Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

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Key words: ESBL; AmpC; carbapenem-resistant Enterobacterales; *Pseudomonas aeruginosa*; CRAB; *Stenotrophomonas maltophilia*

Running Title: AMR Treatment Guidance

Abstract

Background: The Infectious Diseases Society of America (IDSA) is committed to providing up-to-date guidance on the treatment of antimicrobial-resistant infections. This guidance document focuses on infections caused by extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), AmpC β-lactamase-producing Enterobacterales (AmpC-E), carbapenem-resistant Enterobacterales (CRE), *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Stenotrophomonas maltophilia*. This updated document replaces previous versions of the guidance document.

Methods: A panel of six infectious diseases specialists with expertise in managing antimicrobial-resistant infections formulated questions about the treatment of infections caused by ESBL-E, AmpC-E, CRE, DTR-*P. aeruginosa*, CRAB, and *S. maltophilia*. 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 suggested treatment approaches are provided with accompanying rationales, assuming the causative organism has been identified and antibiotic susceptibility results are known. Approaches to empiric treatment, transitioning to oral therapy, duration of therapy, and other management considerations are also discussed briefly. Suggested approaches apply for both adult and pediatric populations, although suggested antibiotic dosages are provided only for adults.

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 December 31, 2022 and will be updated periodically. The most current version of this document, including date of publication, is available at www.idsociety.org/practice-guideline/amr-guidance/.

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Introduction

Antimicrobial resistance (AMR) is a global crisis. Internationally, approximately 1.3 million deaths were estimated to be directly attributable to antimicrobial resistant bacterial pathogens in 2019[1]. In the United States, antimicrobial resistant pathogens caused more than 2.8 million infections and over 35,000 deaths annually from 2012 through 2017, according to the Centers for Disease Control and Prevention (CDC) Antibiotic Resistance Threats in the United States Report[2]. The Infectious Diseases Society of America (IDSA) identified the development and dissemination of clinical practice guidelines and other guidance documents as a top initiative in its 2019 Strategic Plan [3]. 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 GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology. Additionally, when clinical trial data and other robust studies are limited or not available, the development of clinical practice guidelines is challenging. As an alternative to practice guidelines, IDSA endorsed developing more narrowly focused guidance documents for the treatment of infections where data continue to rapidly evolve. Guidance documents are prepared by a small team of experts, who answer questions about treatment based on a comprehensive (but not necessarily systematic) review of the literature, clinical experience, and expert opinion. Documents do not include formal grading of evidence, and are made available online and updated annually.

In the present document, guidance is provided on the treatment of infections caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E), AmpC β-lactamase-producing Enterobacterales (AmpC-E), carbapenem-resistant Enterobacterales (CRE), *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*), carbapenem-resistant *Acinetobacter baumannii* species (CRAB), and *Stenotrophomonas maltophilia*. Many of these pathogens have been designated urgent or serious threats by the CDC[2]. 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 antimicrobial susceptibility testing (AST) methods are included, the document does not provide a comprehensive review of these topics. GRADE methodology was not employed. Due to differences in the molecular epidemiology of resistance and availability of specific antibiotics internationally, treatment recommendations are geared toward antimicrobial resistant infections in the United States. The content of this document is current as of December 31st, 2022. The most current version of this IDSA guidance document and corresponding date of publication is available at: www.idsociety.org/practice-guideline/amr-guidance.

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 suggested treatment approaches for each pathogen group. Answers include a brief discussion of the rationale supporting the suggested approaches. 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, are provided in **Table 1**. Pediatric dosing is not provided.

Table 1. Suggested dosing of antibiotics for the treatment of antimicrobial resistant infections in adults, assuming normal renal and hepatic function[1,2]

Amikacin	**Uncomplicated cystitis**: 15 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 20 mg/kg/dose IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in **Supplemental Material.**
Ampicillin-sulbactam	**Total daily dose of 6-9 grams of sulbactam** **Potential infusion strategies include the following:** 9 grams of ampicillin-sulbactam (6 grams ampicillin, 3 grams sulbactam) IV every 8 hours, infused over 4 hours 27 grams of ampicillin-sulbactam (18 grams ampicillin, 9 grams sulbactam) IV as a continuous infusion 3 grams of ampicillin-sulbactam (2 grams ampicillin, 1 gram sulbactam) IV every 4 hours, infused over 30 minutes Additional information in **Supplemental Material.**
Cefepime	**Uncomplicated cystitis:** 1 gram IV every 8 hours, infused over 30 minutes **All other infections:** 2 grams IV every 8 hours, infused over 3 hours (if possible)
Cefiderocol	2 grams IV every 8 hours, infused over 3 hours
Ceftazidime-avibactam	2.5 grams IV every 8 hours, infused over 3 hours
Ceftazidime-avibactam PLUS aztreonam	**Ceftazidime-avibactam:** 2.5 grams IV every 8 hours, infused over 3 hours **PLUS** **Aztreonam:** 2 grams IV every 6-8 hours (every 6 hour dosing preferred if possible), infused over 3 hours Additional information in **Supplemental Material.**
Ceftolozane-tazobactam	**Cystitis:** 1.5 grams IV every 8 hours, infused over 1 hour

	All other infections: 3 grams IV every 8 hours, infused over 3 hours
Ciprofloxacin	**Cystitis:** 400 milligrams IV every 12 hours or 500 milligrams PO every 12 hours **All other infections:** 400 milligrams IV every 8 hours **OR** 750 milligrams PO every 12 hours
Colistin	Refer to international consensus guidelines on polymyxins (Tsuji BT, et al. Pharmacotherapy. 2019; 39:10-39).
Eravacycline	1 mg/kg per dose IV every 12 hours
Ertapenem	1 gram IV every 24 hours, infused over 30 minutes
Fosfomycin	**Uncomplicated cystitis:** 3 grams PO as a single dose
Gentamicin	**Uncomplicated cystitis**: 5 mg/kg/dose IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 7 mg/kg/dose IV as one dose; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in **Supplemental Material.**
Imipenem-cilastatin	**Uncomplicated cystitis**: 500 mg IV every 6 hours, infused over 30 minutes **All other infections:** 500 mg IV every 6 hours, infused over 3 hours (if possible) Additional information in **Supplemental Material.**
Imipenem-cilastatin-relebactam	1.25 grams IV every 6 hours, infused over 30 minutes Additional information in **Supplemental Material.**
Levofloxacin	750 milligrams IV/PO every 24 hours
Meropenem	**Uncomplicated cystitis:** 1 grams IV every 8 hours, infused over 30 minutes **All other infections:** 2 grams IV every 8 hours, infused over 3 hours (if possible) Additional information in **Supplemental Material.**
Meropenem-vaborbactam	4 grams IV every 8 hours, infused over 3 hours
Minocycline	200 milligrams IV/PO every 12 hours
Nitrofurantoin	**Macrocrystal/monohydrate (Macrobid®)**: 100 mg PO every 12 hours

	Oral suspension: 50 milligrams PO every 6 hours
Polymyxin B	Refer to international consensus guidelines on polymyxins (Tsuji BT, et al. Pharmacotherapy 2019; 39:10-39).
Tigecycline	200 mg IV as a single dose, then 100 mg IV every 12 hours
Tobramycin[c]	**Cystitis**: 5 mg/kg/dose IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 7 mg/kg/dose IV as one dose; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in **Supplemental Material.**
Trimethoprim-sulfamethoxazole	**Cystitis**: 160 mg (trimethoprim component) IV/PO every 12 hours **Other infections**: 8-12 mg/kg/day (trimethoprim component) IV/PO divided every 8 to 12 hours (consider maximum dose of 960 mg trimethoprim component per day) Additional information in **Supplemental Material.**

IV: intravenous; **PO**: enterally; **mg/kg**: milligrams per kilogram

[1]Dosing suggestions limited to organisms and infectious syndromes discussed in the IDSA AMR Treatment Guidance document; [2]Dosing suggested for several agents in table may differ from dosing recommended by the United States Food and Drug Administration.

General Management Recommendations

Suggested treatment approaches in this guidance document assume that the causative organism has been identified and that in vitro activity of antibiotics is demonstrated. If two antibiotics are equally effective, important considerations in selecting a specific agent include safety, cost, convenience, and local formulary availability. The panel recommends that infectious diseases specialists are involved in the management of patients with infections caused by antimicrobial resistant gram-negative 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 those that would be selected for uncomplicated cystitis.

Empiric Therapy

Empiric treatment decisions are outside the scope of this guidance document. However, in general, empiric therapy should be informed by the most likely pathogens, severity of illness of the patient, the likely source of the infection, and any additional patient-specific factors (e.g., severe penicillin allergy, severe immune compromise, chronic kidney disease). When determining empiric treatment for a given patient, clinicians should also consider: (1) previous organisms identified from the patient and associated antimicrobial susceptibility testing (AST) data in the last 12 months, (2) antibiotic exposure within the past 30 days, and (3) local AST patterns for the most likely pathogens. Empiric decisions should be refined based on the identity and AST profile of the pathogen, as well as based on the identification of any prominent β-lactamase genes.

For DTR-*P. aeruginosa*, CRAB, and *S. maltophilia*, in particular, a distinction between bacterial colonization and infection is important as unnecessary antibiotic therapy will only

further the development of resistance and may cause unnecessary antibiotic-related harm to patients. Commonly selected empiric antibiotic regimens are generally not active against CRAB and *S. maltophilia* infections. The decision to target treatment for CRAB and/or *S. maltophilia* in empiric antibiotic regimens should involve a careful risk-benefit analysis after reviewing previous culture results, clinical presentation, individual host risk factors, and antibiotic-specific adverse event profiles.

Duration of Therapy and Transitioning to Oral 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 AST results are available, it may become apparent that inactive antibiotic therapy was initiated empirically. This may impact the duration of therapy. For example, uncomplicated cystitis is typically a mild infection [4]. If an antibiotic not active against the causative organism was administered empirically for uncomplicated cystitis, but clinical improvement nonetheless occurred, the panelists agree that it is generally not necessary to repeat a urine culture, change the antibiotic regimen, or extend the planned treatment course. However, for all other infections, if AST results 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, transitioning to oral 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].

Section 1: 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 a greater number of community-acquired infections [6, 7]. 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 [TMP-SMX], 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*[8-10]. CTX-M enzymes, particularly CTX-M-15, are the most common ESBLs in the United States[10]. 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 they have undergone less rigorous clinical investigation than CTX-M enzymes [11-14]. Routine EBSL testing is not performed by most clinical microbiology laboratories [15, 16]. Rather, non-susceptibility to ceftriaxone (i.e., ceftriaxone minimum inhibitory concentrations [MICs] ≥2 µg/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 [17, 18]. 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.

Question 1.1: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by ESBL-E?

Suggested approach: Nitrofurantoin and TMP-SMX are preferred treatment options for uncomplicated cystitis caused by ESBL-E. Ciprofloxacin, levofloxacin, and carbapenems are alternative agents for uncomplicated cystitis caused by ESBL-E. Although effective, their use is discouraged when nitrofurantoin or TMP-SMX are active. Single dose aminoglycosides and oral fosfomycin (for *E. coli* only) are also alternative treatments for uncomplicated cystitis caused by ESBL-E.

Rationale

Nitrofurantoin and TMP-SMX have been shown to be safe and effective options for uncomplicated cystitis, including uncomplicated ESBL-E cystitis [4, 19, 20]. Although carbapenems and the fluoroquinolones ciprofloxacin or levofloxacin are effective agents against ESBL-E cystitis [21, 22], 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[23-26].

Treatment with a single intravenous (IV) dose of an aminoglycoside is an alternative treatment option for uncomplicated ESBL-E cystitis. Aminoglycosides are nearly exclusively eliminated by the renal route. A single IV dose is generally effective for uncomplicated cystitis, with minimal toxicity, but robust clinical trial data are lacking [27]. Oral fosfomycin is an alternative treatment option exclusively for uncomplicated ESBL-E cystitis caused by *E. coli*. Fosfomycin is not suggested for the treatment of infections caused by *K. pneumoniae* and several other gram-negative organisms which frequently carry *fosA* hydrolase genes that may lead to clinical failure[28, 29]. A randomized open-label trial indicated that a single dose of oral fosfomycin is associated with higher clinical failure than a five-day course of nitrofurantoin for

uncomplicated cystitis [19]. Although this trial was not limited to *E. coli* cystitis, in a subgroup analysis exclusively of *E. coli* infections, outcomes remained poor in the fosfomycin group with day 14 clinical failure at 50% in the fosfomycin group versus 22% in the nitrofurantoin group[19]. The additive benefit of a second dose of oral fosfomycin for uncomplicated cystitis is not known.

The panel does not suggest prescribing amoxicillin-clavulanic acid or doxycycline for the treatment of ESBL-E cystitis. A randomized clinical trial compared a three-day regimen of amoxicillin-clavulanic acid to a three-day course of ciprofloxacin for 370 women with uncomplicated *E. coli* cystitis [21]. Clinical cure was observed in 58% and 77% of the women randomized to the amoxicillin-clavulanic acid and ciprofloxacin arms, respectively. The higher failure rates with amoxicillin-clavulanic acid appear associated with persistent vaginal bacterial colonization, which occurred in 45% and 10% of patients in the amoxicillin-clavulanic acid and ciprofloxacin arms, respectively [21]. The proportion of women in the trial infected with ESBL-E strains is not available. Even though data indicate that clavulanic acid may be effective against ESBLs in vitro[30, 31], this may not translate to clinical efficacy[32]. Robust data indicating that oral amoxicillin-clavulanic acid is effective for uncomplicated ESBL-E UTI are lacking.

Two clinical outcomes studies, published more than 40 years ago, demonstrated that oral tetracyclines may be effective for the treatment of UTIs [33, 34]. 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[35]. Its urinary excretion is limited. Until more convincing data demonstrating the clinical effectiveness of oral doxycycline for the treatment of ESBL-E cystitis are available, the panel suggests 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 1.4**, **Question 1.5**, and **Question 1.6**, respectively.

Question 1.2: What are preferred antibiotics for the treatment of pyelonephritis and cUTI caused by ESBL-E?

Suggested approach: TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis and cUTIs caused by ESBL-E. Ertapenem, meropenem, and imipenem-cilastatin are preferred agents when resistance or toxicities preclude the use of TMP-SMX or fluoroquinolones. Aminoglycosides for a full treatment course are an alternative option for the treatment of pyelonephritis or cUTI.

Rationale

TMP-SMX, ciprofloxacin, and levofloxacin are preferred treatment options for patients with ESBL-E pyelonephritis and cUTIs based on the ability of these agents to achieve adequate and sustained concentrations in the urine, clinical trial results, and clinical experience[36-38]. Carbapenems are also preferred agents, when resistance or toxicities prevent use of TMP-SMX or fluoroquinolones, or early in the treatment course if a patient is critically ill (**Question 1.3**). If a carbapenem is initiated and susceptibility to TMP-SMX, ciprofloxacin, or levofloxacin is demonstrated, transitioning to oral formulations of 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, aminoglycosides (dosed based on therapeutic drug monitoring results) for a full treatment course are an alternative option for the treatment of ESBL-E pyelonephritis or cUTI [39, 40] (**Table 1**, **Supplemental Material**). Once-daily plazomicin was noninferior to meropenem in a clinical trial that included patients with pyelonephritis and cUTIs caused by Enterobacterales [41]. Individual aminoglycosides are equally effective if susceptibility is demonstrated. Of note, in January 2023 the Clinical Laboratory and Standards Institute (CLSI) revised the aminoglycoside breakpoints[16] (**Table 2**).

Fosfomycin is not suggested for the treatment of pyelonephritis or cUTI given its limited renal parenchymal concentrations. However, more data are needed to evaluate the role of oral

fosfomycin as an oral step-down agent for patients with pyelonephritis or cUTI, particularly when administered as a multidose regimen and after several days of preferred therapy. A clinical trial of 97 women with *E. coli* pyelonephritis (approximately half of patients had associated bacteremia) who received up to 5 days of IV therapy and were subsequently transitioned to either once-daily 3 g doses of oral fosfomycin or twice daily 500 mg doses of oral ciprofloxacin for 10 days of total antibiotic therapy identified similar clinical cure percentages in both groups (75% versus 65%, respectively)[42]. However, only approximately 6% of isolates were ESBL-producing, limiting generalizability to pyelonephritis caused by more drug-resistant phenotypes[42]. Fosfomycin is an alternative option for the treatment of prostatitis caused by ESBL-producing *E. coli* when preferred options (i.e., carbapenems, TMP-SMX, or fluoroquinolones) cannot be tolerated or do not test susceptible [43-48]. In an observational study, 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 36 (82%) of 44 males with chronic bacterial prostatitis [43]. Fosfomycin should be avoided for prostatitis caused by gram-negative organisms other than *E. coli* (**Question 1.1**).

