# Infectious Diseases Society of America 2022 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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# Abstract

**Background:** The Infectious Diseases Society of America (IDSA) is committed to providing up-to-date guidance on the treatment of antimicrobial-resistant infections. The initial guidance document on 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*) was published on September 17th, 2020. Over the past year, there have been a number of important publications furthering our understanding of the management of ESBL-E, CRE, and DTR-*P. aeruginosa* infections, prompting a rereview of the literature and this updated guidance document.

**Methods:** A panel of six infectious diseases specialists with expertise in managing antimicrobial-resistant infections reviewed, updated, and expanded previously developed questions and recommendations about the treatment of ESBL-E, CRE, and DTR-*P. aeruginosa* infections. Because of differences in the epidemiology of resistance and availability of specific anti-infectives internationally, this document focuses on the treatment of infections in the United States.

**Results:** Preferred and alternative treatment recommendations are provided with accompanying rationales, assuming the causative organism has been identified and antibiotic susceptibility results are known. Approaches to empiric treatment, duration of therapy, and other management considerations are also discussed briefly. Recommendations apply for both adult and pediatric populations.

**Conclusions:** The field of antimicrobial resistance is highly dynamic. Consultation with an infectious diseases specialist is recommended for the treatment of antimicrobial-resistant infections. This document is current as of October 24th, 2021. The most current versions of IDSA documents, including dates of publication, are available at www.idsociety.org/practice-guideline/amr-guidance/.



**Key words**: Antimicrobial resistance; ceftolozane-tazobactam; ceftazidime-avibactam; cefiderocol; imipenem-cilastatin-relebactam; meropenem-vaborbactam



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# Introduction

The rise in antimicrobial resistance (AMR) continues to be a global crisis. Collectively, antimicrobial-resistant pathogens caused more than 2.8 million infections and over 35,000 deaths annually from 2012 through 2017, according to the 2019 Centers for Disease Control and Prevention (CDC) Antibiotic Resistance Threats in the United States Report [1]. The Infectious Diseases Society of America (IDSA) identified the development and dissemination of clinical practice guidelines and other guidance products for clinicians as a top initiative in its 2019 Strategic Plan [2]. 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, which are based on systematic literature reviews and employ rigorous GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology. As an alternative to practice guidelines, IDSA endorsed developing more narrowly focused guidance documents for the treatment of difficult-to-manage infections. Guidance documents will be prepared by a small team of experts, who will answer questions about treatment based on a comprehensive (but not necessarily systematic) review of the literature, clinical experience, and expert opinion. Documents will not include formal grading of evidence, and they will be made available and updated at least annually online.

In the present document, guidance is provided on 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*) [3]. These pathogens have been designated urgent or serious threats by the CDC [1]. Each pathogen causes a wide range of infections that are encountered in United States hospitals of all sizes, and that carry with them significant morbidity and mortality.

Guidance is presented in the form of answers to a series of clinical questions for each pathogen. Although brief descriptions of notable clinical trials, resistance mechanisms, and susceptibility testing methods are included, the document does not provide a comprehensive review of these topics. Due to differences in the molecular epidemiology of resistance and availability of specific anti-infectives internationally, treatment recommendations are geared toward antimicrobial-resistant infections in the United States. The content of this document is current as of October 24$^{th}$, 2021; updates will be provided periodically.

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# Methodology

IDSA convened a panel of six actively practicing infectious diseases specialists with clinical and research expertise in the treatment of antimicrobial-resistant bacterial infections. Through a series of virtual meetings, the panel developed commonly encountered treatment questions and corresponding answers for each pathogen group. Answers include a brief discussion of the rationale supporting the recommendations. This guidance document applies to both adult and pediatric populations. Suggested antibiotic dosing for adults with antimicrobial-resistant infections, assuming normal renal and hepatic function, is provided in **Table 1**.

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**Table 1.** Suggested dosing of antibiotics for the treatment of infections caused by antimicrobial-resistant organisms

| Agent | Adult Dosage (assuming normal renal and liver function [a]) | Target Organisms [b,c] |
|---|---|---|
| Amikacin | **Cystitis**: 15 mg/kg/dose [d] IV once<br><br>**All other infections**: 20 mg/kg/dose [d] IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation | ESBL-E, AmpC-E, CRE, DTR-*P. aeruginosa* |
| Ampicillin-sulbactam | 9 g IV q8h over 4 hours **OR** 27 g IV q24h as a continuous infusion<br><br>For mild infections caused by CRAB isolates susceptible to ampicillin-sulbactam, it is reasonable to administer 3g IV q4h – particularly if intolerance or toxicities preclude the use of higher dosages. | CRAB |
| Cefepime | **Cystitis:** 1 g IV q8h<br><br>**All other infections:** 2 g IV q8h, infused over 3 hours | AmpC-E |
| Cefiderocol | 2 g IV q8h, infused over 3 hours | CRE, DTR-*P. aeruginosa*, CRAB, *S. maltophilia* |
| Ceftazidime-avibactam | 2.5 g IV q8h, infused over 3 hours | CRE, DTR-*P. aeruginosa* |
| Ceftazidime-avibactam and aztreonam | **Ceftazidime-avibactam:** 2.5 g IV q8h, infused over 3 hours<br>*PLUS*<br>**Aztreonam:** 2 g IV q8h, infused over 3 hours, administered at the same time as ceftazidime-avibactam | Metallo-β-lactamase-producing CRE, *S. maltophilia* |
| Ceftolozane-tazobactam | **Cystitis:** 1.5 g IV q8h, infused over 1 hour<br><br>**All other infections:** 3 g IV q8h, infused over 3 hours | DTR-*P. aeruginosa* |
| Ciprofloxacin | **ESBL-E or AmpC infections:** 400 mg IV q8h-q12h **OR** 500 – 750 mg PO q12h<br><br>**DTR-*P. aeruginosa*, pneumonia:** 400 mg IV q8h **OR** 750 mg PO q12h | ESBL-E, AmpC-E |
| Colistin | Refer to international consensus guidelines on polymyxins [e] | CRE cystitis, DTR-*P. aeruginosa* cystitis, CRAB cystitis |
| Eravacycline | 1 mg/kg/dose IV q12h | CRE, CRAB |
| Ertapenem | 1 g IV q24h, infused over 30 minutes | ESBL-E, AmpC-E |
| Fosfomycin | **Cystitis:** 3 g PO x 1 dose | ESBL-*E. coli* cystitis |

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| Agent | Adult Dosage (assuming normal renal and liver function [a]) | Target Organisms [b,c] |
|---|---|---|
| Gentamicin | **Cystitis**: 5 mg/kg/dose [d] IV once<br><br>**All other infections:** 7 mg/kg/dose [d] IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation | ESBL-E, AmpC-E, CRE, DTR-*P. aeruginosa* |
| Imipenem-cilastatin | **Cystitis (standard infusion)**: 500 mg IV q6h, infused over 30 minutes<br><br>**All other ESBL-E or AmpC-E infections:** 500 mg IV q6h, infused over 30 minutes<br><br>**All other CRE and CRAB infections:** 500 mg IV q6h, infused over 3 hours | ESBL-E, AmpC-E, CRE, CRAB |
| Imipenem-cilastatin-relebactam | 1.25 g IV q6h, infused over 30 minutes | CRE, DTR-*P. aeruginosa* |
| Levofloxacin | 750 mg IV/PO q24h | ESBL-E, AmpC-E, *S. maltophilia* |
| Meropenem | **Cystitis (standard infusion)**: 1 g IV q8h, infused over 30 minutes<br><br>**All other ESBL-E or AmpC-E infections:** 1-2 g IV q8h, infused over 30 minutes<br><br>**All other CRE and CRAB infections:** 2 g IV q8h, infused over 3 hours | ESBL-E, AmpC-E, CRE, CRAB |
| Meropenem-vaborbactam | 4 g IV q8h, infused over 3 hours | CRE |
| Minocycline | 200 mg IV/PO q12h | CRAB, *S. maltophilia* |
| Nitrofurantoin | **Cystitis:** Macrocrystal/monohydrate (Macrobid®) 100 mg PO q12h<br><br>**Cystitis:** Oral suspension: 50 mg PO q6h | ESBL-E cystitis, AmpC-E cystitis |
| Plazomicin | **Cystitis:** 15 mg/kg [d] IV x 1 dose<br><br>**All other infections:** 15 mg/kg [d] IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation | ESBL-E, AmpC-E, CRE, DTR-*P. aeruginosa* |
| Polymyxin B | Refer to international consensus guidelines on polymyxins [e] | DTR-*P. aeruginosa*, CRAB |
| Tigecycline | 200 mg IV x 1 dose, then 100 mg IV q12h | CRE, CRAB, *S. maltophilia* |

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| Agent | Adult Dosage (assuming normal renal and liver function [a]) | Target Organisms [b,c] |
|---|---|---|
| Tobramycin | **Cystitis**: 5 mg/kg/dose [d] IV x 1 dose<br><br>**All other infections**: 7 mg/kg/dose [d] IV x 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation | ESBL-E, AmpC-E, CRE, DTR-*P. aeruginosa* |
| Trimethoprim-sulfamethoxazole | **Cystitis**: 160 mg (trimethoprim component) IV/PO q12h<br><br>**Other infections**: 8-12 mg/kg/day (trimethoprim component) IV/PO divided q8-12h (consider maximum dose of 960 mg trimethoprim component per day) | ESBL-E, AmpC-E, *S. maltophilia* |

**AmpC-E**: AmpC β-lactamase-producing Enterobacterales; **CRAB**: Carbapenem-resistant *Acinetobacter baumannii*; **CRE**: Carbapenem-resistant Enterobacterales; **DTR-*P. aeruginosa***: *Pseudomonas aeruginosa* with difficult-to-treat resistance; ***E. coli***: *Escherichia coli*; **ESBL-E**: Extended-spectrum β-lactamase-producing Enterobacterales; **IV**: Intravenous; **MIC**: Minimum inhibitory concentration; **PO**: By mouth; **q4h**: Every 4 hours; **q6h**: Every 6 hours; **q8h**: Every 8 hours; **q12h**: Every 12 hours; **q24h**: Every 24 hours; ***S. maltophilia***: *Stenotrophomonas maltophilia*

**Explanations/References**

a Dosing suggested for several agents in table differs from dosing recommended by the U.S. Food and Drug Administration.

b Target organisms limited to the following organisms and generally only after susceptibility has been demonstrated: ESBL-E, AmpC-E, CRE, DTR-*P. aeruginosa*, CRAB, and *S. maltophilia*.

c For additional guidance on the treatment of AmpC-E, CRAB, and *S. maltophilia*, refer to: https://www.idsociety.org/practice-guideline/amr-guidance-2.0/.

d Use adjusted body weight for patients >120% of ideal body weight for aminoglycoside dosing.

e Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy **2019**; 39(1): 10-39.

