of the patient's illness, whether the patient is immunocompromised, and the likely source of the infection (eg, presumed ventilator-associated pneumonia typically warrants broader empiric coverage than presumed cystitis).

Duration of Therapy

Recommendations on durations of therapy are not provided, but clinicians are advised that prolonged treatment courses are not necessary against infections by antimicrobial-resistant pathogens per se, compared with infections caused by the same bacterial species with a more susceptible phenotype. After antibiotic susceptibility results are available, it may become apparent that inactive antibiotic therapy was initiated empirically. This may impact the duration of therapy. For example, cystitis is typically a mild infection. If an antibiotic not active against the causative organism was administered empirically for cystitis but clinical improvement nonetheless occurred, it is generally not necessary to repeat a urine culture, change the antibiotic regimen, or extend the planned treatment course [11]. However, for all other

Table 1. Suggested Dosing of Antibiotics for the Treatment of Extended-spectrum β-Lactamase–Producing Enterobacterales, Carbapenem-resistant Enterobacterales, and *Pseudomonas aeruginosa* With Difficult-to-Treat Resistance Infections

Agent	Adult Dosage, Assuming Normal Renal and Liver Function
Amikacin	Cystitis: 15 mg/kg/dose[a] IV once
	All other infections: 20 mg/kg/dose[a] IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation
Amoxicillin-clavulanate	Cystitis: 875 mg (amoxicillin component) PO every 12 hours
Cefiderocol	2 g IV every 8 hours, infused over 3 hours
Ceftazidime-avibactam	2.5 g IV every 8 hours, infused over 3 hours
Ceftazidime-avibactam and aztreonam (infused together)	Ceftazidime-avibactam: 2.5 g IV every 8 hours, infused over 3 hours
	plus
	Aztreonam: 2 g IV every 8 hours, infused over 3 hours
Ceftolozane-tazobactam	Cystitis: 1.5 g IV every 8 hours, infused over 1 hour
	All other infections: 3 g IV every 8 hours, infused over 3 hours
Ciprofloxacin	400 mg IV every 8 hours or 750 mg PO every 12 hours
Colistin	Refer to international consensus guidelines on polymyxins[10]
Eravacycline	1 mg/kg/dose IV every 12 hours
Ertapenem	1 g IV every 24 hours, infused over 30 minutes
Fosfomycin	Cystitis: 3 g PO × 1 dose
Gentamicin	Cystitis: 5 mg/kg/dose[a] IV once
	All other infections: 7 mg/kg/dose[a] IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation
Imipenem-cilastatin	Cystitis (standard infusion): 500 mg IV every 6 hours, infused over 30 minutes
	All other infections (extended-infusion): 500 mg IV every 6 hours, infused over 3 hours
Imipenem-cilastatin-relebactam	1.25 g IV every 6 hours, infused over 30 minutes
Levofloxacin	750 mg IV/PO every 24 hours
Meropenem	Cystitis (standard infusion): 1 g IV every 8 hours
	All other infections (extended-infusion): 2 g IV every 8 hours, infused over 3 hours
Meropenem-vaborbactam	4 g IV every 8 hours, infused over 3 hours
Nitrofurantoin	Cystitis: macrocrystal/monohydrate (Macrobid®)100 mg PO every 12 hours
	Cystitis: Oral suspension: 50 mg every 6 hours
Plazomicin	Cystitis: 15 mg/kg[a] IV × 1 dose
	All other infections: 15 mg/kg[a] IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation
Polymyxin B	Refer to international consensus guidelines on polymyxins[10]
Tigecycline	Uncomplicated intra-abdominal infections (standard dose): 100 mg IV × 1 dose, then 50 mg IV every 12 hours
	Complicated intra-abdominal infections (high dose): 200 mg IV × 1 dose, then 100 mg IV every 12 hours
Tobramycin	Cystitis: 7 mg/kg/dose[a] IV × 1 dose
	All other infections: 7 mg/kg/dose[a] IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation
Trimethoprim-sulfamethoxazole	Cystitis: 160 mg (trimethoprim component) IV/PO every 12 hours
	Other infections: 8–10 mg/kg/day (trimethoprim component) IV/PO divided every 8–12 hours; maximum dose 320 mg PO every 8 hours

Abbreviations: IV, intravenous; PO, by mouth.
[a]Recommend using adjusted body weight for patients >120% of ideal body weight for aminoglycoside dosing.

infections included in this document, if antibiotic susceptibility data indicate a potentially inactive agent was initiated empirically, a change to an active regimen for a full treatment course (dated from the start of active therapy) is recommended. Additionally, important host factors related to immune status, ability to attain source control, and general response to therapy should be considered when determining treatment durations for antimicrobial-resistant infections, as with the treatment of any bacterial infection.

EXTENDED-SPECTRUM β-LACTAMASE–PRODUCING ENTEROBACTERALES

The incidence of ESBL-E infections in the United States increased by 53% from 2012 through 2017, in large part due to increased community-acquired infections [12]. ESBLs are enzymes that inactivate most penicillins, cephalosporins, and aztreonam. ESBL-E generally remain susceptible to carbapenems. ESBLs do not inactivate non–β-lactam agents

(eg, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin). However, organisms that carry ESBL genes often carry additional genes or mutations in genes that mediate resistance to a broad range of antibiotics.