Nitrofurantoin does not achieve adequate concentrations in the renal parenchyma and is not advised for pyelonephritis or cUTI. Doxycycline is also not advised for the treatment of ESBL-E pyelonephritis or cUTIs due to its limited urinary excretion and limited published comparative effectiveness studies (**Question 1.1**) [35]. The roles of piperacillin-tazobactam, cefepime, and the cephamycins for the treatment of pyelonephritis and cUTIs are discussed in **Question 1.4**, **Question 1.5**, and **Question 1.6**, respectively.

Question 1.3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by ESBL-E?

Suggested approach: Meropenem, imipenem-cilastatin, or ertapenem are preferred for the treatment of infections outside of the urinary tract caused by ESBL-E. For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenems. After appropriate clinical response is achieved, transitioning to oral trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin 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, as described below [49]. Meropenem, imipenem-cilastatin, or ertapenem are preferred agents; ertapenem offers a more convenient option for patients needing to continue carbapenem therapy in the outpatient setting when oral treatment options are not available. For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenems.

Ertapenem, in contrast to meropenem and imipenem, is highly protein bound leading to a relatively prolonged serum half-life[50]. In patients with hypoalbuminemia and critical illness, the free fraction of ertapenem increases leading to a significant decrease in the serum half-life[51-53]. An observational study of 279 patients with Enterobacterales infections found that hypoalbuminemia (defined as serum albumin <2.5 g/dL) was associated with an approximately five-times higher odds of 30-day mortality for patients receiving ertapenem compared to those receiving meropenem or imipenem-cilastatin[54]. Clinical literature regarding the use of ertapenem, relative to other carbapenems, in critically ill patients is limited and conflicting[53, 55]. However, given known pharmacokinetic (PK) alterations in patients with critical illness and some limitations in the pharmacokinetic/pharmacodynamic (PK/PD) profile of ertapenem[56,

57], the panel suggests the use of meropenem or imipenem-cilastatin, rather than ertapenem, as initial therapy in critically ill patients with ESBL-E infections.

The clinical trial which established carbapenem therapy as the treatment of choice for ESBL-E bloodstream infections randomized 391 patients with ceftriaxone non-susceptible *E. coli* or *K. pneumoniae* (87% later confirmed to have ESBL genes) bloodstream infections to piperacillin-tazobactam 4.5 g IV every six hours or meropenem 1 g IV every eight hours, both as standard infusions (i.e., over 30 minutes). The primary outcome of 30-day mortality occurred in 12% and 4% of patients receiving piperacillin-tazobactam and meropenem, respectively [49]. Trial data were subsequently reanalyzed only including patients with clinical isolates against which piperacillin-tazobactam MICs were ≤16 µg/mL by broth microdilution, the reference standard for AST [58]. Reanalyzing the data from 320 patients, 30-day mortality was observed in 11% versus 4% of those in the 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%) [58], the panel still suggests carbapenem therapy as the preferred treatment of ESBL-producing bloodstream infections due to the notable 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. Similarly, although the trial evaluated meropenem, the panel suggests extending the findings to imipenem-cilastatin and ertapenem, with the latter limited to patients with normal serum albumin and patients who are not critically ill.

In January 2022, the CLSI lowered the piperacillin-tazobactam breakpoints and piperacillin-tazobactam MICs of ≤8/4 µg/mL are considered susceptible for the Enterobacterales (**Table 2**)[59]. In the clinical trial, 77% and 94% of isolates would have been considered susceptible and susceptible dose-dependent, respectively, to piperacillin-tazobactam if applying revised the piperacillin-tazobactam interpretive criteria, indicating that in the presence of ESBL production, susceptibility may not correlate with clinical success[49, 58].

Data from observational studies support the use of oral step-down therapy for Enterobacterales bloodstream infections, including those caused by antimicrobial resistant isolates, after appropriate clinical milestones are achieved [60, 61]. Based on the known bioavailability and sustained serum concentrations of oral TMP-SMX and fluoroquinolones, 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 hemodynamically stable, (3) reasonable source control has 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. Amoxicillin-clavulanate and doxycycline achieve unreliable serum concentrations.

Omadacycline is a tetracycline derivative with an oral formulation that has limited in vitro activity against ESBL-producing Enterobacterales isolates and has an unfavorable PK/PD profile for the treatment of Enterobacterales infections[62, 63]. Like other tetracyclines, omadacycline efficacy is associated with the 24-hour area under the curve to MIC ratio (AUC/MIC). In in vitro models, an AUC/MIC ratio of ~38 is needed to achieve at least a one-log kill (a standard pharmacodynamic target) for *E. coli*[63]. Standard oral omadacycline dosing achieves a 24-hour AUC of ~13mg*hr/L[64], suggesting limited activity of omadacycline against Enterobacterales, which have an MIC_{50} of 0.5 µg/mL (i.e., AUC/MIC ratio of ~26)[65]. The panel does not suggest omadacycline for the treatment of ESBL-E infections.

Question 1.4: Is there a role for piperacillin-tazobactam in the treatment of infections caused by ESBL-E?

Suggested approach: 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 TMP-SMX, ciprofloxacin, levofloxacin, or carbapenems rather than piperacillin-tazobactam for the treatment of ESBL-E pyelonephritis and cUTI, with the understanding that some data suggest the risk of clinical failure with piperacillin-tazobactam may be low. Piperacillin-tazobactam is not suggested 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[66]. There are several concerns regarding tazobactam's ability to function as an effective β-lactamase inhibitor. First, 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 [58, 67-70]. Second, in vitro data indicate that with increased bacterial inoculum (e.g., abscesses), piperacillin-tazobactam may no longer be effective against ESBL-E when compared to meropenem; however, the clinical implications of these findings are unclear[71-73]. Additionally, the effectiveness of tazobactam may be diminished by organisms with increased expression of ESBL enzymes or by the presence of multiple ESBL or other β-lactamases[74]. Finally, there are ESBL enzymes that are inhibitor resistant (i.e., not inhibited by β-lactamase inhibitors)[75, 76].

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 [77-79]. 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 [77]. A randomized, open-label clinical trial investigating this question was also conducted [80]. The trial included 66 patients with ESBL-producing *E. coli* pyelonephritis or cUTI (with confirmation of the presence of ESBL genes) randomized to either piperacillin-tazobactam 4.5 g IV every six hours or ertapenem 1 g IV 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.

In the subgroup of 231 patients with ESBL-E bloodstream infections from a urinary source in the aforementioned clinical trial comparing the outcomes of patients with *E. coli* or *K. pneumoniae* bloodstream infections treated with piperacillin-tazobactam or meropenem (**Question 1.3**), higher mortality was identified in the piperacillin-tazobactam group (7% vs. 3%) [49], although it did not attain statistical significance. The panel is unable to state that piperacillin-tazobactam should be avoided for pyelonephritis or cUTIs; however, given concerns with the efficacy of tazobactam as an ESBL inhibitor and the clinical trial results, the panel has concerns with the use of piperacillin-tazobactam for the treatment of ESBL-E pyelonephritis or cUTIs, and prefers carbapenem therapy (or oral trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin, if susceptible), particularly in the setting of urosepsis (**Question 1.2**).

Observational studies have had conflicting results regarding the effectiveness of piperacillin-tazobactam for the treatment of ESBL-E bloodstream infections[77-92]. A clinical trial of ESBL-E bloodstream infections indicated inferior results with piperacillin-tazobactam compared to carbapenem therapy (**Question 1.3**) [49]. A second trial investigating the role of piperacillin-tazobactam for the treatment of ESBL-E bloodstream infections is ongoing[93].

Question 1.5: Is there a role for cefepime in the treatment of infections caused by ESBL-E?

Suggested approach: 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 suggests avoiding cefepime for the treatment of pyelonephritis and cUTI. Cefepime is also not suggested for the treatment of infections outside of the urinary tract caused by ESBL-E, even if susceptibility to cefepime is demonstrated.

Rationale

ESBLs commonly hydrolyze cefepime[74, 94]. Furthermore, even if ESBL-producing isolates test susceptible to cefepime, cefepime MIC testing may be inaccurate and/or poorly reproducible with commercial AST methods[95]. Clinical trials designed to compare the outcomes of patients with ESBL-E bloodstream infections treated with cefepime or carbapenem have not been conducted.

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 [80, 96]. 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 IV every 12 hours), despite all isolates having cefepime MICs of 1-2 µg/mL [80]. It is unknown if results would have been more favorable with every 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 a clinical 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 [97-101].

For these reasons, the panel suggests avoiding cefepime for the treatment of invasive ESBL-E infections.

Question 1.6: Is there a role for the cephamycins in the treatment of infections caused by ESBL-E?

Suggested approach: Cephamycins are not suggested 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 generally able to withstand hydrolysis from ESBL enzymes[102, 103]. The cephamycins available in the United States are cefoxitin and cefotetan which are both IV 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 [104-111]. Six of the eight investigations found no difference in clinical outcomes[104, 106-108, 110, 111], while two studies demonstrated poorer outcomes with cephamycins[105]. 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[105]. The second study was the largest published to date, including 380 patients with *E. coli* and *K. pneumoniae* bloodstream infections, and 30-day mortality was 29% versus 13% in the cephamycin and carbapenem arms, respectively [109]. Importantly, all eight studies 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 does not suggest 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. Limited numbers of patients received cefoxitin or cefotetan in published studies [107, 111, 112]. The panel believes more clinical data associated with these agents for the treatment of ESBL-E infections is necessary before advocating for their use—including optimal dosing and frequency of administration—especially in light of the two observational studies suggesting poorer clinical outcomes with cephamycin use. Data

suggest more favorable outcomes with high-dose, continuous infusion cefoxitin (i.e., 6 g per day infused continuously) [111, 112], but this is challenging to administer. As both cefotetan and cefoxitin are only available IV 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.

Question 1.7: What is the role of β-lactam-β-lactamase inhibitor combinations and cefiderocol for the treatment of infections caused by ESBL-E?

Suggested approach: The panel suggests that ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol be preferentially reserved for treating infections caused by organisms exhibiting carbapenem resistance. The panel suggests against the use of ceftolozane-tazobactam for the treatment of ESBL-E infections, with the possible exception of polymicrobial infections.

Rationale

Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol exhibit activity against ESBL-E[113-115]. Avibactam is able to successfully protect ceftazidime against hydrolysis by ESBL enzymes[116]. Clinical trial data support ceftazidime-avibactam effectiveness against ESBL-E infections[117-119]. The carbapenem component of meropenem-vaborbactam and imipenem-cilastatin-relebactam provide sufficient activity against ESBL-E, even without the addition of a β-lactamase inhibitor. Although ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are expected to be effective against ESBL-E infections, the panel suggests that these agents be preferentially reserved for treating infections caused by organisms exhibiting carbapenem resistance, where a greater need for these agents exists. However, in settings of polymicrobial infections or drug interactions/intolerances, one of the newer β-lactam agents may need to be considered (e.g., ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol for coinfection with DTR-*P. aeruginosa* and ESBL-E; ceftazidime-avibactam or cefiderocol in settings of concomitant valproic acid use[120]).

Ceftolozane-tazobactam frequently exhibits in vitro activity against ESBL-E[121-125]. Additionally, clinical data indicate it may be effective for the treatment of ESBL-E infections[122-126]. However, the panel remains concerned with the ability of tazobactam to successfully inhibit ESBL production as discussed in **Question 1.4**. The panel suggests against the use of ceftolozane-tazobactam for the treatment of ESBL-E infections. In polymicrobial infections in which DTR-*P. aeruginosa* and ESBL-E are isolated, the use of ceftolozane-

tazobactam can be considered, after weighing the pros and cons of this approach, to limit exposure to multiple agents and their associated toxicities. However, if this approach is taken, close monitoring of patients for an appropriate clinical response is advised.

Section 2: AmpC β-Lactamase-Producing Enterobacterales

AmpC β-lactamases are β-lactamase enzymes that are produced at basal levels by a number of Enterobacterales and glucose non-fermenting gram-negative organisms. Their primary function is to assist with cell wall recycling[127]. AmpC β-lactamases are capable of hydrolyzing a number of β-lactam agents, some in settings of basal AmpC production and others in settings of increased AmpC production. Increased AmpC production by Enterobacterales generally occurs by one of three mechanisms: (1) inducible chromosomal gene expression, (2) stable chromosomal gene de-repression, or (3) constitutively expressed *ampC* genes (frequently carried on plasmids, but sometimes integrated into the chromosome)[127, 128]. In this document, we will focus on the treatment of infections by Enterobacterales species with a moderate to high likelihood of inducible *ampC* gene expression [129, 130].

Increased AmpC enzyme production resulting from inducible *ampC* expression can occur in the presence of specific antibiotics and results in sufficient enzyme in the periplasmic space to increase MICs and cause resistance to certain antibiotics, most notably ceftriaxone, cefotaxime, and ceftazidime. In this scenario, an Enterobacterales isolate that initially tests as susceptible to ceftriaxone may exhibit non-susceptibility to this agent after treatment with ceftriaxone is initiated. In this guidance document, such organisms are described as having a moderate to high risk for clinically significant AmpC production. Resistance due to *ampC* induction can be observed after even a few doses of ceftriaxone, cefotaxime, or ceftazidime [131].

For the other two mechanisms (i.e., stable chromosomal de-repression or constitutively expressed *ampC* genes), AmpC production is always increased. Isolates with either of these two mechanisms are expected to test non-susceptible to ceftriaxone, cefotaxime, and/or ceftazidime. As such, infections by these organisms generally pose less of a treatment dilemma than infections caused by isolates with inducible *ampC* expression. Regarding the first of these two mechanisms, some Enterobacterales isolates (e.g., certain *Escherichia coli* and *Shigella* spp.) contain mutations in promoters or attenuators of *ampC* or other related genes (e.g.,

ampD, *ampR, ampG*), stably de-repressing gene expression [132]. For the second mechanism, constitutive expression of *ampC* genes (e.g., bla_{CMY}, bla_{FOX}, bla_{DHA}, bla_{ACT}, bla_{MIR}) is most commonly observed in organisms such as *E. coli*, *K. pneumoniae*, and *Salmonella* spp. [133]. These *ampC* genes can be found either on plasmids or be integrated into the bacterial chromosome.

Question 2.1: Which Enterobacterales should be considered at moderate to high risk for clinically significant AmpC production due to an inducible *ampC* gene?

Suggested approach: *Enterobacter cloacae* complex, *Klebsiella aerogenes*, and *Citrobacter freundii* are the most common Enterobacterales at moderate to high risk for clinically significant AmpC production.

Rationale

Quantifying the likelihood of *ampC* induction across bacterial species would be best defined by systematically identifying organisms initially susceptible to certain β-lactam agents (e.g., ceftriaxone) that, on subsequent isolation (and after β-lactam exposure), become resistant, with genotyping and expression studies to confirm that the same organism was recovered and that AmpC production significantly increased. Unfortunately, such studies are not available.

Commonly used acronyms to denote organisms at risk for AmpC production such as "SPACE, SPICE, or ESCPM" obscure the wide range of *ampC* induction potential among gram-negative organisms and ignore variance within bacterial genera [127, 128]. For example, *Citrobacter freundii* harbors a chromosomal *ampC* whereas *Citrobacter koseri* does not [134-136]. Thus, the current acronyms may be overly simplistic and associated with both an "undercalling" and "overcalling" of the likelihood of clinically significant AmpC production among individual bacterial species. As another example, "indole positive *Proteus* species" are often included in existing acronyms. Indole-positive *Proteus* spp. currently refers to organisms such as *P. vulgaris* and *P. penneri*, which generally do not contain chromosomal *ampC* genes. The terminology "indole positive *Proteus* species" previously included *Proteus rettgeri* and *Proteus morganii* (since renamed *Providencia rettgeri* and *Morganella morganii*, respectively) [137], making the inclusion of "indole-positive *Proteus* spp." in mnemonics for organisms at high risk of AmpC production no longer accurate.

The emergence of clinically relevant *ampC* expression during antibiotic treatment has been most frequently described for *E. cloacae* complex (herein, referred to as *E. cloacae* for

simplicity), *K. aerogenes* (formerly *Enterobacter aerogenes*), and *C. freundii.* Clinical reports suggest that the emergence of resistance after exposure to an agent like ceftriaxone may occur in approximately 8-40% of infections caused by these organisms, with most estimates closer to approximately 20% [131, 138-142]. These clinical observations mirror in vitro mutation rate analyses, which also suggest that these organisms are likely to overexpress *ampC* [143]. Therefore, when *E. cloacae*, *K. aerogenes*, or *C. freundii* are recovered in clinical cultures (other than urine cultures in uncomplicated cystitis), the panel suggests avoiding treatment with ceftriaxone or ceftazidime, even if an isolate initially tests susceptible to these agents (**Question 2.2**).