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# General Management Recommendations

Treatment recommendations in this guidance document assume that the causative organism has been identified and that *in vitro* activity of antibiotics is demonstrated. Assuming two antibiotics are equally effective, safety, cost, convenience, and local formulary availability are important considerations in selecting a specific agent. The panel recommends that infectious diseases specialists and physician or pharmacist members of the local antibiotic stewardship program are involved in the management of patients with infections caused by antimicrobial-resistant organisms.

In this document, the term complicated urinary tract infection (cUTI) refers to UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in an adolescent or adult male. In general, the panel suggests cUTI be treated with similar agents and for similar treatment durations as pyelonephritis. For cUTI where the source has been controlled (e.g., removal of a Foley catheter) and ongoing concerns for urinary stasis or indwelling urinary hardware are no longer present, it is reasonable to select antibiotic agents and treatment durations similar to uncomplicated cystitis.

***Empiric Therapy***

Empiric treatment decisions should be guided by the most likely pathogens, severity of illness of the patient, the likely source of the infection, and any additional patient-specific actors (e.g., severe penicillin allergy, chronic kidney disease). When determining empiric treatment for a given patient, clinicians should also consider: (1) previous organisms identified from the patient and associated antibiotic susceptibility data in the last six months, (2) antibiotic exposures within the past 30 days, and (3) local susceptibility patterns for the most likely pathogens. Empiric decisions should be refined based on the identity and susceptibility profile of the pathogen.

***Duration of Therapy***

Recommendations on durations of therapy are not provided, but clinicians are advised that the duration of therapy should not differ for infections caused by organisms with resistant phenotypes compared to infections caused by more susceptible phenotypes. 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 [4]. If an antibiotic not active against the causative organism was administered empirically for cystitis, but clinical improvement nonetheless occurred, the panelists agree that it is generally

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not necessary to repeat a urine culture, change the antibiotic regimen, or extend the planned treatment course. However, for all other infections, 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. Finally, whenever possible, oral step-down therapy should be considered, particularly if the following criteria are met: (1) susceptibility to an appropriate oral agent is demonstrated, (2) the patient is hemodynamically stable, (3) reasonable source control measures have occurred, and (4) concerns about insufficient intestinal absorption are not present [5].

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# Extended-spectrum β-lactamase-Producing Enterobacterales

The incidence of ESBL-E identified in bacterial cultures in the United States increased by 53% from 2012 to 2017, in large part due to increased community-acquired infections [6]. ESBLs are enzymes that inactivate most penicillins, cephalosporins, and aztreonam. EBSL-E generally remain susceptible to carbapenems. ESBLs do not inactivate non-β-lactam agents (e.g., ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin). However, organisms carrying ESBL genes often harbor 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* [7-9]. CTX-M enzymes, particularly CTX-M-15, are the most common ESBLs in the United States [8]. ESBLs other than CTX-M with unique hydrolyzing abilities are also present, including variants of narrow-spectrum TEM and SHV β-lactamases with amino acid substitutions, but have undergone less rigorous clinical investigation than CTX-M enzymes [10-13]. Routine EBSL testing is not performed by most clinical microbiology laboratories [14, 15]. Rather, non-susceptibility to ceftriaxone (i.e., ceftriaxone minimum inhibitory concentrations [MICs] ≥2 mcg/mL), is often used as a proxy for ESBL production, although this threshold has limitations with specificity as organisms not susceptible to ceftriaxone for reasons other than ESBL production may be falsely presumed to be ESBL-producers [16, 17]. For this guidance document, ESBL-E will refer to presumed or confirmed ESBL-producing *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*. Treatment recommendations for ESBL-E infections listed below assume that *in vitro* activity of preferred and alternative antibiotics has been demonstrated.

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## 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 uncomplicated cystitis, including uncomplicated ESBL-E cystitis [4, 18, 19]. Although carbapenems and the fluoroquinolones ciprofloxacin or levofloxacin are effective agents against ESBL-E cystitis [20, 21], their use for uncomplicated cystitis is discouraged when other safe and effective options are available. Limiting use of these agents preserves their activity for future infections when treatment options may be more restricted. Moreover, limiting their use reduces the risk of associated toxicities, particularly with the fluoroquinolones, which have been associated with an increased risk for prolonged QTc intervals, tendinitis and tendon rupture, aortic dissections, seizures, peripheral neuropathy, and *Clostridioides difficile* infections, compared to other antibiotics [22-25].

Amoxicillin-clavulanate, single-dose aminoglycosides, and oral fosfomycin (for *E. coli* only) are alternative treatment options for uncomplicated ESBL-E cystitis. ESBL-E may test susceptible to amoxicillin-clavulanate and observational studies demonstrated clinical success with the use of amoxicillin-clavulanate for ESBL-E infections [26, 27]. A randomized controlled trial (RCT) compared a three-day regimen of amoxicillin-clavulanate to a three-day course of ciprofloxacin for 370 women with uncomplicated *E. coli* cystitis [20]. Clinical cure was observed in 58% and 77% of the women randomized to the amoxicillin-clavulanate and ciprofloxacin arms, respectively. The higher failure rates with amoxicillin-clavulanate appear associated with persistent vaginal bacterial colonization, which occurred in 45% and 10% of patients in the amoxicillin-clavulanate and ciprofloxacin arms, respectively [20]. Although the proportion of women in the trial infected with ESBLE-E strains is not available, the panel suggests caution with the use of amoxicillin-clavulanate for the treatment of uncomplicated ESBL-E cystitis.

Aminoglycosides are nearly exclusively eliminated by the renal route in their active form. A single intravenous dose is generally effective for uncomplicated cystitis, with minimal toxicity, but robust clinical trial data are lacking [28].

Oral fosfomycin is an alternative agent exclusively for treatment of ESBL-producing *E. coli* uncomplicated cystitis as the *fosA* gene, intrinsic to *K. pneumoniae* and several other Gram-negative

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organisms, can hydrolyze the drug and may lead to clinical failure [29, 30]. Randomized controlled trial data indicate that oral fosfomycin is associated with higher clinical failure than nitrofurantoin for uncomplicated cystitis [18].

The panel does not recommend prescribing doxycycline for the treatment of ESBL-E cystitis. Two clinical outcomes studies, published more than 40 years ago, demonstrated that oral tetracyclines may be effective for the treatment of urinary tract infections (UTIs) [31, 32]. Both of these studies, however, primarily focused on *P. aeruginosa*, an organism not susceptible to oral tetracyclines, questioning the impact that antibiotic therapy had on clinical cure. Doxycycline is primarily eliminated through the intestinal tract and its urinary excretion is limited [33]. Until more robust data demonstrating the clinical effectiveness of oral doxycycline for the treatment of ESBL-E cystitis are available, the panel recommends against use of doxycycline for this indication. The roles of piperacillin-tazobactam, cefepime, and the cephamycins for the treatment of uncomplicated cystitis are discussed in **Question 4**, **Question 5**, and **Question 6**.

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## Question 2: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections 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

Carbapenems, ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole are all preferred treatment options for patients with ESBL-E pyelonephritis and cUTIs based on the ability of these agents to achieve high concentrations in the urine, RCT results, and clinical experience [34-37]. 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 use of carbapenem exposure will preserve their activity for future antimicrobial-resistant infections.

In patients in whom the potential for nephrotoxicity is deemed acceptable, once-daily aminoglycosides for a full treatment course are an alternative option for the treatment of pyelonephritis or cUTI [38]. Once-daily plazomicin was noninferior to meropenem in an RCT that included patients with pyelonephritis and cUTIs caused by the Enterobacterales [39]. Individual aminoglycosides are equally effective if susceptibility is demonstrated.

Nitrofurantoin and oral fosfomycin do not achieve adequate concentrations in the renal parenchyma and should be avoided for pyelonephritis and cUTI [40, 41]. However, fosfomycin is an alternative option for the treatment of prostatitis caused by ESBL-producing *E. coli* when preferred options (i.e., carbapenems, fluoroquinolones, or trimethoprim-sulfamethoxazole) cannot be tolerated or do not test susceptible [42-44]. Fosfomycin, dosed at 3 g orally daily for one week, followed by 3 g orally every 48 hours for 6 to 12 weeks, was associated with clinical cure in 82% of patients in an observational study of 44 males with chronic bacterial prostatitis [42]. Fosfomycin should be avoided for prostatitis caused by Gram-negative organisms other than *E. coli* (**Question 1**).