Any gram-negative organism has the potential to harbor ESBL genes; however, they are most prevalent in *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* [13, 14]. CTX-M enzymes, particularly CTX-M-15, are the most common ESBLs in the United States [14]. ESBLs other than CTX-M with unique hydrolyzing abilities have been identified, including variants of narrow-spectrum TEM and SHV β-lactamases with amino acid substitutions [15–17]. Routine EBSL testing is not performed by most clinical microbiology laboratories [18, 19]. Rather, nonsusceptibility to ceftriaxone (ie, ceftriaxone minimum inhibitory concentrations [MICs] ≥2 μg/mL), is often used as a proxy for ESBL production [19]. For this guidance document, ESBL-E refers to presumed or confirmed ESBL-producing *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*. Table 2 outlines preferred and alternative treatment recommendations for ESBL-E infections. Treatment recommendations for ESBL-E infections assume in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 1: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by ESBL-E?

Recommendation: Nitrofurantoin and trimethoprim-sulfamethoxazole are preferred treatment options for uncomplicated cystitis caused by ESBL-E.

Rationale: Nitrofurantoin and trimethoprim-sulfamethoxazole have been shown to be safe and effective options for cystitis [11, 20, 21].

Although fluoroquinolones (ie, ciprofloxacin or levofloxacin) and carbapenems are effective agents for ESBL-E cystitis, their usage for cystitis is discouraged when other safe and effective options are available. Limiting use of these agents serves to both preserve their activity for future infections and to limit associated toxicities, particularly with the fluoroquinolones.

Amoxicillin-clavulanate, single-dose aminoglycosides, and oral fosfomycin are alternative options for ESBL-E cystitis. Amoxicillin-clavulanate is an alternative rather than preferred agent since randomized, controlled trial data have shown it is associated with a higher clinical failure rate than ciprofloxacin for cystitis, presumably due to persistent vaginal bacterial colonization [22]. Aminoglycosides are nearly exclusively eliminated by the renal route in their active form. A single intravenous dose of an aminoglycoside is generally effective for cystitis, with minimal toxicity, but robust trial data are lacking [23]. Oral fosfomycin is an alternative agent exclusively for treatment of ESBL-producing *E. coli* cystitis as the *fosA* gene, intrinsic to *K. pneumoniae* and several other gram-negative organisms, can hydrolyze the drug and may lead to clinical failure [24, 25]. Randomized, controlled trial data indicate that oral fosfomycin is associated with higher clinical failure than nitrofurantoin for uncomplicated cystitis [20]. Doxycycline is not recommended for the treatment of ESBL-E cystitis due to its limited urinary excretion [26].

Question 2: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections (cUTIs) caused by ESBL-E?

Recommendation: Ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole are preferred treatment options for pyelonephritis and cUTIs caused by ESBL-E.

Rationale: A cUTI is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient. Carbapenems, ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole are all preferred treatment options for patients with ESBL-E pyelonephritis and cUTIs based on the

Table 2. Recommended Antibiotic Treatment Options for Presumed or Confirmed Extended-spectrum β-Lactamase–Producing Enterobacterales, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Nitrofurantoin, trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate, single-dose aminoglycosides, fosfomycin (*Escherichia coli* only) Ciprofloxacin, levofloxacin, ertapenem, meropenem, imipenem-cilastatin
Pyelonephritis or complicated urinary tract infection[a]	Ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole	
Infections outside of the urinary tract	Meropenem, imipenem-cilastatin, ertapenem Oral step-down therapy to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole should be considered[b]	

[a]A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[b]Oral step-down therapy can be considered after susceptibility to the oral agent is demonstrated, patients are afebrile and hemodynamically stable, appropriate source control is achieved, and there are no issues with intestinal absorption.

ability of these agents to achieve high concentrations in the urine. If a carbapenem is initiated and susceptibility to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole is demonstrated, transitioning to these agents is preferred over completing a treatment course with a carbapenem. Limiting carbapenem use in these situations will preserve their activity for future antimicrobial-resistant infections. Nitrofurantoin and oral fosfomycin do not achieve adequate concentrations in the renal parenchyma and should be avoided if the upper urinary tract is infected [27, 28]. Doxycycline is not recommended for the treatment of ESBL-E pyelonephritis or cUTIs due to its limited urinary excretion [26].

Question 3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by ESBL-E?

Recommendation: A carbapenem is preferred for the treatment of infections outside of the urinary tract caused by ESBL-E.

Rationale: A carbapenem is recommended as first-line treatment of infections outside of the urinary tract caused by ESBL-E, based largely on data from a multicenter, randomized, controlled trial [29]. In this trial, 30-day mortality was reduced for patients with ESBL *E. coli* and *K. pneumoniae* bloodstream infections treated with meropenem compared with piperacillin-tazobactam [29]. Comparable clinical trial data are not available for infections of other body sites. Nevertheless, the panel recommends extrapolating evidence for ESBL-E bloodstream infections to other common sites of infection, namely, intra-abdominal infections, skin and soft tissue infections, and pneumonia.