In contrast, other organisms historically presumed to be at risk for the development of clinically significant *ampC* expression, such as *Serratia marcescens, Morganella morganii, and Providencia* spp., are unlikely to overexpress *ampC* based on both in vitro analysis [143] and clinical reports [131, 138]. Studies indicate that clinically significant AmpC production occurs in less than 5% of these organisms. When *S. marcescens*, *M. morgannii*, or *Providencia* spp. are recovered from clinical cultures, the panel suggests selecting antibiotic treatment according to AST results.

A number of less commonly encountered pathogens (e.g., *Hafnia alvei, Citrobacter youngae, Yersinia enterocolitica*) that carry inducible chromosomal *ampC* genes have not undergone significant investigation [143-146]. As such, descriptions of their potential for clinically significant AmpC production are very limited. It is reasonable to use AST results to guide treatment decisions if these organisms are recovered in clinical cultures (e.g., administer ceftriaxone if susceptible to ceftriaxone). When treating infections caused by these less commonly recovered organisms (or caused by *S. marcescens*, *M. morgannii*, or *Providencia* spp.) with a high bacterial burden and limited source control (e.g., endocarditis, central nervous system infections); it is alternatively reasonable to consider treatment with cefepime instead of ceftriaxone, even if the organism tests susceptible to ceftriaxone. As with all infections, if an adequate clinical response is not observed after appropriately dosed antibiotic therapy is initiated and necessary source control measures are taken, clinicians should consider the possibility of the emergence of resistance to the initially prescribed agent.

Question 2.2: What features should be considered in selecting antibiotics for infections caused by organisms with moderate to high risk of clinically significant AmpC production due to an inducible *ampC* gene?

Suggested approach: Several β-lactam antibiotics are at relatively high risk of inducing *ampC* genes. Both the ability to induce *ampC* genes and the inability to withstand AmpC hydrolysis should inform antibiotic decision-making.

Rationale

β-lactam antibiotics fall within a spectrum of potential for inducing *ampC* genes. Aminopenicillins (i.e., amoxicillin, ampicillin), narrow-spectrum (i.e., first generation) cephalosporins, and cephamycins are potent *ampC* inducers [147, 148]. However, organisms at moderate to high risk for clinically significant *ampC* induction (e.g., *Enterobacter cloacae*) hydrolyze these antibiotics even at basal *ampC* expression levels. Therefore, such AmpC-E isolates will generally test as non-susceptible to these drugs, averting treatment dilemmas. Imipenem is also a potent *ampC* inducer but it generally remains stable to AmpC-E hydrolysis because of the formation of stable acyl enzyme complexes [147]. The induction potential of ertapenem and meropenem has not been formally investigated but, similar to imipenem, they are generally stable to AmpC hydrolysis [149, 150]. Piperacillin-tazobactam, ceftriaxone, ceftazidime, and aztreonam are relatively weak *ampC* inducers [148, 151]. Available evidence indicates that despite their limited ability to induce *ampC*, the susceptibility of these agents to hydrolysis makes them unlikely to be effective for the treatment of infections by organisms at moderate to high risk for clinically significant AmpC production[150, 152-154].

Cefepime has the advantage of both being a weak inducer of *ampC* and of withstanding hydrolysis by AmpC β-lactamases because of the formation of stable acyl enzyme complexes [155, 156]. Therefore, cefepime is generally an effective agent for the treatment of AmpC-E infections [157]. TMP-SMX, fluoroquinolones, aminoglycosides, tetracyclines, and other non-beta-lactam antibiotics do not induce *ampC* and are also not substrates for AmpC hydrolysis.

Question 2.3: What is the role of cefepime for the treatment of infections caused by Enterobacterales at moderate to high risk of clinically significant AmpC production due to an inducible *ampC* gene?

Suggested approach: Cefepime is suggested for the treatment of infections caused by organisms at moderate to high risk of significant AmpC production (i.e., *E. cloacae* complex, *K. aerogenes*, and *C. freundii)* when the cefepime MIC is ≤2 µg/mL (i.e., susceptible). Limited data suggest a carbapenem may be preferred for infections caused by these organisms when the cefepime MIC is ≥4 µg/mL, assuming carbapenem susceptibility is demonstrated, as ESBL co-production may be present.

Rationale

Cefepime is an oxyimino-cephalosporin that is relatively stable against AmpC enzymes and that also has low *ampC* induction potential [155, 156, 158, 159]. However, several case reports of therapeutic failure of cefepime against infections caused by AmpC-E have led to hesitancy in prescribing this agent [160-162]. Understanding the contribution of AmpC production to cefepime clinical failure in these case reports is challenging as cefepime was generally dosed every 12 hours (as opposed to every 8 hours), co-production of ESBL enzymes was rarely investigated, and outer membrane porin mutations were often identified – also elevating carbapenem MICs, potentially contributing to cefepime treatment failure [159, 163, 164].

Clinical trials comparing clinical outcomes of patients with AmpC-E infections treated with cefepime versus carbapenem therapy are not available. However, several observational studies suggest cefepime is associated with similar clinical outcomes as carbapenem therapy [142, 165, 166]. Furthermore, a meta-analysis including seven studies comparing clinical outcomes of patients receiving cefepime versus carbapenems for *Enterobacter* spp., *Citrobacter* spp., and *Serratia* spp. bloodstream infections did not find differences in clinical outcomes between these treatment regimens, although considerable heterogeneity between studies existed, ill appearing patients were more likely to receive carbapenem therapy, and risk of

AmpC production varied by the included species [157]. In light of both the advantages of cefepime as a compound and no clear clinical failure signals in the literature when administered for the treatment of AmpC-E infections, the panel suggests cefepime as a preferred treatment option for *E. cloacae*, *K. aerogenes*, and *C. freundii* infections with cefepime MICs ≤2 µg/mL (**Table 1**).

Although cefepime may be effective for the treatment of AmpC-E infections, it remains suboptimal against infections caused by ESBL-E [92, 167]. Enterobacterales isolates exhibiting cefepime MICs of 4-8 µg/mL (i.e., susceptible dose-dependent) may have a higher likelihood of co-producing ESBLs compared to isolates with lower cefepime MICs; in one study from Taiwan, 89% of *E. cloacae* isolates with cefepime MICs of 4-8 µg/mL were ESBL-producing [101]. The same study evaluated 217 patients with *E. cloacae* bloodstream infections and found that all 10 patients with infections caused by ESBL-producing isolates with cefepime MICs of 4-8 µg/mL who received cefepime died within 30 days. In contrast, none of the six patients who received cefepime for infections caused by non-ESBL-producing cefepime isolates with MICs of 4-8 µg/mL died within 30 days [101].

A small, single-center United States study also suggests that the likelihood of ESBL production increases in *E. cloacae* as cefepime MICs increase[168]. Contemporary data specific to the United States are needed to better understand how frequently ESBLs are produced by Enterobacterales at moderate to high risk of clinically significant AmpC production. However, in light of available data, we advise caution with administering cefepime for infections caused by *E. cloacae*, *K. aerogenes*, and *C. freundii* with cefepime MICs of 4-8 µg/mL (i.e., susceptible dose-dependent range) [16] (**Table 2**).

Question 2.4: What is the role of ceftriaxone for the treatment of infections caused by Enterobacterales at moderate to high risk of clinically significant AmpC production due to an inducible *ampC* gene?

Suggested approach: Ceftriaxone (or cefotaxime or ceftazidime) is not suggested for the treatment of invasive infections caused by organisms at moderate to high risk of clinically significant AmpC production (e.g., *E. cloacae* complex, *K. aerogenes*, and *C. freundii)*. Ceftriaxone may be a reasonable for uncomplicated cystitis caused by these organisms when susceptibility is demonstrated.

Rationale

Clinical reports differ on how frequently resistance to ceftriaxone emerges during the treatment of infections by Enterobacterales at moderate to high risk for clinically significant *ampC* induction. Several challenges exist when interpreting studies that have attempted to address this question. First, there are no CLSI-endorsed approaches for AmpC detection in clinical isolates, making their accurate identification difficult. Second, these organisms may display ceftriaxone non-susceptibility for other reasons (e.g., ESBL production); however, such mechanisms are rarely investigated in clinical studies for organisms other than *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis*. Third, studies often combine estimates for organisms at low risk for significant AmpC production (e.g., *S. marcescens*, *M. morgannii*) with those posing a higher risk (e.g., *E. cloacae*, *C. freundii*), obscuring our understanding of how frequently resistance to ceftriaxone emerges for organisms truly at high risk for AmpC production [169]. Fourth, studies that evaluate the proportion of isolates exhibiting ceftriaxone non-susceptibility after ceftriaxone exposure do not include confirmation of genetic relatedness of index and subsequent isolates. Additionally, most AmpC clinical studies use pre-2010 CLSI ceftriaxone breakpoints (i.e., ceftriaxone MICs ≤8 µg/mL), making translation of prevalence estimates to current CLSI ceftriaxone susceptibility breakpoints of ≤1 µg/mL challenging [16, 169]. Finally, there is significant heterogeneity in sources of infections, severity of illness, pre-existing medical conditions, co-administration of additional antibiotics, and ceftriaxone dosing and duration across studies, complicating the interpretation of clinical data.

These limitations notwithstanding, available data suggest that the emergence of resistance after ceftriaxone exposure occurs in approximately 20% of infections caused by *E. cloacae*, *K. aerogenes*, or *C. freundii* [131, 138-142],[170-172]. Comparative effectiveness studies addressing the management of presumed AmpC producing infections have mostly focused on the emergence of ceftriaxone resistance, rather than on clinical outcomes. Clinical trials have not compared the clinical outcomes of patients with presumed AmpC-E infections treated with ceftriaxone compared to alternate agents (i.e., cefepime). A number of observational studies compared the clinical outcomes of patients with infections caused by *E. cloacae*, *K. aerogenes*, and *C. freundii* treated with ceftriaxone compared with other β-lactams [139, 170, 171, 173-175]. The most rigorous of these studies is a multicenter observational study that included 381 patients with bloodstream infections caused by *Enterobacter* spp., *Serratia* spp., or *Citrobacter* spp.[173]. Similar to the other observational studies evaluating this question, this study did not identify differences in clinical outcomes when comparing patients treated with ceftriaxone versus carbapenems. However, this study had several of the limitations outlined above.

Nonetheless, since available data indicate a significant risk for the emergence of resistance when ceftriaxone (or ceftazidime) is prescribed for infections caused by organisms at moderate to high risk of AmpC production (i.e., infections caused by *E. cloacae*, *K. aerogenes*, *C. freundii*), the panel suggests generally avoiding ceftriaxone (or ceftazidime) when treating infections caused by these organisms. Based on the mild nature of uncomplicated cystitis and the sufficient urinary excretion of ceftriaxone, ceftriaxone may be adequate therapy for the management of AmpC-E cystitis. Preferred treatment options for AmpC-E cystitis are described in **Question 2.7**.

Question 2.5: What is the role of piperacillin-tazobactam for the treatment of infections caused by Enterobacterales at moderate to high risk of clinically significant AmpC production due to an inducible *ampC* gene?

Suggested approach: Piperacillin-tazobactam is not suggested for the treatment of serious infections caused by Enterobacterales at moderate to high risk of clinically significant inducible AmpC production.

Rationale

Tazobactam is less effective at protecting β-lactams from AmpC hydrolysis than newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam[150, 151, 164, 176]. The role of piperacillin-tazobactam in treating Enterobacterales at moderate to high risk for clinically significant AmpC production remains uncertain. A 2019 meta-analysis summarized the findings of eight observational studies and did not identify a difference in mortality between patients treated with piperacillin-tazobactam and carbapenems for bacteremia by *Enterobacter* spp., *Citrobacter* spp., or *Serratia* spp. [169] However, significant heterogeneity across studies and confounding by indication likely existed (i.e., ill appearing patients were more likely to be prescribed carbapenems). In two observational studies included in this meta-analysis, 30-day mortality among patients treated with piperacillin-tazobactam was numerically higher than among patients treated with carbapenems (15% [6/41 patients] versus 7% [3/41 patients] [177] and 45% [10/22 patients] versus 11% [5/45 patients], respectively) [174]. In an observational study of 103 patients published subsequent to the meta-analysis, piperacillin-tazobactam monotherapy was associated with over twice the odds of death within 30-days, compared to alternative agents[172]

A pilot unblinded clinical trial compared the outcomes of 72 patients with bloodstream infections caused by *Enterobacter* spp., *K. aerogenes, C. freundii*, *M. morganii*, *Providencia* spp., or *S. marcescens* randomized to piperacillin-tazobactam (4.5 grams IV every 6 hours as a standard infusion) or meropenem (1 gram IV every 8 hours as a standard infusion) [178]. There were no significant differences in the primary outcome (a composite outcome including 30-day

mortality, clinical failure, microbiological failure, or microbiological relapse) between the study arms. However, some notable and seemingly conflicting findings were observed between the study arms for individual components of this composite outcome: mortality (0% versus 6%, p=0.13); clinical failure (21% versus 12%, p=0.29); microbiological failure (13% versus 0%), p=0.03), and microbiological relapse (0% versus 9%, p=0.06), for the piperacillin-tazobactam and meropenem arms, respectively. The findings of this trial are challenging to interpret and a larger trial is needed to more definitively determine the role of piperacillin-tazobactam for the treatment of organisms at moderate to high risk for clinically significant *ampC* induction.

In light of the limited ability of tazobactam to protect piperacillin from AmpC hydrolysis in vitro and at least three observational studies identifying increased mortality in patients prescribed piperacillin-tazobactam [171, 174, 177], the panel suggests caution if prescribing piperacillin-tazobactam for serious infections caused by AmpC-E. Piperacillin-tazobactam may be a reasonable treatment option for mild infections such as uncomplicated cystitis.

Question 2.6: What is the role of β-lactam-β-lactamase inhibitor combinations and cefiderocol for the treatment of infections caused by Enterobacterales at moderate to high risk of clinically significant AmpC production due to an inducible *ampC* gene?

Suggested approach: The panel suggests that ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol be preferentially reserved for treating infections caused by organisms exhibiting carbapenem resistance. The panel does not suggest the use of ceftolozane-tazobactam as a treatment option for AmpC-E infections, with the possible exception of polymicrobial infections.

Rationale

Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam generally exhibit in vitro activity against AmpC-E [116, 179, 180]. Although ceftazidime-avibactam is likely to be effective as a treatment for infections caused by AmpC-E, some data suggest it may have slightly higher failure rates compared to ESBL-E infections[118]. Although the frequency is unknown, emergence of resistance of AmpC-E to ceftazidime-avibactam has been described[181, 182].

Cefiderocol demonstrates in vitro activity against AmpC-E [115, 183] and it is likely to be effective in clinical practice, although some case reports indicate the potential for AmpC-E to develop resistance to the drug [181, 182]. Although ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are likely to be effective against AmpC-E infections, the panel suggests that these agents be preferentially reserved for treating infections caused by organisms exhibiting carbapenem resistance, where a greater need for them exists.

Ceftolozane was developed to be more resistant to hydrolysis than earlier cephalosporins against *Pseudomonas*-derived AmpC cephalosporinases; however, much less is known about ceftolozane-tazobactam's activity against AmpC-E. Tazobactam appears less effective at protecting β-lactams from AmpC hydrolysis compared with newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam[150, 151, 164, 176]. While some in

vitro data suggest ceftolozane-tazobactam has activity against AmpC-E [184], in at least one investigation the agent was active against only 19% of *E. cloacae* isolates [185]. Clinical outcomes data for ceftolozane-tazobactam for the treatment of AmpC-E infections are limited; a clinical trial evaluating this question is underway [186]. In light of the concerns described for tazobactam inhibition in **Question 2.5** along with unclear independent activity of ceftolozane against Enterobacterales at moderate to high risk for clinically significant AmpC production, the panel does not suggest the use of ceftolozane-tazobactam as a treatment option for AmpC-E infections.

In polymicrobial infections in which DTR-*P. aeruginosa* and AmpC-E are isolated, the use of ceftolozane-tazobactam can be considered, after weighing the pros and cons of this approach, to limit exposure to multiple agents and their associated toxicities. However, if this approach is taken, close monitoring of patients for an appropriate clinical response is advised.

Question 2.7: What is the role of non-β-lactam therapy for the treatment of infections caused by Enterobacterales at moderate to high risk of clinically significant AmpC production due to an inducible *ampC* gene?

Suggested approach: Nitrofurantoin or TMP-SMX are preferred treatment options for uncomplicated AmpC-E cystitis. Aminoglycosides are alternative treatments for uncomplicated cystitis, pyelonephritis, and cUTI caused by AmpC-E. TMP-SMX or fluoroquinolones can be considered for the treatment of invasive infections caused by organisms at moderate to high risk of clinically significant AmpC production.