Doxycycline is not recommended for the treatment of ESBL-E pyelonephritis or cUTIs due to its limited urinary excretion and limited published comparative effectiveness studies (**Question 1**) [33]. The roles of piperacillin-tazobactam, cefepime, and the cephamycins for the treatment of pyelonephritis and cUTIs are discussed in **Question 4**, **Question 5**, and **Question 6**.

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## 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. After appropriate clinical response is achieved, transitioning to oral fluoroquinolones or trimethoprim-sulfamethoxazole should be considered, if susceptibility is demonstrated.

### Rationale

A carbapenem is recommended as first-line treatment of ESBL-E infections outside of the urinary tract, based primarily on data from a large clinical trial [34]. The clinical trial randomized 391 patients with bloodstream infections due to ceftriaxone non-susceptible *E. coli* or *K. pneumoniae* (87% later confirmed to have ESBL genes) to piperacillin-tazobactam 4.5 g intravenously every six hours or meropenem 1 g intravenously every eight hours, both as standard infusions. The primary outcome of 30-day mortality occurred in 12% and 4% of patients receiving piperacillin-tazobactam and meropenem, respectively [34]. Trial data were subsequently reanalyzed only including patients with available clinical isolates against which piperacillin-tazobactam MICs were ≤16 mcg/mL by broth microdilution, the reference standard for antimicrobial susceptibility testing [45]. Reanalyzing the data from 320 patients, 30-day mortality was observed in 11% vs. 4% of those in piperacillin-tazobactam and meropenem arms, respectively. Although the absolute risk difference was attenuated and no longer significant in the reanalysis (i.e., the 95% confidence interval ranged from −1% to 10%) [45], the panel still recommends carbapenem therapy as the preferred treatment of ESBL-producing bloodstream infections due to the overall direction of the risk difference. Comparable clinical trial data are not available for ESBL-E infections of other body sites. Nevertheless, the panel suggests 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 [46, 47]. Based on the known bioavailability and sustained serum concentrations of oral fluoroquinolones and trimethoprim-sulfamethoxazole, these agents should be treatment considerations for patients with ESBL-E infections if (1) susceptibility to one of these agents is demonstrated, (2) the patient is

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hemodynamically stable, (3) reasonable source control measures have occurred, and (4) concerns about insufficient intestinal absorption are not present [5].

Clinicians should avoid oral step-down to nitrofurantoin, fosfomycin, amoxicillin-clavulanate, doxycycline, or omadacycline for ESBL-E bloodstream infections. Nitrofurantoin and fosfomycin achieve poor serum concentrations [40, 41]. Amoxicillin-clavulanate and doxycycline achieve unreliable serum concentrations [33, 48]. Omadacycline is a tetracycline derivative with an oral formulation that may exhibit activity against ESBL-producing Enterobacterales isolates but has an unfavorable pharmacokinetic-pharmacodynamic profile [49, 50]. Until more clinical data are available investigating omadacycline's role for the treatment of ESBL-E infections, the panel recommends against its use for this indication.

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## Question 4: Is there a role for piperacillin-tazobactam in the treatment of infections caused by ESBL-E?

**Recommendation:** If piperacillin-tazobactam was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary. The panel suggests carbapenems, fluoroquinolones, or trimethoprim-sulfamethoxazole rather than piperacillin-tazobactam for the treatment of ESBL-E pyelonephritis and cUTI, with the understanding that the risk of clinical failure with piperacillin-tazobactam may be low. Piperacillin-tazobactam is not recommended for the treatment of infections outside of the urinary tract caused by ESBL-E, even if susceptibility to piperacillin-tazobactam is demonstrated.

### Rationale

Piperacillin-tazobactam demonstrates *in vitro* activity against a number of ESBL-E [51]. Observational studies have had conflicting results regarding the effectiveness of piperacillin-tazobactam for the treatment of ESBL-E infections. An RCT of ESBL-E bloodstream infections indicated inferior results with piperacillin-tazobactam compared to carbapenem therapy (**Question 3**) [34]. A second RCT investigating the role of piperacillin-tazobactam for the treatment of ESBL-E bloodstream infections is ongoing [52]. If piperacillin-tazobactam was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary, as uncomplicated cystitis often resolves on its own. At least three observational studies have compared the efficacy of piperacillin-tazobactam and carbapenems for the treatment of ESBL-E pyelonephritis or cUTI [53-55]. The most robust observational study included 186 hospitalized patients from five hospitals with pyelonephritis or cUTI caused by *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*, with confirmation of the presence of ESBL genes in all isolates. This study identified no difference in the resolution of clinical symptoms or 30-day mortality between the groups [53]. A randomized, open-label clinical trial investigating this question was also conducted [56]. The trial included 66 patients with ESBL-producing *E. coli* pyelonephritis or cUTI (with confirmation of the presence of an ESBL gene) randomized to either piperacillin-tazobactam 4.5 g every six hours or ertapenem 1 g every 24 hours. Clinical success was similar between both groups at 94% for piperacillin-tazobactam and 97% for ertapenem. These studies suggest non-inferiority between piperacillin-tazobactam and carbapenems for pyelonephritis or cUTIs.

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In the subgroup of 231 patients with ESBL-E bloodstream infections from a urinary source in the aforementioned RCT comparing the outcomes of patients with *E. coli* or *K. pneumoniae* bloodstream infections treated with piperacillin-tazobactam or meropenem (**Question 3**), higher mortality was identified in the piperacillin-tazobactam group (7% vs. 3%) [34], although it did not attain statistical significance. Although the panel is unable to state that piperacillin-tazobactam should be avoided for pyelonephritis or cUTIs, the panel continues to have concerns with the use of piperacillin-tazobactam for the treatment of ESBL-E infections, even if limited to UTIs, and prefers the use of carbapenem therapy (or oral fluoroquinolones or trimethoprim-sulfamethoxazole, if susceptible) [**Question 2**]).

Observational studies have had conflicting results regarding the effectiveness of piperacillin-tazobactam for the treatment of ESBL-E bloodstream infections [26, 53-66]. The effectiveness of piperacillin-tazobactam for 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 [67]. Additionally, piperacillin-tazobactam MIC testing may be inaccurate and/or poorly reproducible when ESBL enzymes are present, or in the presence of other β-lactamase enzymes such as OXA-1, making it unclear if an isolate that tests susceptible to this agent is indeed susceptible [45, 68-71]. For these reasons, the panel recommends avoiding piperacillin-tazobactam for the treatment of invasive ESBL-E infections.

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## Question 5: Is there a role for cefepime in the treatment of infections caused by ESBL-E?

**Recommendation:** Cefepime is not recommended for the treatment of non-urinary infections caused by ESBL-E, even if susceptibility to the agent is demonstrated. If cefepime was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary. The panel recommends avoiding cefepime for the treatment of pyelonephritis and cUTI. Cefepime is also not recommended for the treatment of infections outside of the urinary tract caused by ESBL-E, even if susceptibility to cefepime is demonstrated.

**Rationale**

No clinical trials comparing the outcomes of patients with ESBL-E bloodstream infections treated with cefepime or carbapenem have been conducted. Cefepime MIC testing may be inaccurate and/or poorly reproducible if ESBL enzymes are present [72]. If cefepime was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary, as uncomplicated cystitis often resolves on its own. Limited data are available evaluating the role of cefepime *versus* carbapenems for ESBL-E pyelonephritis and cUTIs [56, 73]. A clinical trial evaluating the treatment of molecularly confirmed ESBL-E pyelonephritis and cUTI was terminated early because of a high clinical failure signal with cefepime (2 g intravenously every 12 hours), despite all isolates having cefepime MICs of 1-2 mcg/mL [56]. It is unknown if results would have been more favorable with 8-hour cefepime dosing. Until larger, more robust comparative effectiveness studies are available to inform the role of cefepime, the panel suggests avoiding cefepime for the treatment of ESBL-E pyelonephritis or cUTI.

Observational studies and a subgroup analysis of 23 patients in an RCT that compared cefepime and carbapenems for the treatment of invasive ESBL-E infections demonstrated either no difference in outcomes or poorer outcomes with cefepime [74-77]. For these reasons, the panel recommends avoiding cefepime for the treatment of invasive ESBL-E infections.

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## Question 6: Is there a role for the cephamycins in the treatment of infections caused by ESBL-E?

**Recommendation:** Cephamycins are not recommended for the treatment of ESBL-E infections until more clinical outcomes data using cefoxitin or cefotetan are available and optimal dosing has been defined.

### Rationale

The cephamycins are cephalosporins that are generally able to retain *in vitro* activity against ESBL enzymes[78, 79]. The cephamycins available in the United States are cefoxitin and cefotetan which are both intravenous agents. At least eight retrospective observational studies have compared the clinical outcomes of patients with ESBL-E infections—generally UTIs or bloodstream infections with urinary sources—treated with cephamycins *versus* carbapenems [80-87]. Six of the eight investigations found no difference in clinical outcomes [80, 82-84, 86, 87], while two studies demonstrated poorer outcomes with cephamycins [81]. One of the two studies included 57 patients with *K. pneumoniae* bloodstream infections, 14-day mortality was 55% and 39% in the cephamycin and carbapenem arms, respectively [81]. The second study was the largest study published to date, including 380 patients with *E. coli* and *K. pneumoniae* bloodstream infections, and 30-day mortality was 29% vs. 13% in the cephamycin and carbapenem arms, respectively [85]. Importantly, all eight studies were generally small, included diverse sources of infection, had notable selection bias, and used a variety of cephamycins with differences in dosing, duration, and frequency of administration.

