Infectious Diseases Society of America Antimicrobial Resistant Treatment Guidance: Gram-Negative Bacterial Infections

A Focus on 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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Introduction

The rise in antimicrobial resistance (AMR) continues to be a global crisis [1, 2]. Collectively, antimicrobial resistant pathogens caused more than 2.8 million infections and over 35,000 deaths annually in the United States from 2012 through 2017, according to the 2019 Centers for Disease Control and Prevention (CDC) Antibiotic Resistant Threats Report [2]. The selection of effective antibiotics for the treatment of infections by resistant pathogens is challenging [3]. Although there has been an increase in the availability of novel antibiotics to combat resistant infections in recent years [3], resistance to a number of these agents has been observed [4]. Three groups of antimicrobial resistant Gram-negative bacteria pose particular therapeutic challenges: (1) extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), (2) carbapenem-resistant Enterobacterales (CRE), and (3) *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa)* [5]. These pathogens have been designated urgent or serious threats by the CDC [2]. They are encountered in US hospitals of all sizes and cause a wide range of serious infections that carry significant morbidity and mortality. Treatment options against ESBL-E, CRE, and DTR-*P. aeruginosa* infections remain limited despite approval of new antibiotics. There is often uncertainty about the precise role(s) of new agents in clinical practice [6-8].

The Infectious Diseases Society of America (IDSA) identified the development and dissemination of clinical practice guidelines and other guidance products for clinicians as a top initiative in its 2019 Strategic Plan [9]. IDSA acknowledged that the ability to address rapidly evolving topics such as AMR was limited by prolonged timelines needed to generate new or updated clinical practice guidelines. As an alternative and complement to comprehensive clinical practice guidelines, IDSA endorsed developing more narrowly focused guidance documents for the treatment of specific infectious processes. Guidance documents will address specific clinical questions for difficult-to-manage infections that are not covered by present guidelines. The documents will be prepared by a small team of experts based on a comprehensive (but not necessarily systematic) review of the literature. Additionally, such guidance documents will not include a formal grading of the evidence, unlike IDSA guidelines, which utilize the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework. Over time, guidance documents may be transitioned to a GRADE format. Content will be disseminated on multiple platforms and updated as new data emerge. Treatment of antimicrobial resistant Gram-negative bacterial infections was chosen as the initial topic for a guidance document.

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

Methodology

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

General Management Recommendations

Preferred and alternative treatment recommendations in this guidance document assume that the causative organism has been identified and *in vitro* activity of antibiotics has been demonstrated. The cost of agents was not considered by the panel. Assuming two antibiotics are equally effective and safe, cost and local formulary availability are important considerations in selecting a specific agent. The

panel recommends that infectious diseases specialists are involved in the management of patients with antimicrobial resistant infections, if feasible.

Empiric Therapy. Empiric treatment recommendations are not provided in this guidance document, since a given host at risk for infection by one of the pathogen groups is usually at risk of infection by other antimicrobial resistant pathogens. Empiric treatment decisions should be guided by local susceptibility patterns for the most likely pathogens. When determining empiric treatment for a given patient, clinicians should consider (1) previous organisms and associated antibiotic susceptibility data in the last six months and (2) antibiotic exposures in the past 30 days (e.g., if a treatment course of piperacillin-tazobactam was recently completed, consider empiric coverage with a Gram-negative agent from a different class that offers comparable spectrum of activity [e.g., meropenem]). Empiric decisions should be refined based on the severity of illness of the patient and the likely source of the infection (e.g., presumed ventilator-associated pneumonia typically warrants broader empiric coverage than presumed cystitis).

Duration of Therapy. Recommendations on durations of therapy are not provided, but clinicians are advised that prolonged treatment courses are not necessary against infections by antimicrobial resistant pathogens *per se*, compared to infections caused by the same bacterial species with a more susceptible phenotype. After antibiotic susceptibility results are available, it may become apparent that inactive antibiotic therapy was initiated empirically. This may impact the duration of therapy. For example, cystitis is typically a mild infection. If an antibiotic not active against the causative organism was administered empirically for cystitis but clinical improvement nonetheless occurred, it is generally not necessary to repeat a urine culture, change the antibiotic regimen, or extend the planned treatment course [10]. However, for all other infections included here, if antibiotic susceptibility data indicate a potentially inactive agent was initiated empirically, a change to an active regimen for a full treatment course (dated from the start of active therapy) is recommended. Additionally, important host factors related to immune status, ability to attain source control, and general response to therapy should be considered when determining treatment durations for antimicrobial resistant infections, as with the treatment of any bacterial infection.

Extended-spectrum β-lactamase-Producing Enterobacterales (ESBL-E)

The incidence of ESBL-E infections in the United States increased by 53% from 2012 through 2017, in large part due to increased community-acquired infections [11]. 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* [12, 13]. CTX-M enzymes, particularly CTX-M-15, are the most common ESBLs in the United States [13]. ESBLs other than CTX-M with unique hydrolyzing abilities have been identified, including variants of narrow-spectrum TEM and SHV β-lactamases with amino acid substitutions [14-16]. Routine EBSL testing is not performed by most clinical microbiology laboratories [17, 18]. Rather, non-susceptibility to ceftriaxone (i.e., ceftriaxone minimum inhibitory concentrations [MICs] $\geq$ 2 mcg/mL), is often used as a proxy for ESBL production [18]. For this guidance document, ESBL-E will refer to presumed or confirmed ESBL-producing *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*. **Table 2** outlines preferred and alternative treatment recommendations for ESBL-E infections. Treatment recommendations for ESBL-E infections assume *in vitro* activity of preferred and alternative antibiotics has been demonstrated.

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

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

Rationale: Nitrofurantoin and trimethoprim-sulfamethoxazole have been shown to be safe and effective options for cystitis [10, 19, 20].

Although fluoroquinolones (i.e., ciprofloxacin or levofloxacin) and carbapenems are effective agents against ESBL-E cystitis, their usage for cystitis is discouraged when other safe and effective

options are available. Limiting use of these agents serves to both preserve their activity for future infections and to limit associated toxicities, particularly with the fluoroquinolones.

Amoxicillin-clavulanate, single-dose aminoglycosides, and oral fosfomycin are alternative options for ESBL-E cystitis. Amoxicillin-clavulanate is an alternative rather than preferred agent since randomized controlled trial data have shown it is associated with a higher clinical failure rate than ciprofloxacin for cystitis, presumably due to persistent vaginal bacterial colonization [21]. Aminoglycosides are nearly exclusively eliminated by the renal route in their active form. A single intravenous dose is generally effective for cystitis, with minimal toxicity, but robust trial data are lacking [22]. Oral fosfomycin is an alternative agent exclusively for treatment of ESBL-producing *E. coli* cystitis as the *fosA* gene, intrinsic to *K. pneumoniae* and several other Gram-negative organisms, can hydrolyze the drug and may lead to clinical failure [23, 24]. Randomized controlled trial data indicate that oral fosfomycin is associated with higher clinical failure than nitrofurantoin for uncomplicated cystitis [19]. Doxycycline is not recommended for the treatment of ESBL-E cystitis due to its limited urinary excretion [25].

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

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

Rationale: cUTIs are defined as a UTI occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient. Carbapenems, ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole are all preferred treatment options for patients with ESBL-E pyelonephritis and cUTIs based on clinical experience and the ability of these agents to achieve high concentrations in the urine. If a carbapenem is initiated and susceptibility to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole is demonstrated, transitioning to these agents is preferred over completing a treatment course with a carbapenem. Limiting use of carbapenem exposure in these situations will preserve their activity for future antimicrobial resistant infections. Nitrofurantoin and oral fosfomycin do not achieve adequate concentrations in the renal parenchyma and should be avoided if

the upper urinary tract is infected [26, 27]. Doxycycline is not recommended for the treatment of ESBL-E pyelonephritis or cUTIs due to its limited urinary excretion [25].