Rationale

Preferred treatment options for AmpC-E uncomplicated cystitis include nitrofurantoin [19] or TMP-SMX [38, 187]. Ciprofloxacin or levofloxacin are alternative treatment options. A single IV dose of an aminoglycoside is an alternative treatment for AmpC-E uncomplicated cystitis [27]. Aminoglycosides are nearly exclusively eliminated by the renal route in their active form. A single IV dose is generally effective for uncomplicated cystitis, with minimal toxicity, but robust clinical outcomes data are limited [27].

In patients in whom the potential for nephrotoxicity is deemed acceptable, aminoglycosides (dosed based on therapeutic drug monitoring results) for a full treatment course are an alternative option for the treatment of AmpC-E pyelonephritis or cUTI [39, 40] (Table 1, **Supplemental Material**). Once-daily plazomicin was noninferior to meropenem in a clinical trial that included patients with pyelonephritis and cUTIs caused by the Enterobacterales [41]. Individual aminoglycosides are equally effective if susceptibility is demonstrated.

The role of TMP-SMX or fluoroquinolones for the treatment of AmpC-E infections outside of the urinary tract has not been formally evaluated in clinical trials or robust observational studies. However, neither TMP-SMX nor fluoroquinolones are substrates for AmpC hydrolysis. Oral step-down therapy with TMP-SMX or fluoroquinolones have been shown to be reasonable treatment considerations for Enterobacterales bloodstream infections,

including those caused by AmpC-E, after appropriate clinical milestones are achieved [60, 61]. Based on the known bioavailability and sustained serum concentrations of oral TMP-SMX and fluoroquinolones, these agents are treatment options for patients with AmpC-E infections if (1) susceptibility to an appropriate oral agent is demonstrated, (2) patients are hemodynamically stable, (3) reasonable source control measures have occurred, and (4) concerns about insufficient intestinal absorption are not present. The panel advises avoiding oral step-down to nitrofurantoin, fosfomycin, doxycycline, or amoxicillin-clavulanate for AmpC-E bloodstream infections. Nitrofurantoin and fosfomycin achieve poor serum concentrations. Amoxicillin-clavulanate and doxycycline achieve unreliable serum concentrations.

Section 3: 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 [188]. The CDC defines CRE as members of the Enterobacterales order resistant to at least one carbapenem antibiotic or producing a carbapenemase enzyme [189]. Resistance to at least one carbapenem other than imipenem is required for bacteria generally not susceptible to imipenem (e.g., *Proteus* spp., *Morganella* spp., *Providencia* spp.) [189]. For the purposes of this guidance document, CRE refers to organisms displaying resistance to either meropenem or imipenem, or those Enterobacterales isolates producing carbapenemase enzymes (**Question 3.1**).

CRE comprise a heterogenous group of pathogens encompassing multiple mechanisms of resistance, broadly divided into those that are not carbapenemase-producing and those that are carbapenemase-producing. CRE that are not carbapenemase-producing may be the result of amplification of non-carbapenemase β-lactamase genes (e.g., ESBL genes) with concurrent outer membrane porin disruption [190]. Carbapenemase-producing isolates account for approximately 35%-59% of CRE cases in the United States, when applying the CDC definition [191, 192].

The most common carbapenemases in the United States are *K. pneumoniae* carbapenemases (KPCs), which are not limited to *K. pneumoniae* isolates. 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) [193, 194]. Knowledge of whether a CRE 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 differentiate carbapenemase and non-carbapenemase-producing CRE [195]. Molecular testing can identify specific carbapenemase gene families (e.g., differentiating bla_{KPC} from $bla_{OXA\text{-}48\text{-}like}$ genes). 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.

Question 3.1: What is the preferred treatment approach for infections caused by Enterobacterales isolates without carbapenemase production that remain susceptible to meropenem and imipenem but are not susceptible to ertapenem?

Suggested approach: For infections caused by Enterobacterales isolates that exhibit susceptibility to meropenem and imipenem (i.e., MICs ≤1 µg/mL), but are not susceptible to ertapenem (i.e., MICs ≥1 µg/mL), the use of extended-infusion meropenem (or imipenem-cilastatin) is suggested, assuming no carbapenemase has been identified.

Rationale

In this guidance document, CRE refers to Enterobacterales isolates resistant to meropenem or imipenem or Enterobacterales producing a carbapenemase enzyme. **Questions 3.2 through 3.9** discuss the treatment of infections caused by CRE isolates. For infections caused by Enterobacterales isolates that exhibit susceptibility to meropenem and imipenem (i.e., MICs ≤1 µg/mL), but are not susceptible to ertapenem (i.e., MICs ≥1 µg/mL), we suggest the use of extended-infusion meropenem (or imipenem-cilastatin), only if no carbapenemase gene has been identified (**Table 1 and 2**). Standard-infusion meropenem or imipenem-cilastatin may be reasonable for uncomplicated cystitis (**Table 1**) .

For isolates susceptible to meropenem but not susceptible to imipenem (and vice versa), in the absence of data to inform the optimal treatment approach, the panel suggests basing the treatment decision on the severity of illness of the patient and site of infection. For example, in this scenario, meropenem may be a reasonable treatment for an uncomplicated cystitis but not for a complex intra-abdominal infection. The panel suggests against the use of meropenem-vaborbactam or imipenem-cilastatin-relebactam to treat ertapenem-resistant, meropenem-susceptible and imipenem-susceptible infections since these agents are unlikely to offer any substantial benefit beyond that of extended-infusion meropenem or imipenem-cilastatin alone.

Question 3.2: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by CRE?

Suggested approach: Nitrofurantoin, TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for uncomplicated cystitis caused by CRE, although the likelihood of susceptibility to any of these agents is low. A single dose of an aminoglycoside, oral fosfomycin (for *E. coli* only), colistin, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, cefiderocol, are alternative treatment options for uncomplicated cystitis caused by CRE.

Rationale

Clinical trial data evaluating the efficacy of most preferred agents for uncomplicated CRE cystitis are not available. However, as nitrofurantoin, TMP-SMX, ciprofloxacin, or levofloxacin all achieve high concentrations in urine, they are expected to be effective for uncomplicated CRE cystitis, if the isolate is susceptible [4, 19-22].

A single dose of an aminoglycoside is an alternative option for CRE uncomplicated cystitis. Aminoglycosides are almost exclusively eliminated by the renal route in their active form. A single IV dose is generally effective for cystitis, with minimal toxicity [27]. 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 [196, 197]. Plazomicin may remain active against isolates resistant to amikacin [198].

Oral fosfomycin is an alternative option for the treatment of uncomplicated CRE cystitis caused by *E. coli* as the *fosA* gene (intrinsic to many gram-negative organisms) can hydrolyze fosfomycin and may lead to clinical failure [28, 29]. Clinical trial data indicate that a single dose of oral fosfomycin is associated with higher clinical failure than a five-day course of nitrofurantoin for uncomplicated cystitis [19].

Colistin (the active form of the commercially available parenteral inactive prodrug colistimethate sodium) is an alternative agent for treating uncomplicated CRE cystitis. Colistin

converts to its active form in the urinary tract; clinicians should remain cognizant of the associated risk of nephrotoxicity [199]. Polymyxin B should not be used as treatment for uncomplicated CRE cystitis, due to its predominantly nonrenal clearance [200].

Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are alternative options for uncomplicated CRE cystitis. They are designated alternative agents to preserve their activity for more invasive CRE infections. 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 [117, 201-205].

Question 3.3: What are preferred antibiotics for the treatment of pyelonephritis and cUTI caused by CRE?

Suggested approach: TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis and cUTI caused by CRE, if susceptibility is demonstrated. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are also preferred treatment options for pyelonephritis and cUTIs. Aminoglycosides are alternative treatment options.

Rationale

Although the minority of CRE are expected to retain susceptibility to TMP-SMX, ciprofloxacin, or levofloxacin, these agents are all preferred agents to treat CRE pyelonephritis or cUTI if susceptibility is demonstrated [36-38].

Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis and cUTIs caused by CRE based on clinical trials showing non-inferiority of these agents to common comparator agents for UTIs [117, 201-205]. Isolates included in these trials were overwhelmingly carbapenem susceptible. Data are insufficient to favor one agent over the others.

In patients in whom the potential for nephrotoxicity is deemed acceptable, aminoglycosides (dosed based on therapeutic drug monitoring results) for a full treatment course are an alternative option for the treatment of CRE pyelonephritis or cUTI [39-41]. (**Table 1**, **Supplemental Material**). Individual aminoglycosides are equally effective if susceptibility is demonstrated.

Question 3.4: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE, when carbapenemase testing results are either not available or negative?

Suggested approach: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for infections outside of the urinary tract caused by CRE, 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, while awaiting AST results to the novel β-lactam agents and carbapenemase testing results.

Rationale

The CDC characterized over 42,000 CRE isolates collected from between 2017-2019 and found that approximately 35% of CRE clinical or surveillance isolates in the United States carry one of the main five carbapenemase genes [191]. Of these 35% of isolates, the specific prevalence by carbapenemase gene family is as follows: bla_{KPC} (86%), bla_{NDM} (9%), bla_{VIM} (<1%), bla_{IMP} (1%), or $bla_{OXA\text{-}48\text{-}like}$ (4%) [191]. 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 $bla_{OXA\text{-}48\text{-}like}$ (3%) [192].

Ceftazidime-avibactam has activity against most KPC- and OXA-48-like-producing CRE isolates [206, 207]. Meropenem-vaborbactam and imipenem-cilastatin-relebactam are active against most Enterobacterales that produce KPC enzymes but not those that produce OXA-48-like carbapenemases[208-216]. 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 in the

United States either do not produce carbapenemases or, if they do, produce KPCs. Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam all have a high likelihood of activity against CRE that do not produce carbapenemases[217, 218]. There do not appear to be differences in the effectiveness of these agents when susceptibility has been demonstrated.

Cefiderocol is suggested as an alternative treatment option for CRE 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 [219]. Once inside the periplasmic space, the cephalosporin moiety dissociates from iron and binds primarily to PBP3 to inhibit bacterial cell wall synthesis [220]. Cefiderocol is highly likely to be active against CRE clinical isolates as it exhibits activity against Enterobacterales producing any of the five major carbapenemase enzymes, as well as CRE isolates not producing carbapenemases [217, 221]. In an effort to preserve cefiderocol activity for infections caused by pathogens where other β-lactam agents may have little to no activity, such as those caused by metallo-β-lactamase-producing Enterobacterales or by non-fermenting gram-negative organisms, the panel suggests cefiderocol as an alternative agent for infections caused by non-metallo-β-lactamase producing CRE. 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 [222] or who 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 yet available), preferred treatment options include the combination of ceftazidime-avibactam plus aztreonam, or cefiderocol as monotherapy (**Question 3.6**).

Tigecycline or eravacycline are alternative options for the treatment of CRE infections not involving the bloodstream or urinary tract (**Question 3.9**). Their activity is independent of the presence or type of carbapenemase.

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 µg/mL [223]. PK/PD data suggested that extended-infusion meropenem may remain active against infections caused by organisms with carbapenem MICs in this range [224-226]. However, subsequent observational and trial 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 [227-238]. Therefore, the panel advises against the use of extended-infusion carbapenems with or without the addition of a second agent for the treatment of CRE infections.

Question 3.5: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if KPC production is present?

Suggested approach: Meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam are preferred treatment options for KPC-producing infections. Cefiderocol is an alternative option.

Rationale

Preferred agents for KPC-producing infections include meropenem-vaborbactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam [206, 208-213, 239, 240]. Although all three agents are 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 regarding clinical outcomes and emergence of resistance. 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 [227-236, 239]. Clinical trials comparing these agents to each other for the treatment of KPC-producing infections are not available.

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 [241]. 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 at 85% and 61% (limited to patients with isolates exhibiting susceptibility to the agent administered) and 12% and 19%, respectively. Although these differences were not statistically significant, they numerically favor meropenem-vaborbactam. Of patients who experienced recurrent CRE infections, 0% (0 of 3) of patients receiving meropenem-vaborbactam and 20% (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 both meropenem-vaborbactam and ceftazidime-avibactam are reasonable treatment options for KPC-producing infections, although the emergence of resistance may be more common with ceftazidime-avibactam (**Question 3.8**). At least two groups that have published their clinical experiences with the use of ceftazidime-avibactam and meropenem-vaborbactam similarly found that patients who received meropenem-vaborbactam had a slightly higher likelihood of clinical cure and survival and a lower risk of emergence of resistance than patients treated with ceftazidime-avibactam[242-245].

Limited clinical data are available for imipenem-cilastatin-relebactam compared with the other novel β-lactam-β-lactamase inhibitor agents. A clinical trial including patients with infections caused by gram-negative organisms not susceptible to imipenem assigned patients to receive either imipenem-cilastatin-relebactam versus imipenem-cilastatin and colistin [230]. 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 [230]. It is difficult to draw meaningful conclusions from these data given the small numbers. However, in vitro activity of imipenem-cilastatin-relebactam against CRE [215, 246-249], clinical experience with imipenem-cilastatin, and the stability of relebactam as a β-lactamase inhibitor [250] suggest imipenem-cilastatin-relebactam is likely to be effective for CRE infections if it tests susceptible.

Cefiderocol is an alternative treatment option for KPC-producing Enterobacterales [221]. A clinical trial identified all-cause mortality at 22% versus 21% for patients with KPC-producing infections treated with cefiderocol versus alternative therapy (mostly polymyxin-based regimens), respectively [205]. Clinical investigations comparing the effectiveness of cefiderocol versus newer β-lactam-β-lactamase inhibitors for KPC-producing Enterobacterales infections are not available. The panel suggests cefiderocol, as monotherapy, as an alternative agent for treating KPC-producing pathogens to reserve it for the treatment of infections caused by metallo-β-lactamase-producing Enterobacterales or glucose non-fermenting gram-negative organisms [219].

Tigecycline or eravacycline are alternative options for the treatment of KPC-producing infections not involving the bloodstream or urinary tract (**Question 3.9**). Their activity is independent of the presence or type of carbapenemases.

Question 3.6: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if NDM production is present?

Suggested approach: Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are preferred treatment options for NDM and other metallo-β-lactamase-producing infections.

Rationale

Preferred antibiotic options for NDM-producing Enterobacterales (or other metallo-β-lactamases), include ceftazidime-avibactam plus aztreonam, or cefiderocol monotherapy[205, 251-258]. NDMs hydrolyze penicillins, cephalosporins, and carbapenems, but not aztreonam. Although aztreonam is active against NDMs, it can be hydrolyzed by ESBLs, AmpC β-lactamases, KPCs, or OXA-48-like carbapenemases which are frequently co-produced by NDM-producing isolates. Avibactam generally remains effective at inhibiting the activity of these latter β-lactamase enzymes. Reliable estimates of the percent of NDM-producing isolates susceptible to the combination of ceftazidime-avibactam and aztreonam are not available due to the lack of a standardized testing approach. Although several groups have described methods used to test susceptibility with this combination of agents[259-266], the CLSI does not currently endorse a specific approach to test in vitro activity with this combination[16].

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 [256]. 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. Strategies for administering the combination of ceftazidime-avibactam and aztreonam are reviewed in **Table 1 and Supplemental Material** [267-269]. Patients should be monitored closely for elevations in liver enzymes[270]. In rare situations where cefiderocol or combination therapy with ceftazidime-avibactam and aztreonam is not possible (e.g., allergy or intolerance), combination therapy

with aztreonam and meropenem-vaborbactam or imipenem-cilastatin-relebactam can be considered, provided OXA-type carbapenemases are not present[253, 271]. Clinical data investigating this approach are limited[272].

A second 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 producing serine β-lactamases, although this is not always associated with frank cefiderocol resistance [221, 273]. Cefiderocol was active against 58% of 12 international NDM-producing CRE isolates [221]. A separate cohort found that cefiderocol was active against 83% of 29 NDM-producing CRE isolates[217]. Two clinical trials including patients with metallo-β-lactamase producing infections (not limited to the Enterobacterales) found that clinical cure occurred in 71% (17 of 24) and 40% (4 of 10) of patients receiving cefiderocol versus alternate therapy (primarily polymyxin-based therapy), respectively[257]. Day 28 mortality occurred in 13% (3 of 24) and 50% (5 of 10) of patients, respectively[257]. Clinical outcomes data comparing ceftazidime-avibactam in combination with aztreonam versus cefiderocol are not available.

Tigecycline or eravacycline are alternative options for the treatment of NDM-producing infections not involving the bloodstream or urinary tract (**Question 3.9**). Their activity is independent of the presence or type of carbapenemases.

Question 3.7: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if OXA-48-like production is present?

Suggested approach: Ceftazidime-avibactam is the preferred treatment option for OXA-48-like-producing infections. Cefiderocol is an alternative treatment option.