The panel hesitates to recommend cephamycins for the treatment of ESBL-E infections, including ESBL-E uncomplicated cystitis. Many of the cephamycins investigated in observational studies are not available in the United States. Only 31 patients received cefoxitin (and none received cefotetan) in published studies [83, 87]. The panel believes more clinical data with use of these agents for the treatment of ESBL-E infections is necessary before recommending their use—including optimal dosing and frequency of administration—especially in light of the two observational studies suggesting poorer clinical outcomes with cephamycin use. At least one study suggested favorable outcomes with high-dose, continuous infusion cefoxitin (i.e., 6 g per day infused continuously) [87], which is challenging to administer. As both cephamycin and cefoxitin are only available intravenously and have relatively short half-lives, there does not appear to be a feasibility advantage with use of these agents over preferred agents for the treatment of ESBL-E infections.

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# Carbapenem-Resistant Enterobacterales

CRE account for more than 13,000 nosocomial infections and contribute to greater than 1,000 deaths in the United States annually [1]. The CDC defines CRE as members of the Enterobacterales order resistant to at least one carbapenem antibiotic or producing a carbapenemase enzyme [88]. Regarding bacteria that are intrinsically not susceptible to imipenem (e.g., *Proteus* spp., *Morganella* spp., *Providencia* spp.), resistance to at least one carbapenem other than imipenem is required [88]. 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. CRE that are not carbapenemase-producing may be the result of amplification of non-carbapenemase β-lactamase genes (other than carbapenemase genes) with concurrent outer membrane porin disruption [89]. Carbapenemase-producing isolates account for approximately 35%-59% of CRE cases in the United States [90, 91].

The most common carbapenemases in the United States are *K. 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 oxacillinases (e.g., OXA-48-like) [92, 93]. Knowledge of whether a CRE clinical isolate is carbapenemase-producing and, if it is, the specific carbapenemase produced is 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 [94]. Molecular testing can identify specific carbapenemase families (e.g., differentiating a KPC from an OXA-48-like carbapenemase). Carbapenemase phenotypic and/or genotypic testing are performed by a minority of clinical microbiology laboratories, but the panel strongly encourages all clinical microbiology laboratories to pursue carbapenemase testing to inform optimal treatment decisions. Treatment recommendations for CRE infections listed below assume that *in vitro* activity of preferred and alternative antibiotics has been demonstrated.

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## 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 (i.e., ertapenem MICs ≥2 mcg/mL) but susceptible to meropenem (i.e., meropenem MICs ≤1 mcg/mL), when carbapenemase testing results are either not available or negative. If none of the preferred agents are active, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol are alternative options for uncomplicated CRE cystitis.

**Rationale**

Clinical trial data evaluating the efficacy of most preferred agents for uncomplicated CRE cystitis are not available. However, as ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside all achieve high concentrations in urine, they are expected to be effective for uncomplicated CRE cystitis, when active [4, 18-21]. Meropenem is a preferred agent against uncomplicated CRE cystitis for isolates that remain susceptible to meropenem since most of these isolates do not produce carbapenemases [95][95][95]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated. There is uncertainty about the accuracy of meropenem MICs in these scenarios and use of meropenem may lead to treatment failure [96]. Some agents listed as alternative options for ESBL-E cystitis (e.g., fluoroquinolones) are recommended as preferred agents for CRE cystitis. These agents are not preferred agents for the treatment of uncomplicated ESBL-E cystitis in order to preserve their activity for more invasive infections. They are, however, preferred agents against uncomplicated 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 is generally effective for cystitis, with minimal toxicity [28]. 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 [97, 98]. Plazomicin may remain active against isolates resistant to amikacin [99].

If none of the preferred agents is active, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are alternative options for uncomplicated CRE

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cystitis. Data are insufficient to favor one agent over the others but all of these agents are reasonable treatment options based on published comparative effectiveness studies [100-105].

Fosfomycin use should be limited to uncomplicated CRE cystitis caused by *E. coli* as the *fosA* gene (intrinsic to certain Gram-negative organisms such as *Klebsiella* spp., *Enterobacter* spp., and *Serratia marcescens*) can hydrolyze fosfomycin and may lead to clinical failure [29, 30]. Randomized controlled trial data indicate that oral fosfomycin is associated with higher clinical failure than nitrofurantoin for uncomplicated cystitis [18].

Colistin is an alternative agent for treating uncomplicated 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 [106]. Polymyxin B should not be used as treatment for uncomplicated CRE cystitis, due to its predominantly nonrenal clearance [107].

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

**Recommendation:** Ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole are preferred treatment options for pyelonephritis and cUTI caused by CRE if susceptibility is demonstrated. Extended-infusion meropenem is a preferred treatment option for pyelonephritis and cUTIs caused by CRE resistant to ertapenem (i.e., ertapenem MICs ≥2 mcg/mL) but susceptible to meropenem (i.e., meropenem MICs ≤1 mcg/mL), when carbapenemase testing results are either not available or negative. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are also preferred treatment options for pyelonephritis and cUTIs caused by CRE resistant to both ertapenem and meropenem.

**Rationale**

Although the minority of CRE are expected to retain susceptibility to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole, these agents are all preferred agents to treat CRE pyelonephritis or cUTI after susceptibility is demonstrated [35-37].

Extended-infusion meropenem is a preferred agent against pyelonephritis and cUTI by CRE that remain susceptible to meropenem, since most of these isolates do not produce carbapenemases (**Table 1**) [90]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated. There is uncertainty about the accuracy of meropenem MICs in these scenarios and use of meropenem may lead to treatment failure [96].

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 RCTs showing non-inferiority of these agents to common comparator agents for UTIs [100-105]. Data are insufficient to favor one agent over the others.

In patients in whom the potential for nephrotoxicity is deemed acceptable, once-daily aminoglycosides for a full treatment course are an alternative option [38]. Once-daily plazomicin was noninferior to meropenem in an RCT that included patients with pyelonephritis and cUTIs caused by the Enterobacterales [39]. 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 [97, 98]. Plazomicin may remain active against isolates resistant to amikacin [97, 98]. Nitrofurantoin and oral fosfomycin do not achieve adequate concentrations in the renal parenchyma and should be avoided for pyelonephritis and cUTI [40, 41].

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## 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 (i.e., ertapenem MICs ≥2 mcg/mL) but susceptible to meropenem (i.e., meropenem MICs ≤1 mcg/mL), when carbapenemase testing results are either not available or negative.

**Rationale**

The panel believes that all clinical microbiology laboratories in the United States should develop approaches to detect carbapenemase production in CRE clinical isolates, including identifying the specific carbapenemase present (e.g., KPC, NDM, OXA-48-like). The panel understands that most U.S. clinical microbiology laboratories do not currently perform this testing and/or that there may be delays in identifying the presence of carbapenemases and in determining susceptibility to novel β-lactam agents (i.e., ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, cefiderocol). Therefore, an understanding of which novel agents may be active against CRE isolates is important.

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 [90]. Recommended dosing for extended-infusion meropenem is provided in **Table 1**. The CDC characterized over 42,000 CRE isolates collected from all regions of the United States between 2017-2019 and found that only approximately 10% of CRE isolates containing a carbapenemase gene retained susceptibility to meropenem [108]. The panel recommends that meropenem be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated. Although studies indicating the optimal treatment approach when phenotypic-genotypic discordance exists are not available, the panel prefers to err on the side of caution.

Ceftazidime-avibactam is recommended as an alternative agent for the treatment of ertapenem-resistant, meropenem-susceptible CRE infections outside of the urinary tract (**Question 4**). The panel prefers to reserve ceftazidime-avibactam for the treatment of infections caused by CRE resistant to all carbapenems to preserve its activity. 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 are unlikely to offer any significant advantage beyond that of extended-infusion meropenem (i.e., the addition of vaborbactam or relebactam is unlikely to provide any incremental benefit compared with a carbapenem alone).

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## 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 (i.e., ertapenem MICs ≥2 mcg/mL) and meropenem (i.e., meropenem MICs ≥4 mcg/mL), when carbapenemase testing results are either not available or negative. For patients with CRE infections who within the previous 12 months have received medical care in countries with a relatively high prevalence of metallo-β-lactamase-producing organisms or who have previously had a clinical or surveillance culture where a metallo-β-lactamase-producing isolate was identified, preferred treatment options include the combination of ceftazidime-avibactam plus aztreonam, or cefiderocol as monotherapy, if carbapenemase testing results are not available.

**Rationale**

CDC data from 2017-2019 indicate that approximately 35% of CRE clinical or surveillance isolates in the United States carry one of the main five carbapenemase genes [90]. Of these 35% of isolates, the specific prevalence by carbapenemase gene is as follows: $bla_{KPC}$ (86%), $bla_{NDM}$ (9%), $bla_{VIM}$ (<1%), $bla_{IMP}$ (1%), or $bla_{OXA-48}$-like (4%) [90]. A separate cohort of 1,040 clinical and surveillance CRE isolates from across the United States demonstrated that 59% of isolates were carbapenemase producing, with the distribution of carbapenemase genes relatively similar: $bla_{KPC}$ (92%), $bla_{NDM}$ (3%), $bla_{VIM}$ (<1%), $bla_{IMP}$ (<1%), and $bla_{OXA-48}$-like (3%) [91].