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

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

Rationale: A carbapenem is recommended as first-line treatment of infections outside of the urinary tract caused by ESBL-E, based largely on data from a multicenter randomized controlled trial [28]. In this trial, 30-day mortality was reduced for patients with ESBL *E. coli* and *K. pneumoniae* bloodstream infections treated with meropenem compared to piperacillin-tazobactam [28]. Comparable clinical trial data are not available for infections of other body sites. Nevertheless, the panel recommends extrapolating evidence for ESBL-E bloodstream infections to other common sites of infection, namely intra-abdominal infections, skin and soft tissue infections, and pneumonia.

The role of oral step-down therapy for ESBL-E non-urinary infections 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 observed [29, 30]. Based on the known bioavailability and sustained serum concentrations of oral fluoroquinolones and trimethoprim-sulfamethoxazole, these agents are reasonable treatment options for patients with ESBL-E infections if (1) susceptibility to the oral agent is demonstrated, (2) patients are afebrile and hemodynamically stable, (3) appropriate source control is achieved, and (4) there are no issues with intestinal absorption.

Clinicians should avoid oral step-down to nitrofurantoin, fosfomycin, doxycycline, or amoxicillin-clavulanate for ESBL-E bloodstream infections. Nitrofurantoin and fosfomycin achieve poor serum concentrations. Amoxicillin-clavulanate and doxycycline achieve unreliable serum concentrations and are not recommended for ESBL-E bloodstream infections.

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

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

Rationale: Piperacillin-tazobactam demonstrates *in vitro* activity against a number of ESBL-E [31]. However, a randomized, controlled trial of ESBL-E bloodstream infections indicated inferior results with piperacillin-tazobactam compared to carbapenem therapy [28]. The effectiveness of piperacillin-tazobactam in the treatment of invasive ESBL-E infections may be diminished by the potential for organisms to have increased expression of the ESBL enzyme or by the presence of multiple β-lactamases [32]. Additionally, piperacillin-tazobactam MIC testing may be inaccurate and/or poorly reproducible when ESBL enzymes are present [33-35].

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

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

Rationale: Observational studies and a subgroup analysis of 23 patients in a randomized trial that compared cefepime and carbapenems for the treatment of invasive ESBL-E infections demonstrated either no difference in outcomes or poorer outcomes with cefepime [36-39]. Cefepime MIC testing may be inaccurate and/or poorly reproducible when ESBL enzymes are present [33, 34, 40].

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

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

Rationale: Currently, there is no Clinical and Laboratory Standards Institute endorsed phenotypic method for confirmatory ESBL testing [18]. For hospitals with clinical microbiology laboratories that do not perform ESBL phenotypic testing, a ceftriaxone MIC $\geq$ 2 mcg/mL should be used as a proxy for ESBL production by *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* [18]. Phenotypic tests (e.g., double-disk synergy test, ETEST®, automated susceptibility platform algorithms) to exclude the possibility of ESBL production by clinical isolates should be interpreted with caution. Results should be used for clinical decision-making only after local laboratory validation of testing [41, 42].

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

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

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

Carbapenem-Resistant Enterobacterales (CRE)

CRE account for more than 13,000 nosocomial infections and contribute to greater than 1,000 deaths annually in the United States [2]. The CDC defines CRE as members of the Enterobacterales order resistant to at least one carbapenem antibiotic or producing a carbapenemase enzyme [2]. A CRE isolate may be resistant to some carbapenems (e.g., ertapenem) but not others (e.g., meropenem). CRE comprise a heterogenous group of pathogens with multiple potential mechanisms of resistance, broadly divided into those that are carbapenemase-producing and those that are not carbapenemase-producing. Carbapenemase-producing isolates account for approximately half of all CRE infections in the United States [43-45]. The most common carbapenemases in the United States are *Klebsiella pneumoniae* carbapenemases (KPCs), which can be produced by any Enterobacterales. Other notable carbapenemases that have all been identified in the United States include New Delhi metallo-β-lactamases (NDMs), Verona integron-encoded metallo-β-lactamases (VIMs), imipenem-hydrolyzing metallo-β-lactamases (IMPs), and oxacillinase (e.g., OXA-48-like) carbapenemases [46, 47]. 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 [48]. Molecular testing can identify specific carbapenemase families (e.g., differentiating a KPC from an OXA-48-like carbapenemase). There are several molecular platforms used in US clinical microbiology laboratories to identify carbapenemase genes (e.g., Verigene® Gram-Negative Blood Culture Test, GenMark ePlex® Blood Culture Identification Gram-negative Panel, BioFire® FilmArray® Blood Culture Identification Panels, etc.). Phenotypic and/or genotypic testing are not performed by all clinical microbiology laboratories. **Table 3** outlines preferred and alternative treatment recommendations for CRE infections. Treatment recommendations for CRE infections assume *in vitro* activity of preferred and alternative antibiotics has been demonstrated.

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

Recommendation: Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single-dose of an aminoglycoside are preferred treatment options for uncomplicated cystitis caused by

CRE. Standard infusion meropenem is a preferred treatment option for cystitis caused by CRE resistant to ertapenem but susceptible to meropenem, when carbapenemase testing results are either not available or negative.

Rationale: Clinical trial data evaluating the efficacy of most preferred agents for CRE cystitis are not available. However, as these agents achieve high concentrations in urine, they are expected to be effective for CRE cystitis, when active. Some agents that are listed as alternative options for ESBL-E cystitis are recommended as preferred agents for CRE cystitis. These agents are preferably avoided in treatment of ESBL-E cystitis in order to preserve their activity for more invasive infections. They are preferred agents against CRE cystitis because there are generally fewer treatment options against 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 [22]. 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 [49, 50]. Plazomicin may remain active against isolates resistant to amikacin.

Meropenem is a preferred agent against CRE cystitis for isolates that remain susceptible to meropenem, since most of these isolates do not produce carbapenemases [44]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated.

If none of the preferred agents is active, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are alternative options for CRE cystitis [51-55]. Data are insufficient to favor one agent over the others. Although a clinical trial demonstrated increased mortality with cefiderocol compared to best available therapy against a variety of infections due to carbapenem-resistant Gram-negative bacteria, these findings do not appear to extend to urinary tract infections [54, 56]. Fosfomycin use should be limited to *E. coli* cystitis as the *fos A* gene (intrinsic to certain Gram-negative organisms such as *Klebsiella* species, *Enterobacter* spp., and *Serratia marcescens*) can hydrolyze fosfomycin and may lead to clinical failure [23, 24]. Randomized controlled trial data indicate that oral fosfomycin is associated with higher clinical failure than nitrofurantoin for uncomplicated cystitis [19].

Colistin is an alternative consideration for treating CRE cystitis only if none of the above agents is an option. Colistin converts to its active form in the urinary tract; clinicians should remain cognizant of the associated risk of nephrotoxity [57]. Polymyxin B should not be used as treatment for CRE cystitis due to its predominantly nonrenal clearance.

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

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis and cUTIs caused by CRE resistant to both ertapenem and meropenem. Extended-infusion meropenem is a preferred treatment option for pyelonephritis and cUTIs caused by CRE resistant to ertapenem but susceptible to meropenem, when carbapenemase testing results are either not available or negative.