Rationale

If an OXA-48-like enzyme is identified in an Enterobacterales clinical isolate, ceftazidime-avibactam is preferred [206, 207, 274-276]; cefiderocol is an alternative option[277, 278]. Meropenem-vaborbactam and imipenem-cilastatin-relebactam have limited to no activity against OXA-48-like producing isolates and are not suggested, even if susceptible in vitro [208-216]. 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 and the panel prefers to reserve their activity for the treatment of metallo-β-lactamase producing organisms and certain non-fermenting organisms[277].

Tigecycline or eravacycline are alternative options for the treatment of OXA-48-like-producing infections not involving the bloodstream or urinary tract (Question 3.9). Their activity is independent of the presence or type of carbapenemases.

Question 3.8: What is the likelihood of the emergence of resistance of CRE isolates to the newer β-lactam agents when used to treat CRE infections?

Suggested approach: The emergence of resistance is a concern with all β-lactams used to treat CRE infections. Available data suggest the frequency may be highest for ceftazidime-avibactam.

Rationale

As with most antibiotic agents, treatment with any 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 most data on the emergence of resistance of novel agents to CRE focuses on KPC-producing isolates. 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 [279-300]. Changes in permeability and efflux are the primary drivers of the emergence of resistance to meropenem-vaborbactam [210, 244, 288, 292, 301-306] and imipenem-cilastatin-relebactam [307-309]. Increases in bla_{KPC} copy numbers have been associated with resistance to all of these agents[310-312].

Diverse mechanisms of resistance to cefiderocol have been described both against KPC-producing isolates and other serine and metallo-β-lactamases producing Enterobacterales [313, 314] including mutations in the TonB-dependent iron transport system [315-318], amino acid changes in AmpC β-lactamases [181, 182], and increased NDM expression[262]. Increasing reports of amino acid insertions in PBP3, the active binding site of cefiderocol and aztreonam, are being described in NDM-producing *E. coli* isolates[295, 319-321] leaving no available β-lactam treatment options. Such reports remain rare in the United States[322].

Estimates of the emergence of resistance after clinical exposure to ceftazidime-avibactam and meropenem-vaborbactam are approximately 10-20% [231, 235, 245, 283] and 3% [241, 244, 323], 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 United States Food and Drug Administration (FDA). Limited data exist on the

frequency of emergence of resistance of CRE to imipenem-cilastatin-relebactam and cefiderocol.

The panel recommends always repeating AST 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 AST 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 AST results are available.

Question 3.9: What is the role of tetracycline derivatives for the treatment of infections caused by CRE?

Suggested approach: 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 suggested 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 [209, 217, 324]. The tetracycline-derivative agents achieve rapid tissue distribution following administration, resulting in limited urine and serum concentrations [325]. Therefore, the panel suggests 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 compared with eravacycline [326-329]. A meta-analysis of 15 clinical 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 [330]. Subsequent investigations have demonstrated that when high-dose tigecycline is prescribed (200 mg IV as a single dose followed 100 mg IV every 12 hours) mortality differences between tigecycline and comparator agents may no longer be evident [331-333]. Thus, if tigecycline is prescribed for the treatment of CRE infections, the panel recommends that high-dosages be administered [334] (Table 1).

Eravacycline MICs are generally 2- to 4-fold lower than tigecycline MICs against CRE [335]. The clinical relevance of the MIC distributions between these agents is unclear because

of differences in the PK/PD profile of tigecycline and eravacycline. Fewer than five patients with CRE infections were included in clinical trials that investigated the efficacy of eravacycline [326, 336] and post-marketing clinical reports describing its efficacy for the treatment of CRE infections are limited [337].

Limited clinical data are also available investigating the effectiveness of minocycline against CRE infections [338, 339], but data suggest a lower proportion of CRE isolates are likely to be susceptible to minocycline compared to tigecycline or eravacycline [217]. 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 IV and oral formulation, against CRE suggests reduced potency relative to other tetracycline derivatives and an unfavorable PK/PD profile (**Question 1.3**) [63, 340-342]. The panel suggests against the use of omadacycline for CRE infections.

Question 3.10: What is the role of polymyxins for the treatment of infections caused by CRE?

Suggested approach: Polymyxin B and colistin are not suggested for the treatment of infections caused by CRE. Colistin can be considered as an alternative agent for uncomplicated CRE cystitis.

Rationale

Observational and clinical data indicate increased mortality and excess nephrotoxicity associated with polymyxin-based regimens relative to comparator agents [227-235]. 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 [16]. The panel suggests 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 [200].

Question 3.11: What is the role of combination antibiotic therapy for the treatment of infections caused by CRE?

Suggested approach: Combination antibiotic therapy (i.e., the use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, tetracycline, or polymyxin) is not suggested 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 [343]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [343].

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 tobramycin). 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 [242]. Thirty-day mortality was essentially identical at approximately 25% in both study arms.

Based on available outcomes data, clinical experience, and known toxicities associated with aminoglycosides, fluoroquinolones, tetracyclines, and polymyxins, the panel does not suggest combination therapy for CRE infections when susceptibility to a preferred β-lactam agent has been demonstrated.

Section 4: *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance

The CDC reports that 32,600 cases of multidrug-resistant (MDR)-*P. aeruginosa* infections occurred in patients hospitalized in the United States in 2017, resulting in 2,700 deaths [188]. 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 [344]. In 2018, the concept of "difficult-to-treat" resistance was proposed [345]. 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.

MDR-*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), increased production of or amino acid substitutions within *Pseudomonas*-derived cephalosporinase (PDC) enzymes (commonly referred to as pseudomonal AmpC enzymes), upregulation of efflux pumps (e.g., MexAB-OprM), mutations in penicillin-binding protein targets, and the presence of expanded-spectrum β-lactamases (e.g., $bla_{\text{OXA-10}}$) [346, 347]. Carbapenemase production is a rare cause of carbapenem resistance in *P. aeruginosa* isolates in the United States[348, 349] but is identified in upwards of 20% of carbapenem-resistant *P. aeruginosa* in other regions of the world, most commonly due to the presence of bla_{VIM} enzymes [350-353]. There are other β-lactamase enzymes rarely identified in *P. aeruginosa* isolates from patients in the United States that may confer elevated MICs to β-lactam agents including some novel β-lactam agents (e.g., Guiana extended-spectrum beta-lactamase [GES], Vietnamese extended-spectrum beta-lactamase [VEB], and *Pseudomonas*-extended resistance [PER] enzymes[14].

Carbapenemase testing for DTR-*P. aeruginosa* is not as critical as carbapenemase testing for CRE clinical isolates in United States hospitals. However, the panel strongly encourages all clinical microbiology laboratories to perform AST for MDR and DTR-*P. aeruginosa* isolates

against novel beta-lactam agents (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol). If AST cannot occur at the local clinical microbiology laboratory, isolates should be sent to a commercial laboratory, local health department, or the Centers for Disease Control and Prevention for AST testing. While send out AST may delay the initiation of effective antibiotic therapy, it is still preferred over no testing as these data can guide treatment of chronic infections and recurrent infections. Treatment recommendations for DTR-*P. aeruginosa* infections listed below assume that in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 4.1: What are preferred antibiotics for the treatment of infections caused by MDR *P. aeruginosa*?

Suggested approach: 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 agent but susceptible to traditional β-lactams, the administration of a traditional agent as high-dose extended-infusion therapy is suggested, and repeat AST is encouraged. For critically ill patients or those with 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 approach.

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 not susceptible to a carbapenem agent (e.g., meropenem or imipenem-cilastatin MICs ≥4 μg/mL) but susceptible to other traditional non-carbapenem β-lactam agents (**Table 2**) constitute approximately 20% to 60% of carbapenem-resistant *P. aeruginosa* isolates [354-360]. This phenotype is generally due to lack of or limited production of OprD, which normally facilitates entry of carbapenem agents into *P. aeruginosa*, with or without overexpression of efflux pumps [356-359]. Comparative effectiveness studies to guide treatment decisions for infections caused by *P. aeruginosa* resistant to carbapenems but susceptible to traditional non-carbapenem β-lactams are not available. When confronted with these scenarios, the panel suggests AST 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**).

An alternative approach is to administer a novel β-lactam agent (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam). This approach is considered an alternative and not a preferred option to preserve the effectiveness of novel β-lactams for future, increasingly antibiotic-resistant infections. However, for critically ill patients or those with poor source control, use of a novel β-lactam for *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 iteratively express additional resistance mechanisms while exposed to antibiotic therapy. Clinicians are advised to request repeat AST of subsequent clinical MDR-*P. aeruginosa* isolates obtained from the same patient to monitor for the development of resistance.

Question 4.2: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by DTR-*P. aeruginosa*?

Suggested approach: Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, cefiderocol, are the preferred treatment options for uncomplicated cystitis caused by DTR-*P. aeruginosa*. A single-dose of tobramycin or amikacin is an alternative treatment 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 clinical trials showing non-inferiority of these agents to common comparator agents for the treatment of UTIs [117, 203-205, 361]. 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 4.4**. The suggested approach for the treatment of uncomplicated cystitis caused by DTR-*P. aeruginosa* isolates confirmed to produce metallo-β-lactamase enzymes (e.g., bla_{VIM}) is reviewed in **Question 4.5.**

A single dose of tobramycin or amikacin is an alternative treatment option for uncomplicated cystitis caused by DTR-*P. aeruginosa*. A single IV dose of tobramycin or amikacin are likely effective for uncomplicated cystitis as aminoglycosides are nearly exclusively eliminated by the renal route in their active form, with minimal toxicity, but robust trial data are lacking [27]. As of January 2023, there are no longer susceptibility criteria for gentamicin for *P. aeruginosa* and susceptibility criteria for tobramycin and amikacin have been lowered[16] (**Table 2**). Tobramycin susceptibility criteria are available for *P. aeruginosa*, regardless of source (susceptible ≤1 µg/mL)[16]. Amikacin susceptibility criteria against *P. aeruginosa* are only available for infections originating from urinary sources (susceptible ≤16 µg/mL)[16]. Plazomicin has neither CLSI nor FDA susceptibility criteria against *P. aeruginosa*. Surveillance studies

indicate that plazomicin is unlikely to provide any incremental benefit against DTR-*P. aeruginosa* if resistance to all other aminoglycosides is demonstrated[362].

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 [199]. 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 [19, 363]. This is in part due to the presence of the *fosA* gene, which is intrinsic to *P. aeruginosa* [28].

Question 4.3: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections caused by DTR-*P. aeruginosa*?

Suggested approach: 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 clinical trials showing non-inferiority of these agents to common comparator agents [117, 203-205, 361]. Data are insufficient to favor one of these agents over the others for the treatment of pyelonephritis and cUTI. Available trials generally do not include patients infected by pathogens with DTR phenotypes. Additional information comparing these agents is described in **Question 4.4**. The suggested approach for the treatment of pyelonephritis and cUTI cystitis caused by DTR-*P. aeruginosa* isolates confirmed to produce metallo-β-lactamase enzymes (e.g., bla_{VIM}) is reviewed in **Question 4.5**. In patients in whom the potential for nephrotoxicity is deemed acceptable, once-daily tobramycin or amikacin are alternative options (**Question 4.2**) [39]. Changes in the aminoglycoside susceptibility criteria that were implemented in January 2023 are reviewed in **Question 4.2**.

Question 4.4: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*?

Suggested approach: Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam are preferred options for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*. Cefiderocol is an alternative treatment option for infections outside of the urinary tract caused by DTR-*P. aeruginosa*.

Rationale

Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam are preferred options for the treatment of DTR-*P. aeruginosa* infections outside of the urinary tract, based on in vitro activity [247, 249, 307, 364-405], observational studies [406-411], and clinical trial data [117, 230, 412-418]. The vast majority of patients in clinical trials receiving newer β-lactam agents were not infected with DTR-*P. aeruginosa*. Comparative effectiveness studies comparing novel agents to each other (e.g., ceftolozane-tazobactam versus ceftazidime-avibactam) are lacking. Rather, available studies focus on comparing novel agents to older agents (e.g., ceftolozane-tazobactam versus polymyxins). The suggested approach for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa* isolates confirmed to produce metallo-β-lactamase enzymes (e.g., bla_{VIM}) is reviewed in **Question 4.5.**

Summarizing international surveillance data, ceftolozane-tazobactam [364, 366, 367, 369-379, 390], ceftazidime-avibactam [365, 378-390], and imipenem-cilastatin-relebactam [247, 249, 307, 390-405] 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 [419, 420]. Available surveillance data generally represent time periods before the novel agents were used clinically and likely overestimate susceptibility percentages observed in clinical practice. Regional differences in susceptibility estimates across the newer agents exist. The panel suggests always obtaining AST results for DTR-*P. aeruginosa* infections to guide treatment decisions.

Ceftolozane and ceftazidime have a similar structure; however, ceftolozane is less impacted by PDC hydrolysis and porin loss than ceftazidime[421, 422]. Ceftolozane does not rely on an inhibitor to restore susceptibility to an otherwise inactive β-lactam agent (i.e., ceftolozane has independent activity against DTR-*P. aeruginosa* and does not need to rely on tazobactam to maintain its 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. By definition, neither ceftazidime nor imipenem are active against DTR-*P. aeruginosa*. Avibactam and relebactam expand activity of these agents mainly through inhibition of PDCs[113].

The panel does not suggest testing meropenem-vaborbactam activity against DTR-*P. aeruginosa* isolates. Vaborbactam only marginally expands the activity of meropenem against DTR-*P. aeruginosa*. There are no CLSI or FDA breakpoints for meropenem-vaborbactam against *P. aeruginosa*. Some *P. aeruginosa* isolates may appear susceptible to meropenem-vaborbactam but not meropenem, if applying the CLSI Enterobacterales breakpoint of 8 µg/mL to *P. aeruginosa* isolates. This is likely an artifact of meropenem-vaborbactam being standardly administered as 2 grams IV every 8 hours, infused over 3 hours. Meropenem breakpoints (i.e. ≤2 µg/mL) are based on a dosage regimen of 1 gram IV administered every 8 hours, as a 30-minute infusion[16]. If meropenem is infused as 2 grams IV every 8 hours over 3 hours it would be expected to achieve a similar likelihood of target attainment as meropenem-vaborbactam (i.e., approximately 8 µg/mL)[423].

Clinical trials comparing effectiveness across the newer β-lactam agents are not available. Observational data and subgroup analysis from clinical trial data provide insights into the effectiveness of the newer agents compared to traditional anti-pseudomonal regimens, with studies generally focusing on MDR-*P. aeruginosa* and not DTR-*P. aeruginosa*. An observational study including 200 patients with MDR-*P. aeruginosa* infections compared the outcomes of patients receiving ceftolozane-tazobactam versus polymyxin- or aminoglycoside-based therapy [406]. Favorable clinical outcomes were observed in 81% of patients receiving ceftolozane-tazobactam versus 61% of patients receiving polymyxin- or aminoglycoside-based therapy; this difference achieved statistical significance. Rigorous data investigating the activity

of ceftazidime-avibactam against comparators are lacking. However, pooled data from five trial 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 [424]. Only 66% of isolates were susceptible to ceftazidime-avibactam making interpretation of the results challenging [424]. A clinical trial 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 [230]. 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.

Cefiderocol is suggested as an alternative treatment option for DTR-*P. aeruginosa* infections outside of the urine. 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 μg/mL) [115, 183, 221, 425-429]. Similar to the novel β-lactam-β-lactamase inhibitors, percent susceptibility to cefiderocol is likely to be reduced after widespread use of this agent.

A clinical trial compared the outcomes of patients with infections due to carbapenem-resistant organisms treated with cefiderocol versus alternative therapy, which largely consisted of polymyxin-based therapy [205]. The trial included 22 unique patients with 29 carbapenem-resistant *P. aeruginosa* infections [430]. Mortality at the end of therapy was 18% in both the cefiderocol and alternative therapy arms for patients infected with *P. aeruginosa*. This trial suggests that cefiderocol performs as well as agents that were previously 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 [230, 406]. Despite the high DTR-*P. aeruginosa* susceptibility to cefiderocol, the panel suggests

cefiderocol as an alternative option when inactivity, intolerance, or unavailability precludes the use of the newer β-lactam-β-lactamase inhibitors.

Question 4.5: What are preferred antibiotics for the treatment of DTR-*P. aeruginosa* that produce metallo-β-lactamase enzymes?

Suggested approach: For patients infected with DTR-*P. aeruginosa* isolates that are metallo-β-lactamase producing, the preferred treatment is cefiderocol.

Rationale

P. aeruginosa harboring metallo-β-lactamases remain uncommon in the United States[348]; such isolates are more common in other regions of the world[249, 431-433]. DTR-*P. aeruginosa* isolates exhibiting resistance to all available β-lactam-β-lactamase inhibitors (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam) should raise suspicion for possible metallo-β-lactamase production. Metallo-β-lactamase-producing *P. aeruginosa* isolates generally remain susceptible to cefiderocol[257, 434].