The role of oral step-down therapy for ESBL-E infections outside of the urinary tract has not been formally evaluated. However, oral step-down therapy has been shown to be a reasonable treatment consideration for Enterobacterales bloodstream infections, including those caused by antimicrobial-resistant isolates, after appropriate clinical milestones are achieved [30, 31]. Based on the known bioavailability and sustained serum concentrations of oral fluoroquinolones and trimethoprim-sulfamethoxazole, these agents are reasonable treatment options for patients with ESBL-E infections if susceptibility to the oral agent is demonstrated, patients are afebrile and hemodynamically stable, appropriate source control has occurred, and there are no concerns with intestinal absorption.

Clinicians should avoid oral step-down to nitrofurantoin, fosfomycin, doxycycline, or amoxicillin-clavulanate for ESBL-E bloodstream infections. Nitrofurantoin and fosfomycin achieve poor serum concentrations. Amoxicillin-clavulanate and doxycycline achieve unreliable serum concentrations.

Question 4: Is there a role for piperacillin-tazobactam in the treatment of infections caused by ESBL-E when in vitro susceptibility to piperacillin-tazobactam is demonstrated?

Recommendation: Piperacillin-tazobactam should be avoided for the treatment of infections caused by ESBL-E, even if susceptibility to piperacillin-tazobactam is demonstrated. If piperacillin-tazobactam is initiated as empiric therapy for cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary.

Rationale: Piperacillin-tazobactam demonstrates in vitro activity against a number of ESBL-E [32]. However, a randomized, controlled trial of ESBL-E bloodstream infections indicated inferior results with piperacillin-tazobactam compared with carbapenem therapy [29]. The effectiveness of piperacillin-tazobactam in the treatment of invasive ESBL-E infections may be diminished by the potential for organisms to have increased expression of the ESBL enzyme or by the presence of multiple β-lactamases [33]. Additionally, piperacillin-tazobactam MIC testing may be inaccurate and/or poorly reproducible when ESBL enzymes are present [34–36].

Question 5: Is there a role for cefepime in the treatment of infections caused by ESBL-E when in vitro susceptibility to cefepime is demonstrated?

Recommendation: Cefepime should be avoided for the treatment of infections caused by ESBL-E, even if susceptibility to cefepime is demonstrated. If cefepime is initiated as empiric therapy for cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary.

Rationale: Observational studies and a subgroup analysis of 23 patients in a randomized trial that compared cefepime and carbapenems for the treatment of invasive ESBL-E infections demonstrated either no difference in outcomes or poorer outcomes with cefepime [37–40]. Cefepime MIC testing may be inaccurate and/or poorly reproducible when ESBL enzymes are present [34, 35, 41].

Question 6: What are preferred antibiotics in the treatment of infections caused by *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* not susceptible to ceftriaxone if confirmatory phenotypic ESBL testing is negative?

Recommendation: Antibiotic treatment selection can be based on susceptibility testing results if a locally validated ESBL phenotypic test does not indicate ESBL production.

Rationale: Currently, there is no Clinical and Laboratory Standards Institute endorsed phenotypic method for confirmatory ESBL testing [19]. For hospitals with clinical microbiology laboratories that do not perform ESBL phenotypic testing, a ceftriaxone MIC ≥2 μg/mL should be used as a proxy for ESBL production by *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* [19]. Phenotypic tests (eg, double-disk synergy test, ETEST, automated susceptibility platform algorithms) to exclude the possibility of ESBL production by clinical isolates should be interpreted with caution. Results should be used for clinical

decision-making only after local laboratory validation of testing [42, 43].

Question 7: What is the preferred antibiotic for the treatment of bloodstream infections caused by ceftriaxone nonsusceptible *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*, if a $bla_{\text{CTX-M}}$ gene is not detected using a molecular platform that includes this target?

Recommendation: Carbapenem therapy is preferred if a $bla_{\text{CTX-M}}$ gene is not detected in *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* isolates that are not susceptible to ceftriaxone since the absence of a $bla_{\text{CTX-M}}$ gene does not exclude the presence of other ESBL genes.

Rationale: Commercially available molecular platforms for β-lactamase gene detection from positive blood cultures (eg, Verigene Gram-Negative Blood Culture Test, GenMark ePlex Blood Culture Identification Gram-negative Panel) limit ESBL detection to $bla_{\text{CTX-M}}$ genes. The absence of $bla_{\text{CTX-M}}$ genes in *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* that are not susceptible to ceftriaxone (ie, ceftriaxone MIC ≥2 μg/mL) does not exclude the presence of other ESBL genes (eg, bla_{SHV}, bla_{TEM} ESBL variants). Therefore, carbapenem therapy is recommended, at least initially.