Rationale: cUTIs are defined as a UTI occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis and cUTIs caused by CRE resistant to both ertapenem and meropenem based on randomized controlled trials showing non-inferiority of these agents to common comparator agents for UTIs [51-55]. Data are insufficient to favor one agent over the others. Although a clinical trial demonstrated increased mortality with cefiderocol compared to best available therapy against a variety of infections due to carbapenem-resistant Gram-negative bacteria, these findings do not appear to extend to UTIs [54, 56].

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 [44]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated.

In patients in whom the potential for nephrotoxicity is deemed acceptable, once-daily aminoglycosides for a full treatment course is an alternative option. Once-daily plazomicin was noninferior to meropenem in a randomized controlled trial that included patients with pyelonephritis

and cUTIs caused by Enterobacterales [58]. 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 [49, 50]. Plazomicin may remain active against isolates resistant to amikacin. Oral fosfomycin does not achieve adequate concentrations in the renal parenchyma and should be avoided if the upper urinary tract is infected [27].

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

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

Rationale: Extended-infusion meropenem is recommended against infections outside of the urinary tract by CRE that remain susceptible to meropenem since most of these isolates do not produce carbapenemases [44]. Meropenem should be avoided if carbapenemase testing is positive, even if susceptibility to meropenem is demonstrated.

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

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

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

Rationale: The vast majority of infections caused by CRE in the United States resistant to both ertapenem and meropenem are caused by organisms that either do not produce carbapenemases or by organisms that produce KPC-carbapenemases [44]. Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are preferred treatment options for CRE infections resistant to both ertapenem and meropenem, without additional information regarding carbapenemase status. These agents are associated with improved clinical outcomes and reduced toxicity compared to other regimens commonly used to treat CRE infections, which are generally polymyxin-based [59-63].

Comparative effectiveness studies between the preferred agents are limited. An observational study including 131 patients with CRE infections found no difference in clinical outcomes between patients treated with ceftazidime-avibactam or meropenem-vaborbactam [64]. Significantly less clinical information is available for imipenem-cilastatin-relebactam than for the other preferred treatment options for the treatment of CRE infections. However, *in vitro* activity of this combination against CRE [65-67], clinical experience with imipenem-cilastatin, and the stability of relebactam as a β-lactamase inhibitor [68] suggest imipenem-cilastatin-relebactam is likely to be effective for CRE infections.

Available data suggest that the emergence of ceftazidime-avibactam resistance is more common than emergence of meropenem-vaborbactam resistance following exposure to the respective agents [64, 69-73]. As each of these drugs is used more extensively, it is anticipated that additional data on resistance and comparative effectiveness will emerge.

Cefiderocol is an alternative treatment option for CRE infections, regardless of the mechanism of resistance to carbapenems. Cefiderocol has reliable *in vitro* activity against CRE, including isolates with otherwise highly resistant phenotypes [74-76]. In a clinical trial, cefiderocol was compared to best available therapy, which frequently consisted of colistin-based regimens, for the treatment of carbapenem-resistant Gram-negative infections in 118 patients; 51% of patients were infected with CRE [56]. Mortality at 28 days was higher in the cefiderocol arm. These findings were most striking for the treatment of pneumonia and bloodstream infections. Until more data are available to define subpopulations in whom cefiderocol can be used effectively and safely beyond the urinary tract, the

panel recommends that this agent be reserved for CRE infections in which preferred agents are unavailable due to intolerance or resistance.

If a patient is infected with a CRE strain with unknown carbapenemase status and the patient has recently traveled from an area where metallo-β-lactamases are endemic (e.g., Middle East, South Asia, Mediterranean) [77], treatment with ceftazidime-avibactam plus aztreonam, or cefiderocol monotherapy are recommended. Preferred treatment approaches for infections caused by metallo-β-lactamase producers also provide activity against bacteria producing KPCs or OXA-48-like enzymes.

In patients with intra-abdominal infections, tigecycline and eravacycline are acceptable monotherapy options; high dose tigecycline may be more effective than standard dose tigecycline for complicated intra-abdominal infections, as listed in Table 1 [78-80]. Their activity is independent of the presence or type of carbapenemases. The use of tigecycline or eravacycline should generally be limited to the treatment of intra-abdominal infections. These agents achieve rapid tissue distribution following administration, resulting in limited concentration in the urine and poor serum concentrations [81].

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

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

Rationale: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam provide activity against Enterobacterales that produce KPC enzymes, the most common carbapenemases in the United States [65, 66, 82-84]. If a disease-causing Enterobacterales is carbapenemase-producing but the specific carbapenemase enzyme is unknown, it is reasonable to treat as if the strain is a KPC producer. Comparative effectiveness studies of the preferred agents are limited. An observational study including 131 patients with CRE infections found no difference in clinical outcomes following treatment with ceftazidime-avibactam or meropenem-vaborbactam [64].

Significantly less clinical information is available for imipenem-cilastatin-relebactam than for the other preferred treatment options for the treatment of CRE infections. However, *in vitro* susceptibility activity of this combination against CRE [65-67], clinical experience with imipenem-cilastatin, and the stability of relebactam as a β-lactamase inhibitor [68] suggest imipenem-cilastatin-relebactam is likely to be effective for CRE infections. Available data suggest that the emergence of ceftazidime-avibactam resistance is more common than emergence of meropenem-vaborbactam resistance following exposure to the respective agents [64, 69-73]. As each of these drugs is used more extensively, it is anticipated that additional data on resistance and comparative effectiveness will emerge.

If a metallo-β-lactamase (i.e., NDM, VIM, or IMP) is identified, preferred antibiotic options include ceftazidime-avibactam plus aztreonam, or cefiderocol monotherapy [85-89]. Clinical outcomes data comparing these two treatment strategies are not available.

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

In patients with intra-abdominal infections, tigecycline and eravacycline are acceptable monotherapy options; high dose tigecycline may be more effective than standard dose tigecycline for complicated intra-abdominal infections, as listed in Table 1 [78-80]. Their activity is independent of the presence of carbapenemases. The panel recommends avoiding tigecycline or eravacycline for the treatment of most CRE infections other than intra-abdominal infections. These agents achieve rapid tissue distribution following administration, resulting in limited concentration in the urine and poor serum concentrations [81].

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

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

Rationale: Observational and randomized-controlled trial data indicate increased mortality and excess nephrotoxicity associated with polymyxin-based regimens relative to comparator agents [59-61, 63]. Concerns about the clinical effectiveness of polymyxins and accuracy of *in vitro* polymyxin susceptibility

testing led the Clinical and Laboratory Standards Institute to eliminate a susceptible category for colistin and polymyxin B [18]. The panel recommends that these agents be avoided for the treatment of CRE infections, with the exception of colistin as a last resort agent against CRE cystitis. Polymyxin B should not be used as treatment for CRE cystitis, due to its predominantly nonrenal clearance.

Question 7: 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 to broaden the likelihood of at least one active therapeutic agent for patients at risk for CRE infections is reasonable, data do not indicate that continued combination therapy – once the β-lactam agent has demonstrated *in vitro* activity – offers any additional benefit [90]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [90].

Observational data and clinical trials comparing ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam to combination regimens to treat CRE infections have not shown the latter to have added value [59-63]. Randomized trial data are not available comparing these 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 expert panel does not recommend combination therapy for CRE infections, when susceptibility to a preferred β-lactam agent has been demonstrated.