Clinical data on the use of cefiderocol as a treatment for metallo-β-lactamase-producing *P. aeruginosa* are limited. Seven patients with metallo-β-lactamase-producing *P. aeruginosa* infections were included in two cefiderocol clinical trials[257]. Although numbers are too small to draw meaningful conclusions, 71% (5 of 7 patients) receiving cefiderocol achieved clinical cure compared to none of the five patients in the alternative therapy arm, which generally consisted of polymyxin-based or meropenem-based therapy[257].

In contrast to metallo-β-lactamase-producing Enterobacterales, the combination of ceftazidime-avibactam plus aztreonam (using data extrapolated from aztreonam-avibactam) appears less likely to provide an incremental benefit over aztreonam alone[350, 435]. There are isolated case reports in the literature suggesting potential clinical success with this combination[258, 436]. It is theoretically possible that simultaneous inhibition of more than one PBP by ceftazidime (PBP1a/1b, PBP3) and aztreonam (PBP3) may add some benefit over aztreonam alone. Although avibactam may help reduce the effectiveness of PDC enzymes, the multiple other mechanisms generally present in DTR-*P. aeruginosa* are likely to hydrolyze aztreonam. Extrapolating data from aztreonam-avibactam, it is anticipated that ceftazidime-avibactam and aztreonam have activity against <10% of metallo-β-lactamase-producing *P. aeruginosa*[435].

Question 4.6: 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?

Suggested approach: The emergence of resistance is a concern with all β-lactams used to treat DTR-*P. aeruginosa* infections. Available data suggest the frequency may 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 PDCs [368, 422, 437-448]. 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 [437, 439, 440, 442, 445, 447-450].

Mechanisms contributing to *P. aeruginosa* resistance to imipenem-cilastatin-relebactam are less clear and are generally presumed to be related to increased production of PDCs in combination with loss of OprD and overexpression of efflux pumps (e.g., MexAB-OprM and/or MexEF-OprN)[307, 451, 452]. A number of diverse mechanisms of *P. aeruginosa* resistance to cefiderocol have been described[314] including mutations in the TonB-dependent iron transport system [315-317, 453] or amino acid changes in the AmpC β-lactamases [453, 454].

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 structural similarities. 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 [448]. 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 ceftolozane-tazobactam described a similar experience [447]. Treatment-emergent PDC changes were identified in 79% of paired isolates.

Limited data on the frequency of emergence of resistance to imipenem-cilastatin-relebactam exist. However, one report identified the emergence of resistance to this agent in 26% (5 of 19) of patients receiving imipenem-cilastatin-relebactam for the treatment of *P. aeruginosa* infections[451]. Similarly, estimates of the frequency of the emergence of resistance of *P. aeruginosa* to cefiderocol since its clinical introduction are incomplete 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 [205].

The panel suggests 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 recurrent infection, the panel suggests considering use of imipenem-cilastatin-relebactam or cefiderocol, particularly if one of these agents tested susceptible previously, at least until culture and AST data are available.

Question 4.7: What is the role of combination antibiotic therapy for the treatment of infections caused by DTR-*P. aeruginosa*?

Suggested approach: Combination antibiotic therapy is not suggested for infections caused by DTR-*P. aeruginosa* if susceptibility to ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol has been confirmed.

Rationale

Although empiric combination antibiotic therapy (e.g., the addition of tobramycin to a β-lactam agent) to broaden the likelihood of at least one active 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 antibiotic [343]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [343].

Clinical trials comparing ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol as monotherapy and as a component of combination therapy are not available (e.g., ceftazidime-avibactam versus ceftazidime-avibactam and tobramycin). Based on toxicities associated with aminoglycosides and polymyxins and previous clinical outcomes data not demonstrating a benefit with the use of combination therapy for *P. aeruginosa* infections[343], the panel does not suggest that combination therapy be routinely administered 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*, tobramycin (if susceptibility is demonstrated) can be considered in combination with either ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol, preferentially selecting the β-lactam 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 μg/mL (intermediate category), imipenem-cilastatin-

relebactam in combination with tobramycin is favored. Data are lacking demonstrating a benefit to this approach and it should be considered as a last resort. This approach is suggested as it may increase the likelihood that at least one active agent is being included in the treatment regimen.

If tobramycin does not test susceptible, polymyxin B can be considered in combination with a novel β-lactam. 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 [455-460].

Question 4.8: What is the role of nebulized antibiotics for the treatment of respiratory infections caused by DTR-*P. aeruginosa*?

Suggested approach: The panel does not suggest the use 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 [461-488]. At least three trials investigated 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 [489]; a second trial compared the outcomes of 142 adults with pneumonia (22% caused by *P. aeruginosa*) treated with nebulized amikacin/fosfomycin versus placebo [490]; and the third trial compared the outcomes of 508 adults with pneumonia (32% caused by *P. aeruginosa*) treated with nebulized amikacin versus placebo [491]. 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 a subgroup analyses of drug-resistant pathogens [489-491]. A meta-analysis of 13 trials including 1,733 adults with ventilator-associated pneumonia indicated that the addition of nebulized antibiotics was associated with at least partial resolution of clinical symptoms of infection compared to the control group; however, there was significant heterogeneity among the pathogens involved and the definition of clinical response across studies[492]. No survival benefit, reduction in intensive care unit length of stay, or reduction in ventilator days was observed in patients receiving nebulized antibiotics[492].

Reasons for the lack of clear clinical benefit with nebulized antibiotics in available trials are unclear. In a PK/PD 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 [493].

However, it is likely that nebulized antibiotics do not achieve sufficient penetration and/or distribution throughout lung tissue to exert significant bactericidal activity [494], likely due in part to the use of parenteral formulations not specifically designed for inhalation in suboptimal delivery devices such as jet nebulizers [495, 496]. Professional societies have expressed conflicting views regarding the role of nebulized antibiotics as adjunctive therapy to IV antibiotics [497-499]. The panel suggests 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 with use of aerosolized antibiotics [500].

Section 5: Carbapenem-Resistant *Acinetobacter baumannii*

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections pose significant challenges in healthcare settings [501, 502]. In this guidance document, for simplicity, we will use the term "CRAB" although we recognize that a laboratory may not be able to accurately separate carbapenem-resistant *A. baumannii* from other species within the *baumannii* and *calcoaceticus* complexes [503].

The management of CRAB infections is difficult for several reasons. First, CRAB is most commonly recovered from respiratory specimens or wounds. Therefore, it is not always clear if an isolate is a colonizing organism in patients who are ill for reasons attributable to their underlying host status (e.g., patients requiring mechanical ventilation, patients with extensive burns), or if CRAB represents a true pathogen capable of contributing to excess mortality, leading to uncertainty about the need for antibiotic therapy. For the same reason, it is challenging to determine if poor clinical outcomes are attributable to suboptimal antibiotic therapy or to underlying host factors.

Second, once *A. baumannii* exhibits carbapenem resistance, it generally has acquired resistance to most other antibiotics expected to be active against wild-type *A. baumannii* leaving few remaining therapeutic options. The production of OXA carbapenemases (e.g., OXA-24/40, OXA-23) mediate resistance to β-lactams [503, 504]. CRAB isolates may also produce metallo-β-lactamases and additional serine carbapenemases (e.g., *Acinetobacter baumannii*-derived cephalosporinases [ADCs]), further limiting the utility of common β-lactam agents. Sulbactam resistance is not completely understood but appears to be driven primarily via mutations targeting PBPs (i.e., PBP1a/1b, and PBP3); β-lactamase production may also contribute [505-507]. Aminoglycoside modifying enzymes or 16S rRNA methyltransferases generally preclude aminoglycosides as treatment options for CRAB [508-510]. Mutations in the chromosomally-encoded quinolone resistance determining regions generally mediate resistance to fluoroquinolones [509].

Finally, there is no clear "standard of care" antibiotic regimen for CRAB infections against which to estimate the effectiveness of various treatment regimens. Robust comparative

effectiveness studies between commonly used agents are limited. Data supporting a prioritization of specific agents with CRAB activity or the additive benefit of commonly used combination regimens for CRAB infections remain incomplete. This guidance document focuses on the treatment of moderate-severe CRAB infections.

Question 5.1: What is the general approach for the treatment of infections caused by CRAB?

Suggested approach: The use of high-dose ampicillin-sulbactam (total daily dose of 6-9 grams of the sulbactam component) in combination with at least one other agent is suggested for the treatment of CRAB infections.

Rationale

Combination therapy with at least two agents is suggested for the treatment of CRAB infections, at least until an appropriate clinical response is observed, given the limited clinical data supporting the effectiveness of any single antibiotic agent. The panel suggests high-dose ampicillin-sulbactam (total daily dose of 6-9 grams of the sulbactam component) be included as a component of the combination therapy regimen. Combination therapy is advised even though only one of eight clinical trials found improved clinical outcomes with the use of combination antibiotic therapy for CRAB infections [511-517] (Question 5.2). Notably, the clinical trial that demonstrated any benefit with combination therapy was the only one that included high-dose ampicillin-sulbactam in the combination therapy arm [516].

Sulbactam's unique activity against *A. baumannii* isolates has been observed through in vitro studies [518-520], animal models [521], and clinical outcomes data [516, 522-525], as described in Question 5.3. Insufficient data exist to determine if standard-dose ampicillin-sulbactam and high-dose ampicillin-sulbactam have equivalent efficacy for CRAB infections caused by isolates susceptible to ampicillin-sulbactam. The panel favors high-dose ampicillin-sulbactam, given the theoretical benefit of saturating sulbactam's PBP targets with higher dosages of sulbactam and the potential inaccuracies with commonly used approaches for ampicillin-sulbactam AST testing for CRAB[526, 527]. When non-susceptibility to ampicillin-sulbactam is demonstrated, high-dose ampicillin-sulbactam may remain an effective treatment option [522, 528, 529].

Additional agents that can be considered as components of combination regimens for the treatment of CRAB infections include polymyxin B (Question 5.4), minocycline (Question 5.5), tigecycline (Question 5.5), or cefiderocol (Question 5.6). Fosfomycin and rifampin are not

suggested as components of combination therapy [513, 515, 517] (**Question 5.2**, **Question 5.8**). As two large clinical trials have not demonstrated a benefit with the use of high-dose extended-infusion carbapenem therapy for the treatment of CRAB infections[512, 530], meropenem or imipenem-cilastatin are not suggested as components of CRAB therapy (**Question 5.7**). The panel also does not suggest the use of nebulized antibiotics as adjunctive therapy for CRAB pneumonia, due to the lack of benefit observed in clinical trials [489-491], concerns regarding unequal distribution in infected lungs, and the potential for respiratory complications such as bronchoconstriction [494-496, 500] (**Question 5.9**).

Question 5.2: What is the role of combination antibiotic therapy for the treatment of infections caused by CRAB?

Suggested approach: Combination therapy with at least two active agents, whenever possible, is suggested for the treatment of CRAB infections, at least until clinical improvement is observed, because of the limited clinical data supporting any single antibiotic agent.

Rationale

Combination therapy is suggested for the treatment of CRAB infections, even if a single agent demonstrates activity. In situations when prolonged durations of therapy may be needed (e.g., osteomyelitis), step-down therapy to a single active agent can be considered. In vitro and animal studies have had conflicting findings but several investigations indicate increased bacterial killing with various combination regimens [531-539]. There are many observational studies evaluating the role of combination therapy versus monotherapy for the treatment of CRAB infections with differing results [529, 539-559]. The heterogeneity in patient populations, infectious sources, inclusion of colonizing isolates, variation in antibiotics and dosages used, small numbers, and imbalances between treatment arms makes interpretation of a number of these studies challenging.

At least eight trials have investigated the role of combination therapy for CRAB infections and only one of the eight trials indicated a potential benefit with combination therapy[512-518, 530]. Of note, because of inconsistent and unclear colistin dosing reported in studies, the panel elected not to report colistin dosing used in individual trials. None of the eight trials that included a polymyxin arm investigated the role of polymyxin B, which has a more favorable PK profile than colistin [200]. Below is a summary of the eight trials, a number of which are limited by small sample sizes.

A trial including 210 ICU patients with invasive CRAB infections compared the outcomes of patients receiving colistin alone versus colistin in combination with rifampicin (known in the United States as rifampin) and found no difference in 30-day mortality with 43% mortality in both study arms [514]. A second trial including 43 patients with CRAB pneumonia also

compared colistin monotherapy and colistin in combination with rifampin [515]. In hospital mortality was 73% in the colistin group and 62% in the colistin-rifampin group, not reaching statistical significance. A third study randomized nine patients with colistin-resistant *A. baumannii* (carbapenem susceptibility status not described) and found no difference in clinical response between the colistin and colistin plus rifampin arms (80% versus 67%, respectively) [517].

A fourth trial including patients with a variety of CRAB infections randomized 94 patients to receive colistin alone or colistin with fosfomycin [513]. Mortality within 28 days was 57% versus 47% and clinical failure was 45% versus 40% in the colistin monotherapy and colistin-fosfomycin arms, respectively. IV fosfomycin is not currently available in the United States, making the results of this trial of limited relevance to this guidance document.

Two large trials evaluated the role of colistin monotherapy versus colistin in combination with meropenem[512, 560]. In the first study, 312 patients with CRAB bacteremia, pneumonia, or urinary tract infections were randomized to colistin alone versus colistin plus meropenem (2 grams IV every 8 hours as a 3-hour infusion)[512]. No differences in 28-day mortality (46% versus 52%) or clinical failure (83% versus 81%) were observed between the groups [512]. The second trial included 329 patients with drug-resistant *A. baumannii* bloodstream infections or pneumonia randomized to colistin alone compared to colistin in combination with meropenem (1 gram IV every 8 hours as a 30-minute infusion)[560]. The 28-day mortality was 46% versus 42% and clinical failure was 68% versus 60% in the colistin monotherapy and combination therapy arms, respectively[560]. For both trials, the addition of meropenem to colistin did not improve clinical outcomes in patients with severe CRAB infections.

A seventh, open label trial compared the outcomes of 47 patients with CRAB pneumonia randomized to meropenem/colistin and meropenem/ampicillin-sulbactam (total daily dose of 6 grams of the sulbactam component) for a 14-day course[561]. Twenty-eight day clinical response was similar in both groups at 75% versus 70%.

The eighth trial included 39 CRAB pneumonia patients, with clinical isolates demonstrating susceptibility to both colistin and sulbactam. Patients were randomized to colistin monotherapy versus colistin in combination with high-dose sulbactam (total daily dose of 8 grams of the sulbactam component) [516]. Clinical improvement by day five was observed in 16% and 70% of patients in the colistin versus colistin-sulbactam arms, respectively, achieving statistical significance. Investigators were unblinded to treatment assignment. Moreover, patients were allowed to transition to other antibiotics after day five, precluding an accurate comparison of 28-day mortality or clinical failure between the groups.

Although only one of eight clinical trials demonstrated any statistically significant benefit with combination therapy for CRAB infections, the panel favors the use of combination therapy for CRAB infections for the following reasons: (1) there is a lack of robust clinical data supporting the treatment of CRAB infections with any single agent demonstrating in vitro activity against CRAB (**Questions 5.3 to 5.6**); (2) high bacterial burdens are expected with CRAB infections due to almost universal delays in initiating effective therapy as common empiric antibiotic regimens are generally not active against CRAB; and (3) antibiotics that initially appear active against CRAB may rapidly develop resistance so combination therapy increases the likelihood that at least one active agent is being administered.

Potential options for consideration as components of combination therapy in addition to high-dose ampicillin-sulbactam include: tetracycline derivatives (with the most experience available for minocycline, followed by tigecycline, and virtually no clinical data available for eravacycline or omadacycline), polymyxin B, or cefiderocol (**Questions 5.3 to 5.6**). The panel suggests ampicillin-sulbactam as a component of combination therapy, even when resistance to this agent has been demonstrated (**Question 5.3**). The combination of meropenem and colistin (or polymyxin B), without the addition of a third agent, is not suggested for the treatment of CRAB infections based on the results of two clinical trials[512, 530]; supportive data for this combination is generally limited to in vitro studies [518-520] (**Question 5.7**). The panel does not consider the available evidence sufficient to suggest fosfomycin or rifampin as components of combination therapy (**Question 5.8**) [513, 515, 517].

Question 5.3: What is the role of ampicillin-sulbactam for the treatment of infections caused by CRAB?

Suggested approach: High-dose ampicillin-sulbactam is suggested as a component of combination therapy for CRAB, regardless of whether susceptibility has been demonstrated.