CARBAPENEM-RESISTANT ENTEROBACTERALES

CRE account for more than 13 000 nosocomial infections and contribute to more than 1000 deaths annually in the United States [2]. The CDC defines CRE as members of the Enterobacterales order resistant to at least 1 carbapenem antibiotic or producing a carbapenemase enzyme [2]. A CRE isolate may be resistant to some carbapenems (eg, ertapenem) but not others (eg, meropenem). CRE comprise a heterogenous group of pathogens with multiple potential mechanisms of resistance, broadly divided into those that are carbapenemase-producing and those that are not carbapenemase-producing. Carbapenemase-producing isolates account for approximately half of all CRE infections in the United States [44–46]. The most common carbapenemases in the United States are *Klebsiella pneumoniae* carbapenemases (KPCs), which can be produced by any Enterobacterales. Other notable carbapenemases that have been identified in the United States include New Delhi metallo-β-lactamases (NDMs), Verona integron-encoded metallo-β-lactamases (VIMs), imipenem-hydrolyzing metallo-β-lactamases (IMPs), and oxacillinase (eg, OXA-48–like) carbapenemases [47, 48]. Knowledge of whether a CRE clinical isolate is carbapenemase-producing and, if it is, the specific carbapenemase produced are important in guiding treatment decisions.

Phenotypic tests such as the modified carbapenem inactivation method and the Carba NP test can differentiate carbapenemase and non-carbapenemase–producing CRE [49]. Molecular testing can identify specific carbapenemase families (eg, differentiating a KPC from an OXA-48–like carbapenemase). There are several molecular platforms used in US clinical microbiology laboratories to identify carbapenemase genes (eg, Verigene Gram-Negative Blood Culture Test, GenMark ePlex Blood Culture Identification Gram-negative Panel, BioFire FilmArray Blood Culture Identification Panels). Carbapenemase phenotypic and/or genotypic testing are not performed by all clinical microbiology laboratories. Table 3 outlines preferred and alternative treatment recommendations for CRE infections. Treatment recommendations for CRE infections assume in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 1: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by CRE?

Recommendation: Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside are preferred treatment options for uncomplicated cystitis caused by CRE. Standard infusion meropenem is a preferred treatment option for cystitis caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative.

Rationale: Clinical trial data evaluating the efficacy of most preferred agents for CRE cystitis are not available. However, as these agents achieve high concentrations in urine, they are expected to be effective for CRE cystitis when active. Some agents listed as alternative options for ESBL-E cystitis are recommended as preferred agents for CRE cystitis. These agents are not preferred agents for the treatment of ESBL-E cystitis in order to preserve their activity for more invasive infections. They are, however, preferred agents for CRE cystitis because there are generally fewer treatment options available for these infections.

Aminoglycosides are almost exclusively eliminated by the renal route in their active form. A single intravenous dose of an aminoglycoside is generally effective for cystitis with minimal toxicity [23]. Individual aminoglycosides are equally effective if susceptibility is demonstrated. In general, higher percentages of CRE clinical isolates are susceptible to amikacin and plazomicin than to other aminoglycosides [50, 51]. Plazomicin may remain active against isolates resistant to amikacin.

Meropenem is a preferred agent against CRE cystitis for isolates that remain susceptible to meropenem since most of these isolates do not produce carbapenemases [45]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated.

If none of the preferred agents is active, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are alternative options for CRE cystitis [52–56]. Data are insufficient to favor one agent over the others. Although a clinical trial suggested increased mortality with cefiderocol compared with best available therapy against a variety of infections due to carbapenem-resistant gram-negative bacteria, these findings do not appear to extend to urinary

Table 3. Recommended Antibiotic Treatment Options for Carbapenem-Resistant Enterobacterales, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol
	Meropenem[a] (standard infusion): only if ertapenem-resistant, meropenem-susceptible, AND carbapenemase testing results are either not available or negative	Colistin (when no alternative options are available)
Pyelonephritis or complicated urinary tract infection[b]	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol	Once-daily aminoglycosides
	Meropenem[a] (extended-infusion): only if ertapenem-resistant, meropenem-susceptible, AND carbapenemase testing results are either not available or negative	
Infections outside of the urinary tract Resistant to ertapenem, susceptible to meropenem, AND carbapenemase testing results are either not available or negative	Meropenem[a] (extended-infusion)	Ceftazidime-avibactam
Infections outside of the urinary tract	Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam	Cefiderocol
Resistant to ertapenem, resistant to meropenem, AND carbapenemase testing results are either not available or negative		Tigecycline, eravacycline (generally limited to intra-abdominal infections)
Klebsiella pneumoniae carbapenemases identified (or carbapenemase positive but identify of carbapenemase unknown[c])	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam	Cefiderocol
		Tigecycline, eravacycline (generally limited to intra-abdominal infections)
Metallo-β-lactamase (ie, NDM, VIM, IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam, cefiderocol	Tigecycline, eravacycline (generally limited to intra-abdominal infections)
OXA-48-like carbapenemase identified	Ceftazidime-avibactam	Cefiderocol
		Tigecycline, eravacycline (generally limited to intra-abdominal infections)

[a]The majority of infections caused by carbapenem-resistant Enterobacterales (CRE) resistant to ertapenem but susceptible to meropenem are caused by organisms that do not produce carbapenemases.