Ceftazidime-avibactam has activity against most KPC- and OXA-48-like-producing CRE [109, 110]. Meropenem-vaborbactam and imipenem-cilastatin-relebactam are active against most Enterobacterales that produce KPC enzymes but not those that produce OXA-48-like carbapenemases [111-119]. Neither ceftazidime-avibactam, meropenem-vaborbactam, nor imipenem-cilastatin-relebactam have activity against metallo-β-lactamase (e.g., NDM)-producing Enterobacterales. As described above, the vast majority of CRE clinical isolates either do not produce carbapenemases or, if they do, produce KPCs. Therefore, all three of these agents (i.e., ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam) are preferred treatment options for CRE clinical isolates outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem when carbapenemase testing results are either not available or

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negative. There do not appear to be differences in the effectiveness of these agents when susceptibility has been demonstrated (**Question 5**).

Previously, it was considered standard practice to administer extended-infusion meropenem in combination with a second agent, frequently polymyxins or aminoglycosides, for the treatment of infections caused by CRE isolates with meropenem MICs as high as 8-16 mcg/mL [120]. Data suggested that extended-infusion meropenem remained active against infections caused by organisms with carbapenem MICs in this range [121-123]. However, subsequent observational and RCT data indicate increased mortality and excess nephrotoxicity associated with polymyxin or aminoglycoside-based regimens relative to newer β-lactam-β-lactamase inhibitor agents for the treatment of CRE infections [124-132]. Therefore, the panel does not recommend the use of extended-infusion carbapenems with or without the addition of a second agent for the treatment of CRE when non-susceptibility to meropenem has been demonstrated.

Cefiderocol is also likely to be active against most CRE clinical isolates as it exhibits activity against Enterobacterales producing any of the five major carbapenemase enzymes [133]. However, the panel recommends cefiderocol as an alternative agent for infections caused by CRE other than metallo-β-lactamase-producing Enterobacterales (e.g., NDM, VIM, IMP) (**Question 5**). Patients with CRE infections who have received medical care in countries with a relatively high prevalence of metallo-β-lactamase-producing CRE within the previous 12 months [134] or who have previously had a clinical or surveillance culture where metallo-β-lactamase-producing organisms were identified have a high likelihood of being infected with metallo-β-lactamase-producing Enterobacterales. For such patients (if carbapenemase results are not available), preferred treatment options include the combination of ceftazidime-avibactam plus aztreonam, or cefiderocol as monotherapy (**Question 5**). However, if carbapenemase testing is available and is negative, monotherapy with ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-cilastatin-relebactam are preferred treatment options. Tigecycline or eravacycline (as monotherapy) are alternative options for the treatment of CRE infections not involving the bloodstream or urinary tract (**Question 7**). Their activity is independent of the presence or type of carbapenemase.

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## 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:** Meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam are 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 infections. Ceftazidime-avibactam is the preferred treatment option for OXA-48-like-producing infections.

**Rationale**

Preferred agents for CRE infections differ based on the identification of specific carbapenemases [135]. Tigecycline or eravacycline, but not omadacycline, are alternative options for the treatment of CRE infections (**Question 7**). Their activity is independent of the presence or type of carbapenemase produced.

KPC producers

For KPC-producing organisms, preferred agents include meropenem-vaborbactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam [109, 111-116, 136]. These agents are associated with improved clinical outcomes and reduced toxicity compared to other regimens commonly used to treat KPC-producing infections, which are often polymyxin-based [124-132, 136].

Comparative effectiveness studies between the preferred agents are limited and no clinical trials exist comparing the novel agents. An observational study compared the clinical outcomes of patients who received either meropenem-vaborbactam or ceftazidime-avibactam for at least 72 hours for the treatment of CRE infections [137]. Carbapenemase status was largely unavailable. Clinical cure and 30-day mortality between the 26 patients who received meropenem-vaborbactam and 105 patients who received ceftazidime-avibactam were similar at 69% and 62% and 12% and 19%, respectively. Of patients who experienced recurrent CRE infections, 0 of 3 patients receiving meropenem-vaborbactam and 3 of 15 patients receiving ceftazidime-avibactam had subsequent CRE isolates that developed resistance to initial therapy. This study had a number of important limitations: likely selection bias due to its observational nature, relatively small numbers of patients, heterogenous sites of CRE infection, more than half of patients had polymicrobial infections, and more than half of patients received additional antibiotic therapy. These limitations notwithstanding, this study suggests that meropenem-vaborbactam and ceftazidime-avibactam are associated with similar clinical outcomes, although the emergence of resistance may be more common with

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ceftazidime-avibactam (**Question 6**). Therefore, the panel expresses a preference for the use of meropenem-vaborbactam over ceftazidime-avibactam for the treatment of KPC-producing organisms, but both are preferred options for this indication.

Limited clinical data are available for imipenem-cilastatin-relebactam compared with the other novel β-lactam-β-lactamase inhibitor agents. A clinical trial randomized patients with infections caused by Gram-negative organisms not susceptible to imipenem receiving imipenem-cilastatin-relebactam versus imipenem-cilastatin and colistin [127]. Of patients with Enterobacterales infections, 40% (2 of 5 patients) and 100% (2 of 2 patients) experienced a favorable clinical response with imipenem-cilastatin-relebactam and imipenem-cilastatin in combination with colistin, respectively [127]. It is difficult to draw meaningful conclusions from these data given the small numbers. However, *in vitro* activity of imipenem-cilastatin-relebactam against CRE [118, 138-141], clinical experience with imipenem-cilastatin, and the stability of relebactam as a β-lactamase inhibitor [142] suggest imipenem-cilastatin-relebactam is likely to be effective for CRE infections if it tests susceptible. Studies comparing the clinical outcomes of imipenem-cilastatin-relebactam and ceftazidime-avibactam or meropenem-vaborbactam for CRE infections are not available. Although ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are all recommended as preferred agents for the treatment of KPC-producing infections, the panel slightly favors meropenem-vaborbactam, followed by ceftazidime-avibactam, and then imipenem-cilastatin-relebactam, based on available data.

Cefiderocol is an alternative treatment option for KPC-producing Enterobacterales [133]. A clinical trial found that clinical cure occurred in 66% (19 of 29) and 45% (5 of 11) of CRE infected patients treated with cefiderocol versus alternative agents (mostly polymyxin-based regimens), respectively [105]. All-cause mortality was 23% (9 of 40) vs. 21% (4 of 19) in patients with carbapenem-resistant *K. pneumoniae* or carbapenem-resistant *E. coli*, treated with cefiderocol vs. alternative agents, respectively. When patients with concomitant *Acinetobacter* infection were excluded, all-cause mortality was 19% (6 of 31) vs. 25% (4 of 16) in patients with *K. pneumoniae* or *E. coli* treated with cefiderocol vs. alternative therapy, respectively. Although clinical investigations comparing the effectiveness of cefiderocol versus newer β-lactam-β-lactamase inhibitors for KPC-producing Enterobacterales infections are not available, available data do not suggest cefiderocol is associated with suboptimal outcomes. However, the panel recommends cefiderocol as an alternative agent for treating KPC-producing pathogens as it prefers its activity be reserved for the treatment of metallo-β-lactamase-producing Enterobacterales (e.g., NDM, VIM, IMP producers) or for select glucose non-fermenting Gram-negative organisms [143].

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NDM producers

If Enterobacterales isolates produce NDMs (or any other metallo-β-lactamase), preferred antibiotic options include ceftazidime-avibactam plus aztreonam, or cefiderocol monotherapy [105, 144-149]. Ceftazidime-avibactam (monotherapy), meropenem-vaborbactam, and imipenem-cilastatin-relebactam are not effective against metallo-β-lactamase producing infections.

NDMs hydrolyze penicillins, cephalosporins, and carbapenems, but not aztreonam. Although aztreonam is active against NDMs, it can be hydrolyzed by ESBLs, AmpC β-lactamases, or OXA-48-like carbapenemases which are frequently co-produced by NDM-producing isolates. Avibactam generally remains effective against these latter β-lactamase enzymes. An observational study of 102 adults with bloodstream infections caused by metallo-β-lactamase-producing Enterobacterales compared the outcomes of 52 patients receiving ceftazidime-avibactam in combination with aztreonam versus 50 patients receiving a combination of other agents, primarily polymyxin or tigecycline-based therapy [149]. Thirty-day mortality was 19% for the ceftazidime-avibactam/aztreonam group and 44% for the alternate arm, highlighting the potential clinical benefit with the former. When the combination of ceftazidime-avibactam and aztreonam are administered to treat metallo-β-lactamase producing infections, it is recommended that they be administered simultaneously rather than sequentially [150].

Another preferred option for the treatment of NDM and other metallo-β-lactamase-producing Enterobacterales is cefiderocol. Surveillance data indicate that NDM-producing Enterobacterales isolates have a higher cefiderocol $MIC_{90}$ than isolates that produce serine β-lactamases, although this is not always associated with frank cefiderocol resistance [133, 151]. Among 151 international CRE isolates, cefiderocol was active against 98% of all isolates [133]. On closer inspection, cefiderocol was active against 100% of 75 KPC-producing Enterobacterales isolates, 100% of 32 OXA-48-like isolates, but only 58% of the 12 NDM-producing Enterobacterales isolates, using cefiderocol MICs of ≤4 mcg/mL as indicative of susceptibility [133]. Similar data on the percent of NDM-producing isolates susceptible to the combination of ceftazidime-avibactam and aztreonam are not available, in part because there is no Clinical and Laboratory Standards Institute (CLSI)-standardized approach to identifying *in vitro* activity of this antibiotic combination against bacterial isolates [15]. A clinical trial including patients with metallo-β-lactamase producing infections (not limited to the Enterobacterales) found that clinical cure occurred in 75% (12 of 16) and 29% (2 of 7) of patients receiving cefiderocol *versus* alternate therapy (primarily polymyxin-based therapy), respectively [105]. Clinical outcomes data comparing ceftazidime-avibactam in combination with aztreonam versus cefiderocol are not available. The panel recommends both treatment options as preferred options for metallo-β-lactamase-producing Enterobacterales.