Difficult-to-Treat Resistance (DTR) *Pseudomonas aeruginosa*

The CDC reports that 32,600 cases of multidrug-resistant *P. aeruginosa* infection occurred in patients hospitalized in the United States in 2017, resulting in 2,700 deaths [2]. Multidrug resistance is defined as non-susceptibility to at least one antibiotic in at least three classes for which *P. aeruginosa* susceptibility is generally expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and

carbapenems. In 2018, the concept of "difficult-to-treat" resistance (DTR) was proposed [5]. In this guidance document, DTR is defined as *P. aeruginosa* exhibiting non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin. **Table 4** outlines preferred and alternative treatment recommendations for DTR-*P. aeruginosa* infections. Treatment recommendations for DTR-*P. aeruginosa* infections assume *in vitro* activity of preferred and alternative antibiotics has been demonstrated.

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

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

Rationale: Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for uncomplicated DTR *P. aeruginosa* cystitis, based on randomized controlled trials showing non-inferiority of these agents to common comparator agents for urinary tract infections [52, 54, 55, 91]. Data are insufficient to favor one of the agents over the others, and available trials generally do not include patients infected by pathogens with DTR phenotypes. Although a clinical trial demonstrated increased mortality with cefiderocol compared to best available therapy against a variety of infections due to carbapenem-resistant Gram-negative bacteria, these findings do not appear to extend to urinary tract infections [54, 56].

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 cystitis, with minimal toxicity, but robust trial data to formally evaluate their activity for cystitis are lacking [22]. Plazomicin is unlikely to provide any incremental benefit against DTR-*P. aeruginosa* if resistance to all other aminoglycosides is demonstrated [92].

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; clinicians should remain cognizant of the associated risk of nephrotoxity [57]. 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 [93, 94]. This is in part due to the presence of the *fos A* gene, which is intrinsic to *P. aeruginosa* [23].

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

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

Rationale: cUTIs are defined as a UTI occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient. Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for DTR-*P. aeruginosa* pyelonephritis and cUTI, based on randomized controlled trials showing non-inferiority of these agents to common comparator agents [52, 54, 55, 91]. Data are insufficient to favor one of the agents over the others and available trials generally do not include DTR phenotypes. Although a clinical trial demonstrated increased mortality with cefiderocol compared to best available therapy against a variety of infections due to carbapenem-resistant Gram-negative bacteria, these findings do not appear to extend to UTIs [54, 56].

In patients in whom the potential for nephrotoxicity is deemed acceptable, once-daily aminoglycosides is an alternative option. Plazomicin is unlikely to provide any incremental benefit against DTR-*P. aeruginosa* if resistance to all other aminoglycosides is demonstrated [92]. Oral fosfomycin should be avoided for DTR-*P. aeruginosa* pyelonephritis and cUTI. This is because of the presence of the *fosA* gene intrinsic to *P. aeruginosa* which confers fosfomycin resistance and because oral fosfomycin does not achieve adequate concentrations in the renal parenchyma [23, 27].

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

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

Rationale: Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam, as monotherapy, are preferred options for the treatment of DTR-*P. aeruginosa* infections outside of the urinary tract, based on known *in vitro* activity, observational studies, and clinical trial data [52, 63, 82, 84, 95-104]. The majority of these observational studies and clinical trial data do not include patients with DTR-*P. aeruginosa* infections. Clinical outcomes studies comparing the effectiveness of these three agents for DTR-*P. aeruginosa* infections are not available.

The percentage of *P. aeruginosa* clinical isolates that are susceptible to ceftolozane-tazobactam is generally higher than percentages susceptible to comparator agents. This is likely because ceftolozane does not rely on an inhibitor to restore susceptibility to an otherwise inactive drug (i.e., ceftolozane has independent activity against DTR-*P. aeruginosa*). Neither ceftazidime nor imipenem is active against DTR-*P. aeruginosa*. Avibactam and relebactam expand activity of these agents mainly through inhibition of AmpC, but other complex resistance mechanisms are unlikely to be impacted. Since ceftolozane-tazobactam and ceftazidime-avibactam are similar in their mechanisms of action [105], cross-resistance between these agents can be observed [106].

Cefiderocol is an alternative treatment option. Cefiderocol has reliable *in vitro* activity against *P. aeruginosa*, including isolates with otherwise highly resistant phenotypes [74-76]. In a clinical trial, cefiderocol was compared to best available therapy, which frequently consisted of colistin-based regimens, for the treatment of carbapenem-resistant Gram-negative infections in 118 patients; 24% of patients were infected with *P. aeruginosa* [56]. Mortality at 28 days was higher in the cefiderocol arm. These findings were most striking for the treatment of pneumonia and bloodstream infections. Until more data are available to define subpopulations in whom cefiderocol can be used effectively and safely beyond the urinary tract, the panel recommends that this agent be reserved for DTR-*P. aeruginosa* infections in which preferred agents are unavailable due to intolerance or resistance.

Aminoglycoside monotherapy (outside of the urinary tract) is an alternative option that should be limited to uncomplicated bloodstream infections (i.e., urinary source or other sources for which control is achieved, such as the removal of an infected vascular catheter) when no preferred treatment

option is available. Plazomicin is unlikely to provide any incremental benefit against DTR-*P. aeruginosa* if resistance to all other aminoglycosides is demonstrated [92].

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

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

Rationale: Although empiric combination antibiotic therapy (i.e., the addition of an aminoglycoside or polymyxin 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 [90]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [90].

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 [63, 98]. 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 available outcomes data, clinical experience, and known toxicities associated with aminoglycosides and polymyxins, the panel agrees that combination therapy is not routinely recommended for DTR-*P. aeruginosa* infections, when susceptibility to a preferred β-lactam agent has been demonstrated.

If no preferred agent demonstrates activity against DTR-*P. aeruginosa*, an aminoglycoside (if susceptibility is demonstrated) can be considered in combination with 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 [18, 107]) and the imipenem-cilastatin-relebactam MIC is 4/4 mcg/mL (intermediate category [107]), imipenem-cilastatin-relebactam in combination with an active aminoglycoside should be 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 favorable clinical outcomes compared to cefiderocol, either as monotherapy or combination therapy. 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 [108-113].

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 AMR Treatment Guidance document will be updated through an iterative review process that will incorporate new evidence-based data. Furthermore, the panel will expand recommendations to include other problematic Gram-negative pathogens in future versions of the document.

Table 1. Suggested dosing of antibiotics for the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and difficult-to-treat resistance (DTR)-*Pseudomonas aeruginosa* infections

Agent	Adult Dosage (assuming normal renal and liver function)
Amikacin	**Cystitis**: 15 mg/kg/dose[1] IV once **All other infections**: 20 mg/kg/dose[1] IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation
Amoxicillin-clavulanate	**Cystitis:** 875 mg (amoxicillin component) PO q12h
Cefiderocol	2 g IV q8h, infused over 3 hours
Ceftazidime-avibactam	2.5 g IV q8h, infused over 3 hours
Ceftazidime-avibactam and aztreonam Ceftazidime-avibactam should be infused concurrently with aztreonam.	**Ceftazidime-avibactam**: 2.5 g IV q8h, infused over 3 hours **PLUS** **Aztreonam**: 2 g IV q8h, infused over 3 hours
Ceftolozane-tazobactam	**Cystitis:** 1.5 g IV q8h, infused over 1 hour **All other infections:** 3 g IV q8h; infused over 3 hours
Ciprofloxacin	400 mg IV q8h or 750 mg PO q12h
Colistin	Refer to international consensus guidelines on polymyxins[1]
Eravacycline	1 mg/kg/dose IV q12h
Ertapenem	1 g IV q24h, infused over 30 minutes
Fosfomycin	**Cystitis:** 3 g PO x 1 dose
Gentamicin	**Cystitis**: 5 mg/kg/dose[1] IV once **All other infections:** 7 mg/kg/dose[1] IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation
Imipenem-cilastatin	**Cystitis (standard infusion)**: 500 mg IV q6h, infused over 30 minutes **All other infections (extended-infusion)**: 500 mg IV q6h; infused over 3 hours
Imipenem-cilastatin-relebactam	1.25 g IV q6h, infused over 30 minutes