[b]A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[c]The vast majority of carbapenemase-producing Enterobacterales infections in the United States are due to bacteria that produce *Klebsiella pneumoniae* carbapenemases (KPC). If a disease-causing Enterobacterales is carbapenemase-producing but the specific carbapenemase enzyme is unknown, it is reasonable to treat as if the strain is a KPC producer. If a patient is infected with a CRE strain with an unknown carbapenemase status and the patient has recently traveled from an area where metallo-β-lactamases are endemic (eg, Middle East, South Asia, Mediterranean), treatment with ceftazidime-avibactam plus aztreonam or cefiderocol as monotherapy is recommended. Preferred treatment approaches for infections caused by metallo-β-lactamase producers also provide activity against KPC and OXA (oxacillinase)-48-like enzymes.

tract infections [55, 57]. Fosfomycin use should be limited to *E. coli* cystitis as the *fosA* gene (intrinsic to certain gram-negative organisms such as *Klebsiella* species, *Enterobacter* spp., and *Serratia marcescens*) can hydrolyze fosfomycin and may lead to clinical failure [24, 25]. Randomized, controlled trial data indicate that oral fosfomycin is associated with higher clinical failure than nitrofurantoin for uncomplicated cystitis [20].

Colistin is an alternative consideration for treating CRE cystitis only if none of the above agents is an option. Colistin converts to its active form in the urinary tract. Clinicians should remain cognizant of the associated risk of nephrotoxicity [58]. Polymyxin B should not be used as treatment for CRE cystitis due to its predominantly nonrenal clearance [59].

Question 2: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections (cUTIs) caused by CRE?

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis and cUTIs caused by CRE resistant to both ertapenem and meropenem.

Extended-infusion meropenem is a preferred treatment option for pyelonephritis and cUTIs caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative.

Rationale: A cUTI is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis and cUTIs caused by CRE resistant to both ertapenem and meropenem based on randomized, controlled trials that show noninferiority of these agents to common comparator agents for UTIs [52–56]. Data are insufficient to favor one agent over the others. Although a clinical trial suggested increased mortality with cefiderocol compared with best available therapy against a variety of infections due to carbapenem-resistant gram-negative bacteria, these findings do not appear to extend to UTIs [55, 57].

Extended-infusion meropenem is a preferred agent against pyelonephritis and cUTIs caused by CRE that remain susceptible to meropenem since most of these isolates do not produce carbapenemases [45]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated.

In patients in whom the potential for nephrotoxicity is deemed acceptable, once-daily aminoglycosides for a full treatment course is an alternative option. Once-daily plazomicin was noninferior to meropenem in a randomized, controlled trial that included patients with pyelonephritis and cUTIs caused by members of the Enterobacterales order [59]. Individual aminoglycosides are equally effective if susceptibility is demonstrated. In general, higher percentages of CRE clinical isolates are susceptible to amikacin and plazomicin than to other aminoglycosides [50, 51]. Plazomicin may remain active against isolates resistant to amikacin. Oral fosfomycin does not achieve adequate concentrations in the renal parenchyma and should be avoided if the upper urinary tract is infected [28].

Question 3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative?

Recommendation: Extended-infusion meropenem is the preferred treatment for infections outside of the urinary tract caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative.

Rationale: Extended-infusion meropenem is recommended against infections outside of the urinary tract caused by CRE that remain susceptible to meropenem since most of these isolates do not produce carbapenemases [45]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated.

Ceftazidime-avibactam is an alternative treatment for ertapenem-resistant, meropenem-susceptible CRE infections outside of the urinary tract. However, the panel prefers to reserve ceftazidime-avibactam for the treatment of infections caused by CRE resistant to all carbapenems in order to preserve its activity. When carbapenemase production is present, infections should be treated as if the causative organism is meropenem-resistant, regardless of the meropenem MIC. The panel recommends against the use of meropenem-vaborbactam or imipenem-cilastatin-relebactam to treat ertapenem-resistant, meropenem-susceptible infections caused by CRE since these agents do not offer any significant advantage beyond that of extended-infusion meropenem.

Question 4: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem when carbapenemase testing results are either not available or negative?

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem when carbapenemase testing results are either not available or negative.

Rationale: In the United States, the vast majority of infections caused by CRE resistant to both ertapenem and meropenem are caused by organisms that either do not produce carbapenemases or by organisms that produce KPC-carbapenemases [45]. Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are preferred treatment options for CRE infections resistant to both ertapenem and meropenem without additional information regarding carbapenemase status. These agents are associated with improved clinical outcomes and reduced toxicity compared with other regimens commonly used to treat CRE infections, which are generally polymyxin-based [60–64].

Comparative effectiveness studies between the preferred agents are limited. An observational study that included 131 patients with CRE infections found no difference in clinical outcomes between patients treated with ceftazidime-avibactam and patients treated with meropenem-vaborbactam [65]. Significantly less clinical information is available for imipenem-cilastatin-relebactam than for the other preferred treatment options for the treatment of CRE infections. However, in vitro activity of this combination against CRE [66–68], clinical experience with imipenem-cilastatin, and the stability of relebactam as a β-lactamase inhibitor [69] suggest imipenem-cilastatin-relebactam is likely to be effective for CRE infections.