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OXA-48-like producers

If an OXA-48-like enzyme is identified, ceftazidime-avibactam is preferred [109, 110, 152] and cefiderocol is an alternative option. Meropenem-vaborbactam and imipenem-cilastatin-relebactam have limited to no activity against CRE producing OXA-48-like enzymes [111-119]. Although OXA-48-like producing isolates are generally expected to test susceptible to cefiderocol, clinical data on cefiderocol treatment of infections by these organisms are limited.

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## Question 6: What is the likelihood of the emergence of resistance of CRE isolates to the newer β-lactam agents when used to treat CRE infections?

**Recommendation:** The emergence of resistance is a concern with all of the novel β-lactams used to treat CRE infections, but the frequency appears to be the highest for ceftazidime-avibactam.

**Rationale**

As with most antibiotic agents, treatment with any of the newer β-lactam agents active against CRE (i.e., ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol) increases the likelihood that subsequent isolates causing infection will no longer be effectively treated with these agents. The emergence of resistance to ceftazidime-avibactam most commonly occurs because of mutations in the $bla_{KPC}$ gene translating to amino acid changes in the KPC carbapenemase [153-169]. Changes in permeability and efflux are the primary drivers of the emergence of resistance to meropenem-vaborbactam [113, 162, 166, 170-176] and imipenem-cilastatin-relebactam [177, 178]. A number of diverse mechanisms of resistance to cefiderocol have been described including mutations in the TonB-dependent iron transport system [179-182], amino acid changes in AmpC β-lactamases [183, 184], and increased NDM expression [185]. The reader is referred to comprehensive review articles on this topic for a more complete understanding of the mechanisms of resistance to the novel β-lactams [143, 186, 187].

Estimates of the emergence of resistance after clinical exposure to ceftazidime-avibactam and meropenem-vaborbactam are approximately 20% [128, 132, 157, 188] and 3% [137, 176, 189], respectively. The most data are available for ceftazidime-avibactam, in part because it was the first of the novel β-lactam agents active against CRE to receive approval from the U.S. Food and Drug Administration. Very limited data exist on the frequency of emergence of resistance to imipenem-cilastatin-relebactam. Whether this is indicative of the successful properties of this combination or the result of limited use is not clear. Similarly, estimates of the frequency of the emergence of resistance to cefiderocol since its clinical introduction are not yet available.

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The panel recommends always repeating antibiotic susceptibility testing for the newer β-lactams when a patient previously infected with a CRE presents with a sepsis-like picture suggestive of a new or relapsed infection. Furthermore, if a patient was recently treated with ceftazidime-avibactam and presents with a sepsis-like condition, the panel suggests considering use of a different novel β-lactam agent at least until culture and susceptibility data are available. For example, if a patient with a KPC-producing bloodstream infection received a treatment course of ceftazidime-avibactam one month earlier and presents to medical care with symptoms suggestive of infection, consider administering an agent such as meropenem-vaborbactam until organism and susceptibility data are available.

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## Question 7: What is the role of tetracycline derivatives for the treatment of infections caused by CRE?

**Recommendation:** Although β-lactam agents remain preferred treatment options for CRE infections, tigecycline and eravacycline are alternative options when β-lactam agents are either not active or unable to be tolerated. The tetracycline derivatives are not recommended as monotherapy for the treatment of CRE urinary tract infections or bloodstream infections.

### Rationale

Tetracycline derivatives function independent of the presence or type of carbapenemase. More specifically, both carbapenemase-producing (e.g., KPC, NDM, OXA-48-like carbapenemases) and non-carbapenemase-producing CRE may test susceptible to these agents [112, 190]. The panel recommends avoiding tigecycline or eravacycline for the treatment of most CRE infections other than intra-abdominal infections. The tetracycline-derivative agents generally achieve rapid tissue distribution following administration, resulting in limited urine and serum concentrations [191]. Therefore, the panel recommends avoiding their use for urinary and bloodstream infections. Tigecycline or eravacycline can be considered as alternative options for intra-abdominal infections, skin and soft tissue infections, osteomyelitis, and respiratory infections when optimal dosing is used (**Table 1**).

Tigecycline has more published experience available for the treatment of CRE infections than eravacycline [192-195]. A meta-analysis of 15 randomized trials suggested that tigecycline monotherapy is associated with higher mortality than alternative regimens used for the treatment of pneumonia, not exclusively limited to pneumonia caused by the Enterobacterales [196]. Subsequent investigations have demonstrated that when high-dose tigecycline is prescribed (200 mg intravenously as a single dose followed 100 mg intravenously every 12 hours) mortality differences between tigecycline and comparator agents may no longer be evident [197-199]. Thus, if tigecycline is prescribed for the treatment of CRE infections, the panel recommends that high-dosages be administered [200] (**Table 1**).

Eravacycline MICs are generally 2- to 4-fold lower than tigecycline MICs against CRE [201]. The clinical relevance of the MIC distributions between these agents is unclear because of differences in the pharmacokinetic/pharmacodynamic profile of tigecycline and eravacycline. Fewer than five patients with CRE infections were included in clinical trials that investigated the efficacy of eravacycline [192, 202] and post-marketing clinical reports describing its efficacy for the treatment of CRE infections are limited [203].

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Limited clinical data are also available investigating the effectiveness of minocycline against CRE infections [204, 205], but data suggest a lower proportion of CRE isolates are likely to be susceptible to minocycline compared to tigecycline or eravacycline. The panel suggests using minocycline with caution for the treatment of CRE infections. Data evaluating the activity of omadacycline, a tetracycline-derivative with both an intravenous and oral formulation, against CRE suggests reduced potency relative to other tetracycline derivatives and an unfavorable pharmacokinetic and pharmacodynamic profile [50, 206-208]. The panel suggests avoiding the use of omadacycline for the treatment of CRE infections.

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## Question 8: 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 an alternative agent for uncomplicated CRE cystitis.

### Rationale

Observational and RCT data indicate increased mortality and excess nephrotoxicity associated with polymyxin-based regimens relative to comparator agents [124-132]. Concerns about the clinical effectiveness of polymyxins and accuracy of polymyxin susceptibility testing led the CLSI to eliminate a susceptible category for colistin and polymyxin B [15]. The panel recommends that these agents be avoided for the treatment of CRE infections, with the exception of colistin as an alternative agent against CRE cystitis. Polymyxin B should not be used as treatment for CRE cystitis, due to its predominantly nonrenal clearance [107].

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## Question 9: What is the role of combination antibiotic therapy for the treatment of infections caused by CRE?

**Recommendation:** Combination antibiotic therapy (i.e., 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 increases the likelihood that at least one active therapeutic agent for patients at risk for CRE infections is being administered, data do not indicate that continued combination therapy—once the β-lactam agent has demonstrated *in vitro* activity—offers any additional benefit [209]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [209].

Observational data and clinical trials comparing ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam to combination regimens (e.g., ceftazidime-avibactam versus meropenem and colistin) for the treatment of CRE infections have not shown the latter to improve clinical outcomes [124-132]. An observational study compared the clinical outcomes of 165 patients receiving ceftazidime-avibactam and 412 patients receiving ceftazidime-avibactam plus a second agent for the treatment of KPC-producing infections [210]. Thirty-day mortality was essentially identical at approximately 25% in both study arms.

Randomized trial data are not available comparing the novel β-lactam agents as monotherapy and as a component of combination therapy (e.g., ceftazidime-avibactam versus ceftazidime-avibactam and amikacin). However, based on available outcomes data, clinical experience, and known toxicities associated with aminoglycosides, fluoroquinolones, and polymyxins, the panel does not routinely recommend combination therapy for CRE infections when susceptibility to a preferred β-lactam agent has been demonstrated.

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# *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance

The CDC reports that 32,600 cases of multidrug-resistant (MDR) *P. aeruginosa* infection occurred in patients hospitalized in the United States in 2017, resulting in 2,700 deaths [1]. MDR *P. aeruginosa* is defined as *P. aeruginosa* not susceptible to at least one antibiotic in at least three antibiotic classes for which *P. aeruginosa* susceptibility is generally expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems [211]. In 2018, the concept of "difficult-to-treat" resistance was proposed [3]. In this guidance document, DTR is defined as *P. aeruginosa* exhibiting non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.

Multidrug-resistant *P. aeruginosa* or DTR-*P. aeruginosa* generally evolve as a result of an interplay of multiple complex resistance mechanisms, including decreased expression of outer membrane porins (OprD), hyperproduction of AmpC enzymes, upregulation of efflux pumps, and mutations in penicillin-binding protein targets [212, 213]. Carbapenemase production is a rare cause of carbapenem resistance in *P. aeruginosa* in the United States but is identified in upwards of 20% of carbapenem-resistant *P. aeruginosa* in other regions of the world [214-216]. Treatment recommendations for DTR-*P. aeruginosa* infections listed below assume that *in vitro* activity of preferred and alternative antibiotics has been demonstrated.

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## Question 1: What are preferred antibiotics for the treatment of infections caused by MDR *P. aeruginosa*?