Rationale

Sulbactam is a competitive, irreversible β-lactamase inhibitor that, in high doses, saturates PBP1a/1b and PBP3 of *A. baumannii* isolates [505, 562]. Sulbactam's unique activity against *A. baumannii* isolates has been demonstrated through in vitro studies [518-520], animal models [521], and clinical outcomes data [516, 522-525]. The panel suggests high-dose ampicillin-sulbactam (total daily dose of 6-9 grams of the sulbactam component) as a component of combination therapy for CRAB infections (**Table 1**).

Ampicillin-sulbactam uses a 2:1 formulation; for example, 3 grams of ampicillin-sulbactam is comprised of 2 grams of ampicillin and 1 gram of sulbactam. Ampicillin-sulbactam total daily dosages of 18-27 grams (equivalent to 6-9 grams of sulbactam) as extended or continuous infusions are suggested (e.g., 9 grams [3 grams of sulbactam] IV every 8 hours infused over 4 hours) [516, 518, 519, 522, 563]. Fewer than 50% of CRAB isolates test susceptible to ampicillin-sulbactam [564, 565]. When non-susceptibility to ampicillin-sulbactam is demonstrated, the panel believes ampicillin-sulbactam may still remain an effective treatment option based on the potential for sulbactam to saturate altered PBP targets [518, 522, 528, 529].

Two meta-analyses have evaluated observational and clinical trial data for various treatment regimens against CRAB infections [524, 525]. A meta-analysis published in 2021 included 18 studies and 1,835 patients and found that ampicillin-sulbactam (total daily dose of at least 6 grams of the sulbactam component) in combination with a second agent was the most effective regimen to reduce mortality in critically ill patients infected with CRAB [524]. Moreover, nephrotoxicity was less apparent with sulbactam-based regimens compared with polymyxin-based regimens. An earlier meta-analysis published in 2017 included 23

observational studies or clinical trials and 2,118 patients with CRAB infections [525]. This analysis identified sulbactam as having the greatest impact on reducing mortality when evaluating sulbactam-based, polymyxin-based, or tetracycline-based regimens. A comparison of adverse events was not undertaken [525].

As described in **Question 5.2**, a clinical trial including 39 CRAB pneumonia patients (with clinical isolates susceptible to both colistin and sulbactam) identified clinical improvement by day 5 in 16% and 70% of patients randomized to colistin monotherapy versus colistin in combination with high-dose sulbactam (total daily dose of at least 8 grams of the sulbactam component) [516]. This trial had a number of limitations including the following: small sample size, all isolates were susceptible to sulbactam, the open-label design may have led to biased outcome assignment, and an appropriate evaluation of long-term outcomes could not be undertaken as patients could transition to other agents after day 5. These limitations notwithstanding, this trial identified clinical improvement with a colistin-sulbactam combination for the treatment of CRAB infections.

Two other clinical trials have not identified a difference in clinical outcomes with the use of ampicillin-sulbactam. An open label trial comparing the outcomes of 47 patients with CRAB pneumonia randomized to meropenem/colistin and meropenem/ampicillin-sulbactam (total daily dose of 6 grams of the sulbactam component) for a 14-day course identified similar clinical responses in both groups[561] (**Question 5.2**). Another trial randomized 28 CRAB pneumonia patients to colistin monotherapy versus ampicillin-sulbactam monotherapy (total daily dose of at least 6 grams of the sulbactam component) [528]. Neither differences in 28-day mortality or clinical failure reached statistical significance (33% versus 30% and 33% versus 38%, among patients in the colistin and ampicillin-sulbactam arms, respectively). Nephrotoxicity was identified in 33% versus 15%, comparing the two groups. Evaluating the totality of in vitro, animal, and clinical data, the panel considers ampicillin-sulbactam a preferred option for the treatment of CRAB infections.

The antibiotic sulbactam-durlobactam completed phase 3 clinical studies but is not currently FDA-approved[566]. The proposed dosing of sulbactam-durlobactam provides insights into ampicillin-sulbactam dosing for CRAB infections. Pre-clinical and clinical studies have

investigated the agent sulbactam-durlobactam against CRAB isolates[567-571]. This agent includes a total daily dose of 4 grams of the sulbactam component, as opposed to the total daily dose of 6-9 grams of sulbactam suggested for ampicillin-sulbactam for the treatment of CRAB infections in this guidance document. Sulbactam is a substrate for both ADCs (Class C enzymes) and OXA enzymes (Class D enzymes) that are produced by CRAB[567, 569]. High-dose sulbactam (i.e., ampicillin-sulbactam) increases the likelihood that sulbactam successfully reaches its PBP targets. Durlobactam is a potent inhibitor of class A, C, and D enzymes commonly produced by CRAB[567, 569], enabling lower doses of sulbactam as sulbactam is more likely to successfully reach its PBP targets with the protection of durlobactam. As ampicillin-sulbactam does not have the added protection of a durlobactam-like beta-lactamase inhibitor, the panel suggests use of high-dose ampicillin-sulbactam as a primary component of combination therapy for CRAB infections.

Question 5.4: What is the role of the polymyxins for the treatment of infections caused by CRAB?

Suggested approach: Polymyxin B can be considered in combination with at least one other agent for the treatment of CRAB infections.

Rationale

The polymyxins, including both colistin and polymyxin B, have reliable in vitro activity against CRAB isolates, with most of the published literature focusing on colistin [519, 520]. The panel preferentially suggests polymyxin B when considering polymyxin-based regimens, based on its more favorable PK profile than colistin [200]. Colistin is favored for CRAB UTIs, although admittedly rare, as it converts to its active form in the urinary tract. There is no CLSI susceptibility category for the polymyxins against *A. baumannii*; most evidence suggests the benefit with polymyxins would be diminished for polymyxin MICs >2 µg/mL [572].

The panel advises against polymyxin monotherapy for the following reasons: First, concentrations of polymyxins in serum achieved with conventional dosing strategies are highly variable and may be inadequate for effective bactericidal activity [200]. Second, dosages required to treat systemic infections approach the threshold for nephrotoxicity making the therapeutic window narrow (i.e., ~2 µg/mL may be required to achieve 1-$\log_{10}$ reduction in bacterial growth, but this is also the threshold associated with nephrotoxicity) [573]. Third, the activity of IV polymyxins in pulmonary epithelial lining fluid is suboptimal and generally does not result in adequate bacterial killing in the lungs [574-576]. Finally, there are several reports of clinical failure and resistance emergence during polymyxin monotherapy [572, 577-580].

Question 5.5: What is the role of tetracycline derivatives for the treatment of infections caused by CRAB?

Suggested approach: High-dose minocycline or high-dose tigecycline can be considered in combination with at least one other agent for the treatment of CRAB infections. The panel prefers minocycline because of the long-standing clinical experience with this agent and the availability of CLSI susceptibility interpretive criteria; however, tigecycline is also a reasonable option.

Rationale

Several tetracycline derivatives have in vitro activity against CRAB including minocycline, tigecycline, and eravacycline. These agents are capable of escaping common tetracycline resistance mechanisms [581, 582]. The frequency of the emergence of resistance to these agents by CRAB isolates is not well defined but occurs through drug efflux stemming from overexpression of various RND-type transporters [583, 584]. A general concern with tetracycline derivatives is that they achieve rapid tissue distribution following administration, resulting in limited concentrations in the urine and poor serum concentrations [35].

There has been considerable clinical experience with the use of minocycline since its introduction in the 1960s [585]. It is commercially available in both oral and IV formulations. International surveillance data suggest minocycline is active against approximately 60-80% of CRAB isolates [586, 587]. PD data suggest high-dose minocycline (700 mg loading dose followed by 350 mg every 12 hours) may be more effective than standard minocycline dosages for the treatment of CRAB infections, particularly when used in combination with high-dose ampicillin-sulbactam and polymyxin B [519]. Clinical data demonstrating the safety and efficacy of minocycline dosages these high are needed before it is recommended in practice. Minocycline has not been subjected to rigorous trials for the treatment of CRAB infections, although case series describing its use are available [339, 588-591]. Drawing conclusions on the effectiveness of minocycline from these observational reports is challenging as they have important limitations (e.g., small sample sizes, selection bias, inadequate distinctions between

colonization and infection, heterogeneous sites of infection). Despite the limitations of available data, the panel considers minocycline a reasonable treatment option for CRAB infections (dosed at 200 mg twice daily either IV or orally) as there are no clear clinical failure signals with its use for treating CRAB infections (**Table 1**).

Tigecycline is a tetracycline derivative only available as an IV formulation. Neither CLSI nor FDA susceptibility interpretive criteria are available for tigecycline against CRAB isolates, and minocycline MICs cannot be used to predict tigecycline MICs as differences in susceptibility percentages across the tetracycline derivatives exist [592]. Several observational studies and a meta-analysis of 15 trials suggested that tigecycline monotherapy is associated with higher mortality than a variety of alternative regimens used for the treatment of pneumonia, not exclusively limited to pneumonia caused by CRAB [330, 546, 593, 594]. Subsequent investigations have suggested that when high-dose tigecycline is prescribed (200 mg IV as a single dose followed 100 by mg IV q12h) mortality differences between tigecycline and comparator agents are no longer evident [331-333]. If tigecycline is prescribed for the treatment of CRAB infections, the panel suggests that high-doses be used (**Table 2**). The panel suggests prescribing minocycline or tigecycline in combination with at least one additional agent for CRAB infections. Both agents are associated with nausea in 20-40% of patients, and this is likely more common with higher dosages [595-597].

Although eravacycline MICs are generally 2- to 8-fold lower than tigecycline MICs against CRAB [592, 598, 599], the clinical relevance of the differences in MIC distributions between these agents is unclear due to differences in the PK profile of tigecycline and eravacycline. As with tigecycline, no CLSI susceptibility interpretive criteria exist for eravacycline. Very small numbers of patients with CRAB infections were included in clinical trials that investigated the efficacy of eravacycline [326, 336]. Limited post-marketing clinical reports describing its efficacy for the treatment of CRAB infections are available[600, 601]. In an observational study of 93 patients with CRAB pneumonia, eravacycline was associated with longer durations of mechanical ventilation (11 versus 7 days) and higher 30-day mortality (33% versus 15%) compared to commonly administered alternative regimens[601]. All four patients with CRAB bloodstream infections receiving eravacycline died. This study did not adjust for

potential confounding by indication. In light of the limited clinical data supporting the use of eravacycline, the panel suggests limiting use of eravacycline to situations when minocycline and tigecycline are either not active or unable to be tolerated. Pre-clinical data evaluating the activity of omadacycline, a tetracycline derivative with both an IV and oral formulation, against CRAB suggests reduced efficacy relative to other tetracycline derivatives and a PK/PD profile which suggests omadacycline has very limited activity [63, 340-342]. Clinical data are limited to a small, uncontrolled case series[602]. The panel does not suggest the use of omadacycline to treat CRAB infections.

Question 5.6: What is the role of cefiderocol therapy for the treatment of infections caused by CRAB?

Suggested approach: Cefiderocol should be limited to the treatment of CRAB infections refractory to other antibiotics or in cases where intolerance or resistance to other agents precludes their use. When cefiderocol is used to treat CRAB infections, the panel suggests prescribing the agent as part of a combination regimen.

Rationale

Cefiderocol is the only novel FDA-approved β-lactam agent with in vitro activity against CRAB isolates. International surveillance studies indicate that approximately 95% of CRAB isolates are susceptible to cefiderocol using the CLSI susceptibility criteria ≤4 μg/mL (**Table 2**)[220, 273, 427, 428, 603, 604]. Determining CRAB susceptibility to cefiderocol is challenging, in part due to variable iron concentrations in media. Moreover, MIC results are not always reproducible across methods, with heteroresistance often observed[605, 606].

The percent free time above the MIC of cefiderocol required for a 1-$\log_{10}$ reduction in *A. baumannii* was higher than for Enterobacterales, *P. aeruginosa*, or *S. maltophilia* in a murine lung infection model[603].

A clinical trial including 54 patients with CRAB infections identified mortality at the end of study to be 49% versus 18% in the cefiderocol versus an alternative therapy arm (largely composed of polymyxin–based regimens), respectively [205]. Poor outcomes with cefiderocol were observed in patients with pneumonia and bloodstream infections. A second randomized trial specifically evaluating patients with pneumonia randomized to cefiderocol or high-dose extended-infusion meropenem found no difference in clinical outcomes between the two treatment regimens, including among 36 patients with CRAB pneumonia – suggesting outcomes were similar between cefiderocol and a relatively inactive agent [607]. Because of the heterogeneity of regimens used in the alternative arms in the first trial and the relatively small numbers of patients with CRAB when combining both trials, contextualizing the results is challenging [219]. In a subsequent observational study, 30-day mortality was 34% versus 56%

for 124 patients with CRAB infections receiving cefiderocol versus colistin-based regimens, respectively[608]. Recurrent CRAB infection, however, was more likely in the cefiderocol arm (17% versus 7%). Among the 8 patients in the cefiderocol group who experienced a recurrent CRAB infection, 50% had subsequent isolates exhibiting resistance to cefiderocol.

Combining the results of pre-clinical and clinical data, the panel suggests that if cefiderocol is prescribed for the treatment of CRAB infections, it should be used with caution and as a component of combination therapy, to increase the likelihood that at least one effective agent is included as part of the treatment regimen. The panel also suggests limiting consideration of cefiderocol for CRAB infections after other regimens have been exhausted.

Question 5.7: What is the role of extended-infusion meropenem or imipenem-cilastatin for the treatment of infections caused by CRAB?

Suggested approach: High-dose, extended-infusion meropenem or imipenem-cilastatin are not suggested as a component for the treatment of CRAB infections.

Rationale

In vitro data suggest that triple-combination therapies consisting of (1) meropenem, ampicillin-sulbactam, and minocycline or (2) meropenem, ampicillin-sulbactam, and polymyxin B may lead to eradication of CRAB [518-520]. As described in **Question 5.2**, two large trials evaluated the role of colistin monotherapy versus colistin plus meropenem and neither trial demonstrated a benefit with the combination of colistin plus meropenem for the treatment of CRAB infections[512, 530]. A secondary analysis of the first trial investigated the association between the presence of in vitro synergy between colistin-meropenem and clinical outcomes in patients who received the combination of colistin plus meropenem[512, 560]. Improved clinical outcomes were not observed when in vitro synergy was present.

Imipenem-cilastatin may retain activity against some meropenem-resistant isolates [609-611]; however, by definition, CRAB isolates have meropenem and/or imipenem MICs ≥8 µg/mL and carbapenem MICs are almost always significantly higher than 8 µg/mL[512, 560]. With highly elevated MICs, it appears unlikely that either meropenem or imipenem-cilastatin would offer any incremental benefit when used in combination with other CRAB regimens. As high-dose ampicillin-sulbactam is being suggested as a core component of combination treatment for CRAB infections, the panel advises against the use of meropenem or imipenem-cilastatin as they may lead to additive beta-lactam toxicity without clinical benefit.

Question 5.8: What is the role of the rifamycins for the treatment of infections caused by CRAB?

Suggested approach: The panel does not suggest the use of rifabutin or other rifamycins as a component of CRAB therapy.

Rationale

The rifamycin class of antibiotics includes agents such as rifampin, rifabutin, and rifapentine that inhibit bacterial RNA polymerase [612]. Data indicate that rifabutin has potent activity against *A. baumannii* in both in vitro and animal models, which is significantly greater than that exhibited by rifampin [613-615]. Synergy between rifabutin and the polymyxins has been proposed due to the latter's ability to disrupt bacterial membrane permeability, which may facilitate intracellular penetration of rifamycin and subsequent inhibition of bacterial protein synthesis [614].

Three clinical trials compared the clinical outcomes of CRAB-infected patients receiving colistin alone versus colistin in combination with rifampin (Question 5.2) [514, 515, 517]. A trial including 210 ICU patients with invasive CRAB infections compared the outcomes of patients receiving colistin alone versus colistin in combination with rifampin and found 43% mortality in both study arms [514]. A second trial including 43 patients with CRAB pneumonia also compared colistin monotherapy and colistin in combination with rifampin [515] and identified in hospital mortality to be 73% in the colistin group and 62% in the colistin-rifampin group, not achieving statistical significance. A third study randomized nine patients with colistin-resistant *A. baumannii* and found no difference in clinical response between the colistin (80%) and colistin plus rifampin arms (67%) [517].

Admittedly, there are limitations to all these trials including suboptimal dosing of colistin and small sample sizes. It is unknown if a clinical benefit would have been observed if rifabutin had been used in place of rifampin [616]. In light of the known toxicities and drug interactions associated with the rifamycins [617] and the absence of a benefit observed in

available clinical trials, the panel does not favor the use of rifabutin as a component of CRAB therapy.

Question 5.9: What is the role of nebulized antibiotics for the treatment of respiratory infections caused by CRAB?

Suggested approach: The panel does not suggest adding nebulized antibiotics for the treatment of respiratory infections caused by CRAB.