Available data suggest that the emergence of ceftazidime-avibactam resistance is more common than emergence of meropenem-vaborbactam resistance following exposure to the respective agents [65, 70–74]. As each of these drugs is used more extensively, it is anticipated that additional data on resistance and comparative effectiveness will emerge.

Cefiderocol is an alternative treatment option for CRE infections regardless of the mechanism of resistance to carbapenems. Cefiderocol has reliable in vitro activity against CRE, including isolates with otherwise highly resistant phenotypes [75–77]. In a clinical trial, cefiderocol was compared to best available therapy, which frequently consisted of colistin-based regimens, for the treatment of carbapenem-resistant gram-negative infections in 118 patients; 51% of patients were infected with CRE [57]. Mortality at 28 days was higher in the cefiderocol arm. These findings were most striking for the treatment of pneumonia and bloodstream infections. Until more data are available to define subpopulations in whom cefiderocol can be used effectively and safely beyond the urinary tract, the panel recommends that this agent be reserved for CRE infections for which preferred agents are unavailable due to intolerance or resistance.

If a patient is infected with a CRE strain with unknown carbapenemase status and the patient recently traveled from an area where metallo-β-lactamases are endemic (eg, Middle East, South Asia, Mediterranean) [78], treatment with ceftazidime-avibactam plus aztreonam or cefiderocol monotherapy is recommended. Preferred treatment approaches for infections caused by metallo-β-lactamase producers also provide activity against bacteria that produce KPCs or OXA-48–like enzymes.

In patients with intra-abdominal infections, tigecycline and eravacycline are acceptable monotherapy options [79–81]; high-dose tigecycline may be more effective than standard-dose tigecycline for complicated intra-abdominal infections, as listed in Table 1. Their activity is independent of the presence or type of carbapenemases. The use of tigecycline or eravacycline should generally be limited to the treatment of intra-abdominal infections. These agents achieve rapid tissue distribution following administration, resulting in limited concentration in the urine and poor serum concentrations [82].

Question 5: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if carbapenemase production is present?

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for KPC-producing infections outside of the urinary tract. Ceftazidime-avibactam in combination with aztreonam or cefiderocol as monotherapy are preferred treatment options for NDM and other metallo-β-lactamase–producing CRE infections. Ceftazidime-avibactam is the preferred treatment for OXA-48-like–producing CRE infections.

Rationale: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam provide activity against Enterobacterales that produce KPC enzymes, the most common carbapenemases in the United States [66, 67, 83–85]. If a disease-causing Enterobacterales is carbapenemase-producing but the specific carbapenemase enzyme is unknown, it is reasonable to treat as if the strain is a KPC producer. Rationale supporting these recommendations is provided in Question 4.

If a metallo-β-lactamase (ie, NDM, VIM, or IMP) is identified, preferred antibiotic options include ceftazidime-avibactam plus aztreonam or cefiderocol monotherapy [86–90]. Clinical outcomes data comparing these 2 treatment strategies are not available.

If an OXA-48–like enzyme is identified, ceftazidime-avibactam is preferred, and cefiderocol is an alternative option. Meropenem-vaborbactam and imipenem-cilastatin-relebactam have limited to no activity against CRE-producing OXA-48-like enzymes.

In patients with intra-abdominal infections, tigecycline and eravacycline are acceptable monotherapy options [79–81]. The use of tigecycline or eravacycline should generally be limited to the treatment of intra-abdominal infections for reasons discussed in the rationale for Question 4. High-dose tigecycline may be more effective than standard-dose tigecycline for complicated intra-abdominal infections, as listed in Table 1.

Question 6: What is the role of polymyxins for the treatment of infections caused by CRE?

Recommendation: Polymyxin B and colistin should be avoided for the treatment of infections caused by CRE. Colistin can be considered as a last resort for uncomplicated CRE cystitis.

Rationale: Observational and randomized, controlled trial data indicate increased mortality and excess nephrotoxicity associated with polymyxin-based regimens relative to comparator agents [60–62, 64]. Concerns about the clinical effectiveness of polymyxins and accuracy of in vitro polymyxin susceptibility testing led the Clinical and Laboratory Standards Institute to eliminate a susceptible category for colistin and polymyxin B [19]. The panel recommends that these agents be avoided for the treatment of CRE infections, with the exception of colistin as a last resort agent against CRE cystitis. Polymyxin B should not be used as treatment for CRE cystitis due to its predominantly nonrenal clearance [59].

Question 7: What is the role of combination antibiotic therapy for the treatment of infections caused by CRE?

Recommendation: Combination antibiotic therapy (ie, the use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, or polymyxin) is not routinely recommended for the treatment of infections caused by CRE.

Rationale: Although empiric combination antibiotic therapy to broaden the likelihood of at least 1 active therapeutic agent for patients at risk for CRE infections is reasonable, data do not indicate that continued combination therapy, once the β-lactam agent has demonstrated in vitro activity, offers any additional benefit [91]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [91].