**Recommendation:** When *P. aeruginosa* isolates test susceptible to traditional non-carbapenem β-lactam agents (i.e., piperacillin-tazobactam, ceftazidime, cefepime, aztreonam), they are preferred over carbapenem therapy. For infections caused by *P. aeruginosa* isolates not susceptible to any carbapenem agents but susceptible to traditional β-lactams, the administration of a traditional agent as high-dose extended-infusion therapy is suggested, after antibiotic susceptibility testing results are confirmed. For patients with moderate to severe disease or poor source control with *P. aeruginosa* isolates resistant to carbapenems but susceptible to traditional β-lactams, use of a novel β-lactam agent that tests susceptible (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam) is also a reasonable treatment option.

**Rationale**

In general, when a *P. aeruginosa* isolate tests susceptible to multiple traditional β-lactam agents (i.e., piperacillin-tazobactam, ceftazidime, cefepime, aztreonam) or fluoroquinolones (i.e., ciprofloxacin, levofloxacin), the panel prefers these agents be prescribed over carbapenem therapy in an attempt to preserve the activity of carbapenems for future, increasingly drug-resistant infections.

*P. aeruginosa* isolates not susceptible to a carbapenem agent (e.g., meropenem or imipenem-cilastatin MICs ≥4 mcg/mL) but susceptible to other traditional non-carbapenem β-lactam agents (e.g., piperacillin-tazobactam MIC ≤16/4 mcg/mL, ceftazidime ≤8 mcg/mL, cefepime ≤8 mcg/mL, or aztreonam ≤8 mcg/mL) [15] constitute approximately 20% to 60% of carbapenem-resistant *P. aeruginosa* isolates [217-223]. This phenotype is generally due to lack of or limited production of OprD, which normally facilitates entry of carbapenem agents into bacteria [219-222]. Comparative effectiveness studies to guide treatment decisions for infections caused by *P. aeruginosa* resistant to carbapenems but susceptible to other traditional non-carbapenem β-lactams are not available. When confronted with these scenarios, the panel suggests repeating susceptibility testing to confirm antibiotic MICs. If the isolate remains susceptible to a traditional non-carbapenem β-lactam (e.g., cefepime) on repeat testing, the panel's preferred approach is to administer the non-carbapenem agent as high-dose extended-infusion therapy (e.g., cefepime 2 g IV every 8 hours, infused over 3 hours); (**Table 1**).

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An alternative approach is to administer a novel β-lactam agent (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam), selecting an agent that tests susceptible. This approach is considered an alternative option to preserve the effectiveness of novel β-lactams for future, increasingly antibiotic-resistant infections. However, for patients with moderate to severe infection or with poor source control, use of a novel β-lactam for MDR *P. aeruginosa* infections resistant to carbapenems but susceptible to non-carbapenem β-lactams is a reasonable consideration. Regardless of the antibiotic agent administered, patients infected with *P. aeruginosa* should be closely monitored to ensure clinical improvement as *P. aeruginosa* exhibits an impressive capacity to acquire additional resistance mechanisms while exposed to antibiotic therapy.

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## Question 2: 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 RCTs showing non-inferiority of these agents to common comparator agents for the treatment of UTIs [101, 103-105, 224]. Data are insufficient to favor one of these agents over the others for the treatment of uncomplicated cystitis, and available trials generally do not include patients infected by pathogens with DTR phenotypes. Additional information comparing these agents is described in Question 4.

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 is generally effective for uncomplicated cystitis, with minimal toxicity, but robust trial data are lacking [28]. Plazomicin is unlikely to provide any incremental benefit against DTR-*P. aeruginosa* if resistance to all other aminoglycosides is demonstrated [225].

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 [106]. 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 [18, 226]. This is in part due to the presence of the *fosA* gene, which is intrinsic to *P. aeruginosa* [29].

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

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

### Rationale

Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for DTR-*P. aeruginosa* pyelonephritis and cUTI, based on RCTs showing non-inferiority of these agents to common comparator agents [101, 103-105, 224]. Data are insufficient to favor one of these agents over the others for the treatment of pyelonephritis and cUTI, and available trials generally do not include patients infected by pathogens with DTR phenotypes. Additional information comparing these agents is described in **Question 4**.

In patients in whom the potential for nephrotoxicity is deemed acceptable, once-daily aminoglycosides are an alternative option [38]. Plazomicin is unlikely to provide any incremental benefit against DTR-*P. aeruginosa* if resistance to all other aminoglycosides is demonstrated [225].

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## Question 4: 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 preferred 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 infections outside of the urinary tract, based on *in vitro* activity [139, 141, 177, 227-268], observational studies [269], and clinical trial data [101, 127, 270-276]. The vast majority of patients in clinical trials receiving the novel β-lactam-β-lactamase inhibitors were not infected with DTR-*P. aeruginosa*.

Summarizing international surveillance data, ceftolozane-tazobactam [227, 229, 230, 232-242, 253], ceftazidime-avibactam [228, 241-253], and imipenem-cilastatin-relebactam [139, 141, 177, 253-268] are active against approximately 76%, 74%, and 69% of carbapenem-resistant *P. aeruginosa* isolates, respectively, with lower percent susceptibilities exhibited by isolates from patients with cystic fibrosis [277, 278]. Available surveillance data generally represent time periods before the novel agents were used clinically and likely overestimate susceptibility percentages observed in clinical practice. Ceftolozane does not rely on an inhibitor to restore susceptibility to an otherwise inactive drug (i.e., ceftolozane has independent activity against DTR-*P. aeruginosa*), which may explain its slightly higher likelihood of activity against DTR-*P. aeruginosa* compared to other novel β-lactam-β-lactamase inhibitors. 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. Regional differences in susceptibility estimates across the newer agents likely exist. The panel recommends always obtaining antibiotic susceptibility testing results for DTR-*P. aeruginosa* infections to guide treatment decisions.

Clinical trials comparing effectiveness across the newer agents are not available, but observational data and subgroup analysis from clinical trial data provide insights into the effectiveness of the newer β-lactam agents compared to traditional anti-pseudomonal regimens. An observational study including 200 patients with MDR *P. aeruginosa* compared the outcomes of patients receiving ceftolozane-tazobactam versus polymyxin or aminoglycoside-based therapy [269]. Favorable clinical outcomes were observed in 81% of patients receiving ceftolozane-tazobactam



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versus 61% of patients receiving polymyxin- or aminoglycoside-based therapy; this difference achieved statistical significance. An RCT including 24 patients infected with imipenem-non-susceptible *P. aeruginosa* identified a favorable clinical response in 81% of patients receiving imipenem-cilastatin-relebactam compared to 63% receiving imipenem-cilastatin in combination with colistin [127]. While not achieving statistical significance, potentially due to the small sample size, the numerical differences suggest improved outcomes with use of imipenem-cilastatin-relebactam over more traditional regimens. Rigorous data investigating the activity of ceftazidime-avibactam against comparators are lacking. However, pooled data from five RCTs explored differences in clinical responses for patients with MDR *P. aeruginosa* infections receiving ceftazidime-avibactam *versus* more traditional regimens with a favorable clinical response observed in 57% (32 of 56 patients) *versus* 54% (21 of 39) of patients in the two treatment arms, respectively [279]. An important limitation to these data were that only 66% of isolates were susceptible to ceftazidime-avibactam making interpretation of the results challenging [279].

Cefiderocol is recommended as an alternative treatment option for DTR-*P. aeruginosa* infections outside of the urine. Cefiderocol is a synthetic conjugate composed of a cephalosporin moiety and a catechol-type siderophore, which binds to iron and facilitates bacterial cell entry using active iron transporters [143]. Once inside the periplasmic space, the cephalosporin moiety dissociates from iron and binds primarily to penicillin-binding protein 3 to inhibit bacterial cell wall synthesis [280]. Combining data from 1,500 carbapenem-non-susceptible *P. aeruginosa* isolates in surveillance studies, over 97% of isolates exhibited susceptibility to cefiderocol (i.e., MICs ≤4 mcg/mL) [133, 281-286]. Similar to the novel β-lactam-β-lactamase inhibitors, percent susceptibility to cefiderocol is likely to be reduced after widespread use of this agent.

An RCT compared the outcomes of patients with infections due to carbapenem-resistant organisms treated with cefiderocol *versus* best available therapy, which was largely polymyxin-based therapy [105]. The trial included 22 unique patients with 29 CR-*P. aeruginosa* infections, including six patients with UTIs, 17 patients with pneumonia, and six patients with bloodstream infections [287]. Mortality at the end of therapy was 18% in both the cefiderocol and best available therapy arms for patients infected with *P. aeruginosa*. This trial suggests that cefiderocol performs as well as agents that were the mainstay of treatment against DTR-*P. aeruginosa* in the past such as combinations of extended-infusion meropenem, polymyxins, and aminoglycosides, but may not be associated with improved outcomes, as has been observed with some of the newer β-lactam-β-lactamase inhibitors [127, 269]. Despite the high likelihood of cefiderocol activity against DTR-*P. aeruginosa*, the panel recommends cefiderocol as an alternative option when inactivity, intolerance, or unavailability precludes the use of the newer β-lactam-β-lactamase inhibitors.

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## Question 5: What is the likelihood of the emergence of resistance of DTR-*P. aeruginosa* isolates to the newer β-lactam agents when used to treat DTR-*P. aeruginosa* infections?

**Recommendation:** The emergence of resistance is a concern with all of the novel β-lactams used to treat DTR-*P. aeruginosa* infections, but the frequency appears to be the highest for ceftolozane-tazobactam and ceftazidime-avibactam.