Levofloxacin	750 mg IV/PO q24h
Meropenem	**Cystitis (standard infusion)**: 1 g IV q8h **All other infections (extended-infusion)**: 2 g IV q8h, infused over 3 hours
Meropenem-vaborbactam	4 g IV q8h, infused over 3 hours
Nitrofurantoin	**Cystitis:** Macrocrystal/monohydrate (Macrobid®) 100 mg PO q12h **Cystitis:** Oral suspension: 50 mg q6h (M
Plazomicin	**Cystitis:** 15 mg/kg[1] IV x x1 dose **All other infections:** 15 mg/kg[1] IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation
Polymyxin B	Refer to international consensus guidelines on polymyxins[2]
Tigecycline	**Uncomplicated intra-abdominal infections (standard dose)**: 100 mg IV x 1 dose, then 50 mg IV q12h **Complicated intra-abdominal infections (high dose):** 200 mg IV x 1 dose, then 100 mg IV q12h
Tobramycin	**Cystitis**: 7 mg/kg/dose[1] IV x 1 dose **All other infections**: 7 mg/kg/dose[1] IV x 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation
Trimethoprim-sulfamethoxazole	**Cystitis**: 160 mg (trimethoprim component) IV/PO q12h **Other infections**: 8-10 mg/kg/day (trimethoprim component) IV/PO divided q8-12h; maximum dose 320 mg PO q8h

[1]Recommend using adjusted body weight for patients >120% of ideal body weight for aminoglycoside dosing.

[2] 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.

Table 2. Recommended antibiotic treatment options for presumed or confirmed extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), assuming *in vitro* susceptibility to agents in table

Source of Infection	**Preferred Treatment**	**Alternative Treatment** (first-line options not available or tolerated)
Cystitis	Nitrofurantoin, trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate, single-dose aminoglycosides, fosfomycin (*E. coli* only) Ciprofloxacin, levofloxacin, ertapenem, meropenem, imipenem-cilastatin
Pyelonephritis or cUTI[1]	Ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole	
Infections outside of the urinary tract	Meropenem, imipenem-cilastatin, ertapenem Oral step-down therapy to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole can be considered[2].	

[1]cUTI: Complicated urinary tract infections are defined as UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[2]Oral step-down therapy can be considered after (1) susceptibility to the oral agent is demonstrated, (2) patients are afebrile and hemodynamically stable, (3) appropriate source control is achieved, and (4) there are no issues with intestinal absorption.

Table 3. Recommended antibiotic treatment options for carbapenem-resistant Enterobacterales (CRE), assuming *in vitro* susceptibility to agents in table

Source of Infection	**Preferred Treatment**	**Alternative Treatment** (first-line options not available or tolerated)
Cystitis	Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single-dose of an aminoglycoside Meropenem[1] (standard-infusion): only if ertapenem resistant, meropenem susceptible, AND carbapenemase testing results are either not available or negative.	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol Colistin (only when no alternative options are available)
Pyelonephritis or cUTI[2]	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol Meropenem[1] (extended-infusion): only if ertapenem resistant, meropenem susceptible, AND carbapenemase testing results are either not available or negative.	Once-daily aminoglycosides
Infections outside of the urinary tract Resistant to ertapenem, susceptible to meropenem, AND carbapenemase testing results are either not available or negative	Meropenem[1] (extended-infusion)	Ceftazidime-avibactam
Infections outside of the urinary tract Resistant to ertapenem, meropenem, AND carbapenemase testing results are either not available or negative	Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)
KPC identified (Or carbapenemase positive but identity of carbapenemase unknown[3])	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)

Metallo-β-lactamase (i.e., NDM, VIM, or IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam, cefiderocol	Tigecycline, eravacycline (intra-abdominal infections)
OXA-48-like carbapenemase identified	Ceftazidime-avibactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)

[1]The majority of infections caused by CRE resistant to ertapenem but susceptible to meropenem are caused by organisms that do not produce carbapenemases.

[2]cUTI: Complicated urinary tract infections are defined as UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

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

Table 4. Recommended antibiotic treatment options for difficult-to-treat (DTR) *Pseudomonas aeruginosa*, assuming *in vitro* susceptibility to agents in table

Source of Infection	**Preferred Treatment**	**Alternative Treatment** (when first-line options not available/tolerated)
Cystitis	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol, or a single-dose of an aminoglycoside	Colistin
Pyelonephritis or cUTI[1]	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol	Once-daily aminoglycosides
Infections outside of the urinary tract	Ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam	Cefiderocol Aminoglycoside monotherapy: limited to uncomplicated bloodstream infections with complete source control[2]

[1]cUTI: Complicated urinary tract infections are defined as UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

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

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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, the 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 Guideline Committee and, if necessary, the Conflicts of Interest (COI) and Ethics Committee. The assessment of disclosed relationships for possible COI 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). The reader of this guidance should be mindful of this when the list of disclosures is reviewed.

S.A served on the advisory panel for Merck; served on the advisory board for Paratek, Medicines Company, Zavante, Shionogi, Sempra, Theravance; receives research funding paid to his institution from Melinta and Merck; serves as Chair, Society of Infectious Diseases Pharmacists Guidelines Committee; is a faculty member of Infectious Diseases Board Certification Preparatory Course- American Society of Health-System Pharmacists. **R.B.** receives research funding paid to his institution from VenatoRx, Merck, Entasis, and Tetraphase. **A.M.** served as an advisor for Rempex; serves as a consultant/advisory panel for Qpex Biopharma, Acceclerate Diagnostics, VenatoRX; Antimicrobial Resistance Services; receives research funding (paid to the institution) from Centers for Disease Control and Prevention (CDC) and Wallace H. Coulter Endowment; serves as a member of Antimicrobial Testing Committee, Clinical Laboratory and Standards Institute and is an elected member to the Council on Microbial Sciences,

American Society of Microbiology. **D.D** serves as member of the advisory group for Qpex Biopharma; served as an advisory board member for Shionogi, Entasis, Merck, Roche, Allergan and Achaogen; receives research funding paid to institution from National Institutes of Health (NIH); Member of European Congress of Clinical Microbiology & Infectious Diseases Program Committee. **C.C** served on the advisory board for Merck, Qpex Biopharma, Shionogi; serves as an advisory Board member for Astellas, Cidara, Scynexis; Consultant for Needham & Associates; receives research funding paid to his institution from NIH, Veteran's Administration, Astellas and Merck. All other authors: no disclosures reported.