Observational data and clinical trials that compare ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam to combination regimens for the treatment of CRE infections have not shown the latter to have added value [60–64]. Data from randomized trials that compare these agents as monotherapy and as a component of combination therapy (eg, ceftazidime-avibactam vs ceftazidime-avibactam and amikacin) are not available. However, based on available outcomes data, clinical experience, and known toxicities associated with aminoglycosides, fluoroquinolones, and polymyxins, routine combination therapy for CRE infections is not recommended when susceptibility to a preferred β-lactam agent has been demonstrated.

PSEUDOMONAS AERUGINOSA WITH DIFFICULT-TO-TREAT RESISTANCE

The CDC reports that 32 600 cases of multidrug-resistant *P. aeruginosa* infection occurred in patients hospitalized in the United States in 2017, resulting in 2700 deaths [2]. Multidrug resistance is defined as nonsusceptibility to at least 1 antibiotic in at least 3 classes for which *P. aeruginosa* susceptibility is generally expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems. In 2018, the concept of "difficult-to-treat" resistance (DTR) was proposed [5]. In this guidance document, DTR is defined as *P. aeruginosa* that exhibits nonsusceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin. Table 4 outlines preferred and alternative treatment recommendations for DTR-*P. aeruginosa* infections. Treatment recommendations for DTR-*P. aeruginosa* infections assume in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 1: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by DTR-*P. aeruginosa*?

Recommendation: Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, cefiderocol, or a single dose of an aminoglycoside are the preferred treatment options for uncomplicated cystitis caused by DTR-*P. aeruginosa*.

Rationale: Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for uncomplicated DTR *P. aeruginosa* cystitis based on randomized, controlled trials that showed noninferiority of these agents to common comparator agents for urinary tract infections [53, 55, 56, 92]. Data are insufficient to favor one of the agents over the others, and available trials generally do not include patients infected by pathogens with DTR phenotypes. Although a clinical trial suggested increased mortality with cefiderocol compared with best available therapy against a variety of infections due to carbapenem-resistant gram-negative bacteria, these findings do not appear to extend to urinary tract infections [55, 57].

A single dose of an aminoglycoside is also a preferred treatment option. Aminoglycosides are nearly exclusively eliminated by the renal route in their active form. A single intravenous dose of an aminoglycoside is generally effective for cystitis, with minimal toxicity, but robust trial data to formally evaluate their activity for cystitis are lacking [23]. Plazomicin is unlikely to provide any incremental benefit against DTR-*P. aeruginosa* if resistance to all other aminoglycosides is demonstrated [93].

Colistin, but not polymyxin B, is an alternate consideration for treating DTR-*P. aeruginosa* cystitis as it converts to its active form in the urinary tract [58]. Clinicians should remain cognizant of the associated risk of nephrotoxicity. The panel does not recommend the use of oral fosfomycin for DTR-*P. aeruginosa* cystitis as it is associated with a high likelihood of clinical failure [94, 95]. This is, in part, due to the presence of the *fosA* gene, which is intrinsic to *P. aeruginosa* [24].

Table 4. Recommended Antibiotic Treatment Options for Difficult-to-Treat *Pseudomonas aeruginosa*, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol, or a single dose of an aminoglycoside	Colistin
Pyelonephritis or complicated urinary tract infection[a]	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol	Once-daily aminoglycosides
Infections outside of the urinary tract	Ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam	Cefiderocol Aminoglycoside monotherapy: limited to uncomplicated bloodstream infections with complete source control[b]

[a]A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[b]Uncomplicated bloodstream infections include a bloodstream infection that is due to a urinary source or a catheter-related bloodstream infection with removal of the infected vascular catheter.

Question 2: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections (cUTI) caused by DTR-*P. aeruginosa*?

Recommendation: Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are the preferred treatment options for pyelonephritis and cUTIs caused by DTR-*P. aeruginosa*.

Rationale: A cUTI is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient. Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for DTR-*P. aeruginosa* pyelonephritis and cUTIs based on randomized, controlled trials that showed noninferiority of these agents to common comparator agents [53, 55, 56, 92], as discussed in Question 1. In patients in whom the potential for nephrotoxicity is deemed acceptable, once-daily aminoglycosides is an alternative option. Plazomicin is unlikely to provide any incremental benefit against DTR-*P. aeruginosa* if resistance to all other aminoglycosides is demonstrated [93]. Oral fosfomycin should be avoided for DTR-*P. aeruginosa* pyelonephritis and cUTIs. This is because of the presence of the *fosA* gene, which is intrinsic to *P. aeruginosa* and confers fosfomycin resistance, and because oral fosfomycin does not achieve adequate concentrations in the renal parenchyma [24, 28].

Question 3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*?

Recommendation: Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam as monotherapy are the preferred treatment options for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*.

Rationale: Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam as monotherapy are preferred options for the treatment of DTR-*P. aeruginosa* infections outside of the urinary tract based on known in vitro activity, observational studies, and clinical trial data [53, 64, 83, 85, 96–105]. The majority of these observational studies and clinical trials did not include patients with DTR-*P. aeruginosa* infections. Clinical outcomes studies that compare the effectiveness of these 3 agents for DTR-*P. aeruginosa* infections are not available.