**Rationale**

As with most antibiotic agents, treatment of DTR-*P. aeruginosa* with any of the newer β-lactam agents (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol) increases the likelihood that subsequent infections will no longer be effectively treated with these agents. The emergence of resistance to ceftolozane-tazobactam most commonly occurs because of amino acid substitutions, insertions, or deletions in *Pseudomonas*-derived cephalosporinase (PDC), the chromosomally encoded class C β-lactamase of *P. aeruginosa*, commonly referred to as "the pseudomonal AmpC" [8, 231, 288-299]. These alterations occur most commonly in or adjacent to a particular region of the PDC known as the "omega loop." Similarly, acquired resistance of *P. aeruginosa* to ceftazidime-avibactam is most frequently the result of alterations in PDCs [288, 290, 291, 293, 296, 298-301].

Mechanisms contributing to *P. aeruginosa* resistance to imipenem-cilastatin-relebactam are less clear and may be related to increased production of PDCs in combination with loss of OprD [177, 302]. A number of diverse mechanisms of *P. aeruginosa* resistance to cefiderocol have been described including mutations in the TonB-dependent iron transport system [179-181, 303] or amino acid changes in the AmpC β-lactamases [303, 304]. The reader is referred to comprehensive review articles on this topic for a more complete understanding of the mechanisms of resistance to the novel β-lactams [143, 186, 187].

Based on available data thus far, the emergence of resistance of *P. aeruginosa* to novel β-lactams appears most concerning for ceftolozane-tazobactam and ceftazidime-avibactam. Cross-resistance between these agents is high because of similar mechanisms of resistance. In a cohort of 28 patients with DTR-*P. aeruginosa* infections treated with ceftolozane-tazobactam, 50% of patients were infected with subsequent DTR-*P. aeruginosa* isolates no longer susceptible to ceftolozane-tazobactam [299]. Remarkably, over 80% of patients with index isolates susceptible to ceftazidime-avibactam had subsequent isolates with high-level resistance to ceftazidime-avibactam after ceftolozane-tazobactam exposure, and in the absence of ceftazidime-avibactam exposure. Another cohort study including 23 patients with index and subsequent *P. aeruginosa* isolates after

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ceftolozane-tazobactam described a similar experience [298]. Treatment-emergent mutations in *ampC* were identified in 79% of paired isolates. Limited data on the frequency of emergence of resistance to imipenem-cilastatin-relebactam exist. Whether this is indicative of the successful properties of this combination or the result of its limited clinical use is not clear. Similarly, estimates of the frequency of the emergence of resistance of *P. aeruginosa* to cefiderocol since its clinical introduction are not yet available but in a clinical trial, three of 12 carbapenem-resistant isolates had at least 4-fold increases in cefiderocol MICs (though not necessarily frank resistance) after exposure to this agent [105].

The panel recommends always repeating antibiotic susceptibility testing for the newer β-lactams when a patient previously infected with a DTR-*P. aeruginosa* presents with a sepsis-like picture suggestive of a new or relapsed infection. Furthermore, if a patient was recently treated with ceftolozane-tazobactam or ceftazidime-avibactam and presents to medical care with symptoms of infection, the panel suggests considering use of a different novel β-lactam agent at least until culture and susceptibility data are available.

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## Question 6: 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 (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam) has been confirmed.

### Rationale

Although empiric combination antibiotic therapy (e.g., the addition of an aminoglycoside to a β-lactam agent) to broaden the likelihood of at least one 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 [209]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [209].

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 [127, 269]. Randomized trial data comparing ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam as monotherapy and as a component of combination therapy are not available (e.g., ceftazidime-avibactam versus ceftazidime-avibactam and amikacin). Based on existing outcomes data, clinical experience, and known toxicities associated with aminoglycosides and polymyxins, the panel does not recommend that combination therapy be routinely administered for DTR-*P. aeruginosa* infections when susceptibility to a preferred β-lactam agent has been demonstrated.

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If no preferred agent demonstrates activity against DTR-*P. aeruginosa*, an aminoglycoside (if susceptibility is demonstrated) can be considered in combination with either 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 mcg/mL (highly resistant) and the imipenem-cilastatin-relebactam MIC is 4/4 mcg/mL (intermediate category), imipenem-cilastatin-relebactam in combination with an active aminoglycoside is favored. Data are lacking demonstrating a benefit to this approach and it should be considered as a last resort. Similarly, data are lacking whether this approach will yield more favorable clinical outcomes compared to cefiderocol, either as monotherapy or combination therapy. This approach is suggested as it may increase the likelihood that at least one active agent is being included in the treatment regimen.

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 non-urinary tract infections because (1) it is not administered as a prodrug and therefore can achieve more reliable plasma concentrations than colistin, and (2) it has a reduced risk of nephrotoxicity, although limitations across studies preclude accurate determination of the differential risk of nephrotoxicity [305-310].

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## Question 7: What is the role of nebulized antibiotics for the treatment of respiratory infections caused by DTR-*P. aeruginosa*?

**Recommendation:** The panel does not recommend the routine addition of nebulized antibiotics for the treatment of respiratory infections caused by DTR-*P. aeruginosa*.

### Rationale

There have been conflicting findings for the clinical effectiveness of nebulized antibiotics for the treatment of Gram-negative pneumonia in observational studies [311-338]. Three RCTs compared the outcomes of patients with Gram-negative ventilator-associated pneumonia comparing nebulized antibiotics *versus* placebo. All three trials allowed for the use of systemic antibiotics, at the discretion of the treating clinician. In brief, one trial compared the outcomes of 100 adults with pneumonia (34% caused by *P. aeruginosa*) treated with nebulized colistin versus placebo [339]; a second trial compared the outcomes of 142 adults with pneumonia (22% caused by *P. aeruginosa*) treated with nebulized amikacin/fosfomycin versus placebo [340]; and the third trial compared the outcomes of 508 adults with pneumonia (32% caused by *P. aeruginosa*) treated with nebulized amikacin *versus* placebo [341]. None of the three clinical trials demonstrated improved clinical outcomes or a survival benefit with the use of nebulized antibiotics compared with placebo for the treatment of ventilator-associated pneumonia, including in subgroup analyses of drug-resistant pathogens [339-341].

Reasons for the lack of clinical benefit in these trials are unclear. In a pharmacokinetic-pharmacodynamic modeling study, aerosolized delivery of the prodrug of colistin to critically ill patients achieved high active drug levels in epithelial lining fluid of the lungs [342]. However, it is likely that nebulized antibiotics do not achieve sufficient penetration and/or distribution throughout lung tissue to exert significant bactericidal activity [343], likely due in part to the use of parenteral formulations not specifically designed for inhalation in suboptimal delivery devices such as jet nebulizers [344, 345]. Professional societies have expressed conflicting views regarding the role of nebulized antibiotics as adjunctive therapy to intravenous antibiotics [346-348]. The panel recommends against the use of nebulized antibiotics as adjunctive therapy for DTR-*P. aeruginosa* pneumonia due to the lack of benefit observed in clinical trials, concerns regarding unequal distribution in infected lungs, and concerns for respiratory complications such as bronchoconstriction in 10-20% of patients receiving aerosolized antibiotics [349].

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# 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 resistance. This treatment guidance focusing on ESBL-E, CRE, and DTR-*P. aeruginosa* will be updated annually and is available at: https://www.idsociety.org/practice-guideline/amr-guidance/. A second AMR treatment guidance focusing on the treatment of infections caused by AmpC-producing Enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* infections is available at: https://www.idsociety.org/practice-guideline/amr-guidance-2.0/.

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# Notes

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**Conflict of Interest Summary:** The following list is a reflection of what has been reported to IDSA. To provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guidance topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the Board of Directors liaison to the Standards and Practice Guidelines Committee and, if necessary, the Conflicts of Interest and Ethics Committee. The assessment of disclosed relationships for possible conflicts of interests is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). Readers of this guidance should be mindful of this when the list of disclosures is reviewed. **P.D.T.** has nothing to disclose and does not receive any funding from any commercial groups. **S.L.A.** serves as advisor to Shionogi and Entasis Therapeutics; served on the advisory panel for Merck, Paratek, Medicines Company, Zavante, Shionogi, Sempra, and Theravance; and received research funding paid from Melinta and Merck. **R.A.B**. receives research funding from the National Institute of Allergy and Infectious Diseases, Veterans Health Administration, Shionogi, VenatoRx, Merck, Allecra, Wockhardt, Shionogi, AstraZeneca, Harrington Foundation, and Entasis; received research funding from Tetraphase and Steris; and served on the editorial boards for *Antimicrobial Agents and Chemotherapy*, *mBio*, and the Veterans Affairs Society for Prevention of Infectious Diseases. **A.J.M.** serves as a consultant/advisor for Merck, Shionogi, Qpex Biopharma, Accelerate Diagnostics, and VenatoRX; received research grants from the CDC and Wallace H. Coulter Endowment; and served as an advisor for Rempex and Antimicrobial Resistance Services. **D.v.D.** serves as member of the advisory group for Qpex Biopharma, Shionogi, and Merck; receives honoraria from Shionogi and Pfizer; receives other numeration from the British Society for Antimicrobial Chemotherapy; receives research grants from Shionogi; served as an advisory board member for Entasis, Roche, Allergan, Utility, and Achaogen; served as non-promotional speaker for Entasis and Pfizer; received research funding from the National Institutes of Health and Merck; serves as editor-in-chief for *JAC-Antimicrobial Resistance*; and is on the program committee for the European Society of Clinical Microbiology and Infectious Diseases. **C.J.C.** served on the advisory board for Merck, Qpex Biopharma,

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and Shionogi; serves as an advisory Board member for Astellas, Cidara, and Scynexis; serves as a consultant for Needham & Associates; and receives research funding from Astellas and Merck. All other authors: no disclosures reported. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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