References

1. World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS) Report: Early Implementation 2017-2018, **2019**.
2. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019.
3. Talbot GH, Jezek A, Murray BE, et al. The Infectious Diseases Society of America's 10 x '20 Initiative (10 New Systemic Antibacterial Agents US Food and Drug Administration Approved by 2020): Is 20 x '20 a Possibility? Clin Infect Dis **2019**; 69(1): 1-11.
4. Ho S, Nguyen L, Trinh T, MacDougall C. Recognizing and Overcoming Resistance to New Beta-Lactam/Beta-Lactamase Inhibitor Combinations. Curr Infect Dis Rep **2019**; 21(10): 39.
5. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin Infect Dis **2018**; 67(12): 1803-14.
6. Clancy CJ, Potoski BA, Buehrle D, Nguyen MH. Estimating the Treatment of Carbapenem-Resistant Enterobacteriaceae Infections in the United States Using Antibiotic Prescription Data. Open Forum Infect Dis **2019**; 6(8): ofz344.
7. Strich JR, Warner S, Lai YL, et al. Needs assessment for novel Gram-negative antibiotics in US hospitals: a retrospective cohort study. Lancet Infect Dis **2020**.
8. Satlin MJ. Languid Uptake of Ceftazidime-Avibactam for Carbapenem-Resistant Gram-Negative Infections and Continued Reliance on Polymyxins. Clin Infect Dis **2020**.
9. Sears CL, File TM, Alexander BD, et al. Charting the Path Forward: Development, Goals and Initiatives of the 2019 Infectious Diseases of America Strategic Plan. Clin Infect Dis **2019**; 69(12): e1-7.
10. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis **2011**; 52(5): e103-20.
11. Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients, 2012-2017. N Engl J Med **2020**; 382(14): 1309-19.
12. Tamma PD, Sharara SL, Pana ZD, et al. Molecular Epidemiology of Ceftriaxone Non-Susceptible Enterobacterales Isolates in an Academic Medical Center in the United States. Open Forum Infect Dis **2019**; 6(8): ofz353.
13. Doi Y, Iovleva A, Bonomo RA. The ecology of extended-spectrum beta-lactamases (ESBLs) in the developed world. J Travel Med **2017**; 24(suppl_1): S44-S51.
14. Bush K, Bradford PA. Epidemiology of beta-Lactamase-Producing Pathogens. Clin Microbiol Rev **2020**; 33(2): e00047-e19.
15. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother **2010**; 54(3): 969-76.
16. Castanheira M, Farrell SE, Krause KM, Jones RN, Sader HS. Contemporary diversity of beta-lactamases among Enterobacteriaceae in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent beta-lactamase groups. Antimicrob Agents Chemother **2014**; 58(2): 833-8.
17. Robberts FJ, Kohner PC, Patel R. Unreliable extended-spectrum beta-lactamase detection in the presence of plasmid-mediated AmpC in Escherichia coli clinical isolates. J Clin Microbiol **2009**; 47(2): 358-61.

18. Clinical and Laboratory Standards Institute. M100 Performance Standards for Antimicrobial Susceptibility Testing. 30 ed. Wayne, PA, **2020**.
19. Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. JAMA **2018**; 319(17): 1781-9.
20. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med **2007**; 167(20): 2207-12.
21. Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA **2005**; 293(8): 949-55.
22. Goodlet KJ, Benhalima FZ, Nailor MD. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? Antimicrob Agents Chemother **2018**; 63(1): e02165-18.
23. Ito R, Mustapha MM, Tomich AD, et al. Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal fosA Gene. mBio **2017**; 8(4): e00749-17.
24. Elliott ZS, Barry KE, Cox HL, et al. The Role of fosA in Challenges with Fosfomycin Susceptibility Testing of Multispecies Klebsiella pneumoniae Carbapenemase-Producing Clinical Isolates. J Clin Microbiol **2019**; 57(10): e00634-19.
25. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother **2006**; 58(2): 256-65.
26. Procter and Gamble Pharmaceuticals, Inc. MACROBID - nitrofurantoin monohydrate and nitrofurantoin, macrocrystalline capsule [package insert]. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2009/020064s019lbl.pdf. Accessed 5 August 2020.
27. U.S. Food and Drug Administration. MONUROL (fosfomycin tromethamine) SACHET [package insert]. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2008/050717s005lbl.pdf. Accessed 5 August 2020.
28. Harris PNA, Tambyah PA, Lye DC, et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. JAMA **2018**; 320(10): 984-94.
29. Tamma PD, Conley AT, Cosgrove SE, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. JAMA Intern Med **2019**; 179(3): 316-23.
30. Punjabi C, Tien V, Meng L, Deresinski S, Holubar M. Oral Fluoroquinolone or Trimethoprim-sulfamethoxazole vs. beta-lactams as Step-Down Therapy for Enterobacteriaceae Bacteremia: Systematic Review and Meta-analysis. Open Forum Infect Dis **2019**; 6(10): ofz364.
31. Bush K, Macalintal C, Rasmussen BA, Lee VJ, Yang Y. Kinetic interactions of tazobactam with beta-lactamases from all major structural classes. Antimicrob Agents Chemother **1993**; 37(4): 851-8.
32. Tamma PD, Rodriguez-Bano J. The Use of Noncarbapenem beta-Lactams for the Treatment of Extended-Spectrum beta-Lactamase Infections. Clin Infect Dis **2017**; 64(7): 972-80.
33. Livermore DM, Andrews JM, Hawkey PM, et al. Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly? J Antimicrob Chemother **2012**; 67(7): 1569-77.
34. Zhou M, Wang Y, Liu C, et al. Comparison of five commonly used automated susceptibility testing methods for accuracy in the China Antimicrobial Resistance Surveillance System (CARSS) hospitals. Infect Drug Resist **2018**; 11: 1347-58.

35. Paterson DL, Henderson A, Harris PNA. Current evidence for therapy of ceftriaxone-resistant Gram-negative bacteremia. Curr Opin Infect Dis **2020**; 33(1): 78-85.
36. Wang R, Cosgrove SE, Tschudin-Sutter S, et al. Cefepime Therapy for Cefepime-Susceptible Extended-Spectrum beta-Lactamase-Producing Enterobacteriaceae Bacteremia. Open Forum Infect Dis **2016**; 3(3): ofw132.
37. Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. Clin Infect Dis **2013**; 56(4): 488-95.
38. Chopra T, Marchaim D, Veltman J, et al. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae and Escherichia coli. Antimicrob Agents Chemother **2012**; 56(7): 3936-42.
39. Zanetti G, Bally F, Greub G, et al. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. Antimicrob Agents Chemother **2003**; 47(11): 3442-7.
40. Burgess DS, Hall RG, 2nd. In vitro killing of parenteral beta-lactams against standard and high inocula of extended-spectrum beta-lactamase and non-ESBL producing Klebsiella pneumoniae. Diagn Microbiol Infect Dis **2004**; 49(1): 41-6.
41. Drieux L, Brossier F, Sougakoff W, Jarlier V. Phenotypic detection of extended-spectrum beta-lactamase production in Enterobacteriaceae: review and bench guide. Clin Microbiol Infect **2008**; 14 Suppl 1: 90-103.
42. Garrec H, Drieux-Rouzet L, Golmard JL, Jarlier V, Robert J. Comparison of nine phenotypic methods for detection of extended-spectrum beta-lactamase production by Enterobacteriaceae. J Clin Microbiol **2011**; 49(3): 1048-57.
43. Guh AY, Bulens SN, Mu Y, et al. Epidemiology of Carbapenem-Resistant Enterobacteriaceae in 7 US Communities, 2012-2013. JAMA **2015**; 314(14): 1479-87.
44. Tamma PD, Goodman KE, Harris AD, et al. Comparing the Outcomes of Patients With Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae Bacteremia. Clin Infect Dis **2017**; 64(3): 257-64.
45. van Duin D, Arias CA, Komarow L, et al. Molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in the USA (CRACKLE-2): a prospective cohort study. Lancet Infect Dis **2020**.
46. Aitken SL, Tarrand JJ, Deshpande LM, et al. High Rates of Nonsusceptibility to Ceftazidime-avibactam and Identification of New Delhi Metallo-beta-lactamase Production in Enterobacteriaceae Bloodstream Infections at a Major Cancer Center. Clin Infect Dis **2016**; 63(7): 954-8.
47. Senchyna F, Gaur RL, Sandlund J, et al. Diversity of resistance mechanisms in carbapenem-resistant Enterobacteriaceae at a health care system in Northern California, from 2013 to 2016. Diagn Microbiol Infect Dis **2019**; 93(3): 250-7.
48. Tamma PD, Simner PJ. Phenotypic Detection of Carbapenemase-Producing Organisms from Clinical Isolates. J Clin Microbiol **2018**; 56(11): e01140-18.
49. Sutherland CA, Verastegui JE, Nicolau DP. In vitro potency of amikacin and comparators against E. coli, K. pneumoniae and P. aeruginosa respiratory and blood isolates. Ann Clin Microbiol Antimicrob **2016**; 15(1): 39.
50. Castanheira M, Davis AP, Mendes RE, Serio AW, Krause KM, Flamm RK. In Vitro Activity of Plazomicin against Gram-Negative and Gram-Positive Isolates Collected from U.S. Hospitals and Comparative Activities of Aminoglycosides against Carbapenem-Resistant Enterobacteriaceae and Isolates Carrying Carbapenemase Genes. Antimicrob Agents Chemother **2018**; 62(8): e00313-18.

51. Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. Clin Infect Dis **2016**; 63(6): 754-62.
52. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis **2016**; 16(6): 661-73.
53. Kaye KS, Bhowmick T, Metallidis S, et al. Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. JAMA **2018**; 319(8): 788-99.
54. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis **2018**; 18(12): 1319-28.
55. Sims M, Mariyanovski V, McLeroth P, et al. Prospective, randomized, double-blind, Phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections. J Antimicrob Chemother **2017**; 72(9): 2616-26.
56. Shionogi, Inc. Antimicrobial Drugs Advisory Committee Cefiderocol Briefing Document, NDA # 209445. Available at: www.fda.gov/media/131705/download. Accessed 6 August 2020.
57. Sorli L, Luque S, Li J, et al. Colistin for the treatment of urinary tract infections caused by extremely drug-resistant Pseudomonas aeruginosa: Dose is critical. J Infect **2019**; 79(3): 253-61.
58. Wagenlehner FME, Cloutier DJ, Komirenko AS, et al. Once-Daily Plazomicin for Complicated Urinary Tract Infections. N Engl J Med **2019**; 380(8): 729-40.
59. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. Antimicrob Agents Chemother **2017**; 61(8): e00883-17.
60. van Duin D, Lok JJ, Earley M, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis **2018**; 66(2): 163-71.
61. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infect Dis Ther **2018**; 7(4): 439-55.
62. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by Klebsiella pneumoniae Carbapenemase-producing K. pneumoniae. Clin Infect Dis **2019**; 68(3): 355-64.
63. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections. Clin Infect Dis **2020**; 70(9): 1799-808.
64. Ackley R, Roshdy D, Meredith J, et al. Meropenem-Vaborbactam versus Ceftazidime-Avibactam for Treatment of Carbapenem-Resistant Enterobacteriaceae Infections. Antimicrob Agents Chemother **2020**; 64(5): e02313-19.
65. Canver MC, Satlin MJ, Westblade LF, et al. Activity of Imipenem-Relebactam and Comparator Agents against Genetically Characterized Isolates of Carbapenem-Resistant Enterobacteriaceae. Antimicrob Agents Chemother **2019**; 63(9): e00672-19.
66. Kulengowski B, Burgess DS. Imipenem/relebactam activity compared to other antimicrobials against non-MBL-producing carbapenem-resistant Enterobacteriaceae from an academic medical center. Pathog Dis **2019**; 77(4).

67. Zhanel GG, Lawrence CK, Adam H, et al. Imipenem-Relebactam and Meropenem-Vaborbactam: Two Novel Carbapenem-beta-Lactamase Inhibitor Combinations. Drugs **2018**; 78(1): 65-98.
68. Papp-Wallace KM, Barnes MD, Alsop J, et al. Relebactam Is a Potent Inhibitor of the KPC-2 beta-Lactamase and Restores Imipenem Susceptibility in KPC-Producing Enterobacteriaceae. Antimicrob Agents Chemother **2018**; 62(6): e00174-18.
69. Humphries RM, Yang S, Hemarajata P, et al. First Report of Ceftazidime-Avibactam Resistance in a KPC-3-Expressing Klebsiella pneumoniae Isolate. Antimicrob Agents Chemother **2015**; 59(10): 6605-7.
70. Nelson K, Hemarajata P, Sun D, et al. Resistance to Ceftazidime-Avibactam Is Due to Transposition of KPC in a Porin-Deficient Strain of Klebsiella pneumoniae with Increased Efflux Activity. Antimicrob Agents Chemother **2017**; 61(10): e00989-17.
71. Shields RK, Chen L, Cheng S, et al. Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne blaKPC-3 Mutations during Treatment of Carbapenem-Resistant Klebsiella pneumoniae Infections. Antimicrob Agents Chemother **2017**; 61(3): e02097-16.
72. Shields RK, Nguyen MH, Press EG, Chen L, Kreiswirth BN, Clancy CJ. Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in Klebsiella pneumoniae Carbapenemase-Producing K pneumoniae: A Case Report and Review of Literature. Open Forum Infect Dis **2017**; 4(3): ofx101.
73. Shields RK, McCreary EK, Marini RV, et al. Early experience with meropenem-vaborbactam for treatment of carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis **2019**; 71(3): 667-71.
74. Golden AR, Adam HJ, Baxter M, et al. In Vitro Activity of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacilli Isolated from Patients in Canadian Intensive Care Units. Diagn Microbiol Infect Dis **2020**: 115012.
75. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against Carbapenem-Nonsusceptible and Multidrug-Resistant Isolates of Gram-Negative Bacilli Collected Worldwide in 2014 to 2016. Antimicrob Agents Chemother **2018**; 62(2): e01968-17.
76. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against a Recent Collection of Clinically Relevant Gram-Negative Bacilli from North America and Europe, Including Carbapenem-Nonsusceptible Isolates (SIDERO-WT-2014 Study). Antimicrob Agents Chemother **2017**; 61(9).
77. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence **2017**; 8(4): 460-9.
78. Solomkin J, Evans D, Slepavicius A, et al. Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. JAMA Surg **2017**; 152(3): 224-32.
79. Eckmann C, Montravers P, Bassetti M, et al. Efficacy of tigecycline for the treatment of complicated intra-abdominal infections in real-life clinical practice from five European observational studies. J Antimicrob Chemother **2013**; 68 Suppl 2: ii25-35.
80. Babinchak T, Ellis-Grosse E, Dartois N, et al. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. Clin Infect Dis **2005**; 41 Suppl 5: S354-67.
81. Falagas ME, Karageorgopoulos DE, Dimopoulos G. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of tigecycline. Curr Drug Metab **2009**; 10(1): 13-21.
82. Castanheira M, Duncan LR, Mendes RE, Sader HS, Shortridge D. Activity of Ceftolozane-Tazobactam against Pseudomonas aeruginosa and Enterobacteriaceae Isolates Collected from

Respiratory Tract Specimens of Hospitalized Patients in the United States during 2013 to 2015. Antimicrob Agents Chemother **2018**; 62(3): e02125-17.