The percentage of *P. aeruginosa* clinical isolates that are susceptible to ceftolozane-tazobactam is generally higher than percentages susceptible to comparator agents. This is likely because ceftolozane does not rely on an inhibitor to restore susceptibility to an otherwise inactive drug (ie, ceftolozane has independent activity against DTR-*P. aeruginosa*). Neither ceftazidime nor imipenem is active against DTR-*P. aeruginosa*. Avibactam and relebactam expand activity of these agents mainly through inhibition of AmpC, but other complex resistance mechanisms are unlikely to be impacted. Since ceftolozane-tazobactam and ceftazidime-avibactam are similar in their mechanisms of action [106], cross-resistance between these agents can be observed [107].

Cefiderocol is an alternative treatment option. Cefiderocol has reliable in vitro activity against *P. aeruginosa*, including isolates with otherwise highly resistant phenotypes [75–77]. In a clinical trial, cefiderocol was compared to best available therapy, which frequently consisted of colistin-based regimens, for the treatment of carbapenem-resistant gram-negative infections in 118 patients; 24% of patients were infected with *P. aeruginosa* [57]. Mortality at 28 days was higher in the cefiderocol arm. These findings were most striking for the treatment of pneumonia and bloodstream infections. Until more data are available to define subpopulations in whom cefiderocol can be used effectively and safely beyond the urinary tract, the panel recommends that this agent be reserved for DTR-*P. aeruginosa* infections in which preferred agents are unavailable due to intolerance or resistance.

Aminoglycoside monotherapy is an alternative option that should be limited to uncomplicated bloodstream infections (ie, urinary source or other sources for which control is achieved, such as the removal of an infected vascular catheter) when no preferred treatment option is available. Plazomicin is unlikely to provide any incremental benefit against DTR-*P. aeruginosa* if resistance to all other aminoglycosides is demonstrated [93].

Question 4: What is the role of combination antibiotic therapy for the treatment of infections caused by DTR-*P. aeruginosa*?

Recommendation: Combination antibiotic therapy is not routinely recommended for infections caused by DTR-*P. aeruginosa* if in vitro susceptibility to a first-line antibiotic (ie, ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam) has been confirmed.

Rationale: Although empiric combination antibiotic therapy (ie, the addition of an aminoglycoside or polymyxin to a β-lactam agent) to broaden the likelihood of at least 1 active therapeutic agent for patients at risk for DTR-*P. aeruginosa* infections is reasonable, data do not indicate that continued combination therapy, once the β-lactam agent has demonstrated in vitro activity, offers any additional benefit over monotherapy with the β-lactam [91]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [91].

Observational data and clinical trials that have compared ceftolozane-tazobactam and imipenem-cilastatin-relebactam, usually given as monotherapy, to combination regimens for drug-resistant *P. aeruginosa* infections have not shown the latter to have added value [64, 99]. Randomized trial data that compared ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam as monotherapy and as a component of combination therapy are not available (eg, ceftazidime-avibactam vs ceftazidime-avibactam and amikacin). Based on available outcomes data, clinical experience, and known toxicities associated with aminoglycosides and polymyxins, the

panel agrees that combination therapy is not routinely recommended for DTR-*P. aeruginosa* infections when susceptibility to a preferred β-lactam agent has been demonstrated.

If no preferred agent demonstrates activity against DTR-*P. aeruginosa*, an aminoglycoside (if susceptibility is demonstrated) can be considered in combination with ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam, preferentially selecting the β-lactam-β-lactamase inhibitor agent for which the MIC is closest to its susceptibility breakpoint. For example, if ceftolozane-tazobactam and ceftazidime-avibactam MICs against a DTR-*P. aeruginosa* isolate are both >128/4 μg/mL (highly resistant [19, 108]) and the imipenem-cilastatin-relebactam MIC is 4/4 μg/mL (intermediate category [108]), imipenem-cilastatin-relebactam in combination with an active aminoglycoside should be favored. Data that demonstrate a benefit to this approach are lacking, and it should be considered as a last resort. Similarly, data that indicate whether this approach will yield favorable clinical outcomes compared with cefiderocol, either as monotherapy or combination therapy, are lacking. If no aminoglycoside demonstrates in vitro activity, polymyxin B can be considered in combination with the β-lactam-β-lactamase inhibitor. Polymyxin B is preferred over colistin for nonurinary tract infections because it is not administered as a prodrug and therefore can achieve more reliable plasma concentrations than colistin and it has a reduced risk of nephrotoxicity, although limitations across studies preclude accurate determination of the differential risk of nephrotoxicity [109–114].

CONCLUSIONS

The field of AMR is dynamic and rapidly evolving, and the treatment of antimicrobial-resistant infections will continue to challenge clinicians. As newer antibiotics against resistant pathogens are incorporated into clinical practice, we are learning more about their effectiveness and propensity to develop resistance. This AMR Treatment Guidance will be updated through an iterative review process that will incorporate new evidence-based data. Furthermore, the panel will expand recommendations to include other problematic gram-negative pathogens in future versions of this guidance document.

Notes

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