83. Castanheira M, Doyle TB, Kantro V, Mendes RE, Shortridge D. Meropenem-Vaborbactam Activity against Carbapenem-Resistant Enterobacterales Isolates Collected in U.S. Hospitals during 2016 to 2018. Antimicrob Agents Chemother **2020**; 64(2): e01951-19.
84. Sader HS, Castanheira M, Shortridge D, Mendes RE, Flamm RK. Antimicrobial Activity of Ceftazidime-Avibactam Tested against Multidrug-Resistant Enterobacteriaceae and Pseudomonas aeruginosa Isolates from U.S. Medical Centers, 2013 to 2016. Antimicrob Agents Chemother **2017**; 61(11): e01045-17.
85. Shaw E, Rombauts A, Tubau F, et al. Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing Klebsiella pneumoniae infection. J Antimicrob Chemother **2018**; 73(4): 1104-6.
86. Hobson CA, Bonacorsi S, Fahd M, et al. Successful Treatment of Bacteremia Due to NDM-1-Producing Morganella morganii with Aztreonam and Ceftazidime-Avibactam Combination in a Pediatric Patient with Hematologic Malignancy. Antimicrob Agents Chemother **2019**; 63(2): e02463-18.
87. Biagi M, Wu T, Lee M, Patel S, Butler D, Wenzler E. Searching for the Optimal Treatment for Metallo- and Serine-beta-Lactamase Producing Enterobacteriaceae: Aztreonam in Combination with Ceftazidime-avibactam or Meropenem-vaborbactam. Antimicrob Agents Chemother **2019**; 63(12): e01426-19.
88. Sieswerda E, van den Brand M, van den Berg RB, et al. Successful rescue treatment of sepsis due to a pandrug-resistant, NDM-producing Klebsiella pneumoniae using aztreonam powder for nebulizer solution as intravenous therapy in combination with ceftazidime/avibactam. J Antimicrob Chemother **2020**; 75(3): 773-5.
89. Benchetrit L, Mathy V, Armand-Lefevre L, Bouadma L, Timsit JF. Successful treatment of septic shock due to NDM-1-producing Klebsiella pneumoniae using ceftazidime/avibactam combined with aztreonam in solid organ transplant recipients: report of two cases. Int J Antimicrob Agents **2020**; 55(1): 105842.
90. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clin Microbiol Rev **2012**; 25(3): 450-70.
91. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet **2015**; 385(9981): 1949-56.
92. Walkty A, Adam H, Baxter M, et al. In vitro activity of plazomicin against 5,015 gram-negative and gram-positive clinical isolates obtained from patients in canadian hospitals as part of the CANWARD study, 2011-2012. Antimicrob Agents Chemother **2014**; 58(5): 2554-63.
93. Yayan J, Ghebremedhin B, Rasche K. Antibiotic Resistance of Pseudomonas aeruginosa in Pneumonia at a Single University Hospital Center in Germany over a 10-Year Period. PLoS One **2015**; 10(10): e0139836.
94. Neuner EA, Sekeres J, Hall GS, van Duin D. Experience with fosfomycin for treatment of urinary tract infections due to multidrug-resistant organisms. Antimicrob Agents Chemother **2012**; 56(11): 5744-8.
95. Carvalhaes CG, Castanheira M, Sader HS, Flamm RK, Shortridge D. Antimicrobial activity of ceftolozane-tazobactam tested against gram-negative contemporary (2015-2017) isolates from hospitalized patients with pneumonia in US medical centers. Diagn Microbiol Infect Dis **2019**; 94(1): 93-102.

96. Shortridge D, Pfaller MA, Arends SJR, Raddatz J, DePestel DD, Flamm RK. Comparison of the In Vitro Susceptibility of Ceftolozane-Tazobactam With the Cumulative Susceptibility Rates of Standard Antibiotic Combinations When Tested Against Pseudomonas aeruginosa From ICU Patients With Bloodstream Infections or Pneumonia. Open Forum Infect Dis **2019**; 6(6): ofz240.
97. Fraile-Ribot PA, Zamorano L, Orellana R, et al. Activity of Imipenem-Relebactam against a Large Collection of Pseudomonas aeruginosa Clinical Isolates and Isogenic beta-Lactam-Resistant Mutants. Antimicrob Agents Chemother **2020**; 64(2): e02165-19.
98. Pogue JM, Kaye KS, Veve MP, et al. Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant Pseudomonas Aeruginosa. Clin Infect Dis **2019**; 71(2): 304-10.
99. Kollef MH, Novacek M, Kivistik U, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis **2019**; 19(12): 1299-311.
100. Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI). Clin Infect Dis **2015**; 60(10): 1462-71.
101. Titov I, Wunderink RG, Roquilly A, et al. RESTORE-IMI 2: randomised, double-blind, phase III trial comparing efficacy and safety of imipenem/cilastatin (IMI)/relebactam (REL) versus piperacillin/tazobactam (PIP/TAZ) in adult patients with hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP). ECCMID **2020**; 2020 Annual meeting(abstract 771).
102. Lucasti C, Vasile L, Sandesc D, et al. Phase 2, Dose-Ranging Study of Relebactam with Imipenem-Cilastatin in Subjects with Complicated Intra-abdominal Infection. Antimicrob Agents Chemother **2016**; 60(10): 6234-43.
103. Torres A, Zhong N, Pachl J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis **2018**; 18(3): 285-95.
104. Mazuski JE, Gasink LB, Armstrong J, et al. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. Clin Infect Dis **2016**; 62(11): 1380-9.
105. Barnes MD, Taracila MA, Rutter JD, et al. Deciphering the Evolution of Cephalosporin Resistance to Ceftolozane-Tazobactam in Pseudomonas aeruginosa. mBio **2018**; 9(6).
106. Tamma PD, Beisken S, Bergman Y, et al. Modifiable Risk Factors for the Emergence of Ceftolozane-Tazobactam Resistance [in press]. Clin Infect Dis **2020**.
107. U.S. Food and Drug Administration. Antibacterial Susceptibility Test Interpretive Criteria. Available at: https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria. Accessed 28 May 2020.
108. Kwa A, Kasiakou SK, Tam VH, Falagas ME. Polymyxin B: similarities to and differences from colistin (polymyxin E). Expert Rev Anti Infect Ther **2007**; 5(5): 811-21.
109. Akajagbor DS, Wilson SL, Shere-Wolfe KD, Dakum P, Charurat ME, Gilliam BL. Higher incidence of acute kidney injury with intravenous colistimethate sodium compared with polymyxin B in critically ill patients at a tertiary care medical center. Clin Infect Dis **2013**; 57(9): 1300-3.
110. Phe K, Lee Y, McDaneld PM, et al. In vitro assessment and multicenter cohort study of comparative nephrotoxicity rates associated with colistimethate versus polymyxin B therapy. Antimicrob Agents Chemother **2014**; 58(5): 2740-6.

111. Tuon FF, Rigatto MH, Lopes CK, Kamei LK, Rocha JL, Zavascki AP. Risk factors for acute kidney injury in patients treated with polymyxin B or colistin methanesulfonate sodium. Int J Antimicrob Agents **2014**; 43(4): 349-52.
112. Rigatto MH, Oliveira MS, Perdigao-Neto LV, et al. Multicenter Prospective Cohort Study of Renal Failure in Patients Treated with Colistin versus Polymyxin B. Antimicrob Agents Chemother **2016**; 60(4): 2443-9.
113. Oliveira MS, Prado GV, Costa SF, Grinbaum RS, Levin AS. Polymyxin B and colistimethate are comparable as to efficacy and renal toxicity. Diagn Microbiol Infect Dis **2009**; 65(4): 431-4.