Rationale

There have been conflicting findings regarding the clinical effectiveness of nebulized antibiotics for the treatment of gram-negative pneumonia in observational studies [461-488]. At least three trials evaluated 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 (65% caused by *A. baumannii*) treated with nebulized colistin versus placebo [489]; a second trial compared the outcomes of 142 adults with pneumonia (20% caused by *A. baumannii*) treated with nebulized amikacin/fosfomycin versus placebo [490]; and the third trial compared the outcomes of 508 adults with pneumonia (29% caused by *A. baumannii*) treated with nebulized amikacin versus placebo [491]. 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 [489-491].

A meta-analysis of 13 trials including 1,733 adults with ventilator-associated pneumonia indicated that the addition of nebulized antibiotics was associated with at least partial resolution of clinical symptoms of infection compared to the control group; however, there was significant heterogeneity among the pathogens involved and the definition of clinical response across studies[492]. No survival benefit, reduction in intensive care unit lengths of stay, or reduction in ventilator days was observed in patients receiving nebulized antibiotics[492].

Reasons for the lack of clinical benefit in these trials are unclear. In a PK/PD 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 [493]. However, it is likely that nebulized antibiotics do not achieve sufficient penetration and/or distribution throughout lung tissue to exert significant bactericidal activity [494], likely due in part to the use of parenteral formulations not specifically designed for inhalation in suboptimal delivery devices such as jet nebulizers [495, 496]. Professional societies have expressed conflicting views regarding the role of nebulized antibiotics as adjunctive therapy to IV antibiotics [497-499]. The panel suggests against the use of nebulized antibiotics as adjunctive therapy for CRAB 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 patients receiving aerosolized antibiotics [500].

Section 6: *Stenotrophomonas maltophilia*

Stenotrophomonas maltophilia is an aerobic, glucose non-fermenting, gram-negative bacillus that is ubiquitous in water environments[618]. The organism has a long history of changing nomenclatures and a complicated phylogeny [619-621]. Although generally believed to be less pathogenic than many other nosocomial organisms, *S. maltophilia* produces biofilm and virulence factors that can enable colonization or infection in vulnerable hosts, such as those with underlying lung disease and hematological malignancies[622].

S. maltophilia infections pose management challenges very similar to those of CRAB infections. First, although *S. maltophilia* has the potential to cause serious disease, it is often unclear if *S. maltophilia* represents a colonizing organism or a true pathogen, particularly in patients with underlying pulmonary conditions such as cystic fibrosis or ventilator dependency [623-627]. *S. maltophilia* is often recovered as a component of a polymicrobial infection – further challenging the need for targeted *S. maltophilia* therapy [619, 628]. Importantly, *S. maltophilia* can be a true pathogen that causes considerable morbidity and mortality in the hematologic malignancy population primarily due to hemorrhagic pneumonia or bacteremia [629-635].

Second, treatment selection is hampered by the impressive number of antimicrobial resistance genes and gene mutations carried by *S. maltophilia* isolates [619, 621, 636]. An L1 metallo β-lactamase and L2 serine β-lactamase render most conventional β-lactams ineffective against *S. maltophilia*. L1 hydrolyzes penicillins, cephalosporins, and carbapenems, but not aztreonam. L2 has extended cephalosporin activity as well as the ability to hydrolyze aztreonam [619]. *S. maltophilia* exhibits intrinsic resistance to aminoglycosides via chromosomal aminoglycoside acetyl transferase enzymes [637]. Furthermore, *S. maltophilia* can accumulate multidrug efflux pumps that reduce the activity of TMP-SMX, tetracyclines, and fluoroquinolones, and chromosomal Sm*qnr* genes that further reduce the effectiveness of fluoroquinolones [638-641].

Third, a "standard of care" antibiotic regimen for *S. maltophilia* infections against which to estimate the effectiveness of various treatment regimens is not evident. Robust comparative effectiveness studies between commonly used agents for *S. maltophilia* are lacking. Data to prioritize among agents with activity against *S. maltophilia* and to determine the additive benefit of commonly used combination therapy regimens remain incomplete.

Lastly, *S. maltophilia* AST determination is problematic. The CLSI has established susceptibility interpretive criteria for seven agents against *S. maltophilia*: TMP-SMX, ticarcillin-clavulanate, ceftazidime, cefiderocol, levofloxacin, minocycline, and chloramphenicol. Ticarcillin-clavulanate manufacturing has been discontinued and chloramphenicol is rarely used in the United States due to significant toxicities [642], leaving five agents for which interpretable antibiotic MIC data can be provided to clinicians. Confidence in MIC interpretive criteria is undermined by concerns about the reproducibility of ceftazidime and levofloxacin MICs using testing methods commonly employed in clinical laboratories [643, 644], the limited PK/PD data used to inform breakpoints for most agents, and insufficient data to identify correlations between MICs and clinical outcomes. The CLSI is actively undertaking a comprehensive re-evaluation of current antibiotic breakpoints against *S. maltophilia*.

There are no CLSI susceptibility criteria established for the polymyxins [16, 645]. Incomplete *S. maltophilia* growth inhibition often occurs in polymyxin wells, suggestive of heteroresistance. Challenges exist in both the accuracy and reproducibility of polymyxin MICs [646, 647]. The panel does not suggest polymyxins for the treatment of *S. maltophilia* infections. This guidance document focuses on the treatment of moderate-severe *S. maltophilia* infections.

Question 6.1: What is a general approach for the treatment of infections caused by *S. maltophilia*?

Suggested approach: Any of two approaches are suggested for the treatment of *S. maltophilia* infections: (1) the use of two of the following agents: TMP-SMX, minocycline/tigecycline, cefiderocol, or levofloxacin or (2) the combination of ceftazidime-avibactam and aztreonam, when significant clinical instability is evident or intolerance to or inactivity of other agents is identified.

Rationale

In situations of *S. maltophilia* infection, either of two approaches are suggested. Firstly, combination therapy with at least two active agents (i.e., TMP-SMX, minocycline/tigecycline, cefiderocol, or levofloxacin) is suggested at least until clinical improvement is observed, primarily because of the limited clinical data supporting any individual agent (Questions 6.2 to 6.5). Alternatively, the combination of ceftazidime-avibactam and aztreonam can be considered in situations of significant clinical instability, when clinical failure with other agents occurs, or if there is intolerance to other agents (Question 6.6).

In vitro data are conflicting but several investigations suggest synergy between agents with activity against *S. maltophilia* including minocycline, cefiderocol, and fluoroquinolones [648-651]. Clinical outcomes data comparing monotherapy and combination therapy are similarly conflicting and limited to observational studies plagued with concerns such as selection bias, small sample sizes, and significant heterogeneity in patient, microbial, and treatment characteristics [652-654]. As this document focuses on moderate-severe disease due to *S. maltophilia*, the panel favors combination therapy to increase the likelihood that at least one active agent is being administered.

Question 6.2: What is the role of trimethoprim-sulfamethoxazole for the treatment of infections caused by S. *maltophilia*?

Suggested approach: TMP-SMX as a component of combination therapy, at least until clinical improvement is observed, is a preferred therapy for the treatment of *S. maltophilia* infections.

Rationale

TMP-SMX has been the historic first-line therapy for *S. maltophilia* infections. Surveillance studies have consistently shown that TMP-SMX has more than a 90% likelihood of activity against *S. maltophilia* [655, 656], although there is an increasing recognition of *S. maltophilia* isolates resistant to TMP-SMX [650, 655, 657, 658]. Furthermore, there is extensive clinical experience with the use of TMP-SMX to treat *S. maltophilia* infections.

Despite the frequency with which TMP-SMX is prescribed for *S. maltophilia* infections, rigorous clinical data investigating its effectiveness are lacking. An observational study of 1,581 patients with *S. maltophilia* identified in respiratory or blood cultures and treated with TMP-SMX or levofloxacin monotherapy was undertaken using an administrative database[659]. This work suggested that levofloxacin may be protective against mortality in patients with *S. maltophilia* recovered from respiratory cultures and marginally protective against mortality regardless of the culture site. However, these findings were no longer significant when adjusting for time to culture collection. Moreover, there are significant limitations to this study making its findings challenging to interpret (e.g., wide study interval [2005-2017] during which many changes in clinical practice likely occurred, inability to distinguish colonization and infection, inability to adjust for source control, incomplete AST data, inclusion of polymicrobial infections). Given these limitations, the applicability to guide clinical practice is unclear.

Prior to the publication of this work, the largest study evaluating TMP-SMX treatment was a case series of 91 patients with *S. maltophilia* bloodstream infections, in whom mortality was 25% within 14 days [654]. The small number of patients in the study who received an agent other than TMP-SMX precluded a comparative effectiveness evaluation. Several relatively small observational studies comparing TMP-SMX and other agents (namely tetracycline derivatives or

fluoroquinolones) have been undertaken and generally demonstrated similar outcomes between treatment agents [660-666]; these studies have a number of notable limitations as further described in **Question 6.3** and **Question 6.5**. Moreover, there is no established PK/PD index for efficacy or toxicity to inform optimal TMP-SMX dosing for *S. maltophilia* infections and a PD model suggests that TMP-SMX achieves limited activity even against susceptible *S. maltophilia*[648, 667].

Given the toxicity of TMP-SMX (e.g., nausea/vomiting, hyperkalemia, fluid overload, possible nephrotoxicity), particularly at higher doses, no established dose-response relationship[668], the absence of clinical evidence supporting any particular dose, and evidence that TMP dosing of >15 mg/kg/day may lead to serum sulfamethoxazole levels higher than necessary[669], the panel suggests a dose range of 8-12 mg/kg (trimethoprim component) of TMP/SMX for patients with *S. maltophilia* infections (**Table 1**).

Acknowledging the paucity of clinical data supporting this suggestion, the panel still considers TMP-SMX a preferred treatment option for *S. maltophilia* infections, given the long-standing experience with its use and no clear clinical failure signals. As described in **Question 6.1**, when prescribing TMP-SMX for *S. maltophilia* infections, the addition of a second agent (e.g., minocycline/tigecycline, cefiderocol, levofloxacin), at least until clinical improvement is observed, is suggested.

Question 6.3: What is the role of tetracycline derivatives for the treatment of infections caused by *S. maltophilia*?

Suggested approach: High-dose minocycline (i.e., 200 milligrams IV/orally every 12 hours) as a component of combination therapy, at least until clinical improvement is observed, is a preferred therapy for the treatment of *S. maltophilia* infections. Because of the slightly more favorable in vitro data with minocycline, availability of CLSI breakpoints, oral formulation, and likely improved tolerability of minocycline relative to tigecycline, the panel favors minocycline over tigecycline, although tigecycline is also a reasonable treatment option for *S. maltophilia* infections.

Rationale

Tetracycline derivatives generally have low MICs when tested against *S. maltophilia* [651, 670-673]. Surveillance studies report that minocycline and tigecycline have activity against approximately 70-90% of *S. maltophilia* isolates, with a lower (and hence, more favorable) MIC_{90} generally observed for minocycline [651, 670-673]. Amongst tetracycline derivatives, CLSI susceptibility criteria are only available for minocycline [16]. Greater than 90% target attainment is achieved with minocycline dosages of 100 mg IV every 12 hours compared to approximately 75% target attainment with tigecycline dosed at 100 mg IV every 12 hours [671]. Both minocycline and tigecycline have extensive penetration into lung tissue [674-677].

Clinical outcomes data investigating the role of tetracycline derivatives for the treatment of *S. maltophilia* infections are limited. An observational study comparing the clinical outcomes of 45 patients with *S. maltophilia* infections at a variety of body sites demonstrated no difference in outcomes for patients treated with TMP-SMX or minocycline [662]. Another observational study evaluating 119 patients with *S. maltophilia* infections who received minocycline reported clinical success in approximately 80% of patients [678]; there was no comparator arm. An observational study including 45 patients with *S. maltophilia* infections treated with TMP-SMX or tigecycline did not find differences in clinical outcomes [663]. A fourth observational study compared 46 patients receiving standard-dose tigecycline and 36

patients receiving fluoroquinolones (levofloxacin or moxifloxacin)[679]. Outcomes were as follows comparing the tigecycline and fluoroquinolone groups: clinical cure 33% versus 64%, 28-day mortality 48% versus 28%. There are a number of limitations to these studies including selection bias, small sample sizes, heterogeneity in host and microbial data, and the use of additional active agents.

These limitations notwithstanding, there are no clear clinical failure signals indicating that high-dose minocycline or high-dose tigecycline are not reasonable treatment options for *S. maltophilia* infections. Because of the slightly more favorable in vitro data with minocycline, more favorable PK/PD data, oral formulation, and likely improved tolerability of minocycline relative to tigecycline, the panel favors minocycline. Extrapolating largely from treatment data for infections by other drug-resistant pathogens, high-dose regimens are recommended when prescribing minocycline or tigecycline for *S. maltophilia* infections [588, 680, 681] (**Table 1**). At higher dosages (i.e., 200 mg twice daily) both IV and oral formulations of minocycline are expected to provide adequate drug levels.

In vitro and in vivo data on the role of eravacycline against *S. maltophilia* are scarce. Omadacycline, a tetracycline derivative with oral and IV formulations, has limited in vitro activity against *S. maltophilia* relative to other tetracycline derivatives [670]. The panel does not suggest the use of eravacycline or omadacycline for the treatment of *S. maltophilia* infections.

A general concern with tetracycline derivatives is that they achieve rapid tissue distribution following administration, resulting in limited concentrations in the urine and poor serum concentrations [35]. Therefore, they are not suggested for *S. maltophilia* UTIs. They are only advised as a component of combination therapy for the treatment of *S. maltophilia* bloodstream infections. Nausea and emesis are reported in as many as 20-40% of patients receiving minocycline or tigecycline [595-597].

Question 6.4: What is the role of cefiderocol for the treatment of infections caused by *S. maltophilia*?

Suggested approach: Cefiderocol as a component of combination therapy, at least until clinical improvement is observed, is a preferred therapy for the treatment of *S. maltophilia* infections.

Rationale

Surveillance studies indicate susceptibility of *S. maltophilia* isolates approaches 100%, even against isolates resistant to other commonly prescribed agents [425, 427, 650, 682, 683], with the caveat that investigations were generally conducted before widespread clinical use of the drug. The likelihood of adequate target attainment of cefiderocol is high based on in vitro modeling data, including for pulmonary and bloodstream infections [684]. Neutropenic thigh and lung murine infection models demonstrate potent activity of cefiderocol and indicate that in vivo efficacy against *S. maltophilia* appears to correlate with in vitro efficacy under iron-depleted conditions, using simulated human dosing [603, 685-687].

A clinical trial evaluating the role of cefiderocol for carbapenem-resistant infections included five patients with *S. maltophilia* infections [205, 688]. All five patients were assigned to the cefiderocol arm, precluding comparisons between treatment regimens. Four out of five patients died. If limiting the analysis to the three patients with *S. maltophilia* infections without *A. baumannii* co-infection, two of three patients died. Other clinical data evaluating the role of cefiderocol for the treatment of *S. maltophilia* infections are limited to case reports[689-691]. Despite the limited availability of clinical data, in vitro data and animal models are encouraging for the use of cefiderocol in treating *S. maltophilia* infections. Data are not available to guide the decision to use cefiderocol as a component of combination therapy or as monotherapy. The panel suggests cefiderocol be considered as a component of combination therapy at least until clinical improvement is observed.

Question 6.5: What is the role of fluoroquinolones for the treatment of infections caused by *S. maltophilia*?

Suggested approach: Levofloxacin is suggested only as a component of combination therapy for the treatment of *S. maltophilia* infections. Transitioning to levofloxacin monotherapy for *S. maltophilia* infections is not advised.

Rationale

S. maltophilia isolates frequently harbor Sm*qnr* resistance determinants that interfere with fluoroquinolone binding to gyrase and topoisomerase, leading to increased fluoroquinolone MICs [621, 638]. Fluoroquinolone MICs may increase further as a result of overexpression of multidrug-resistant efflux pumps [655, 692-694]. Baseline susceptibility percentages of *S. maltophilia* to levofloxacin vary from approximately 30% to 80% in surveillance studies [650, 651, 673, 695]. Several studies have shown that *S. maltophilia* isolates that test susceptible to levofloxacin can develop elevated levofloxacin MICs during therapy [661, 664, 666, 696]. CLSI susceptibility criteria exist for levofloxacin against *S. maltophilia*, but not for ciprofloxacin or moxifloxacin [16]. In January 2023, the CLSI elected to include a comment suggesting levofloxacin should be used only as a component of combination therapy for the treatment of *S. maltophilia* infections[16].

Time-kill curves evaluating ciprofloxacin, levofloxacin, and moxifloxacin monotherapy generally indicate that these agents are inadequate at sustained inhibition of *S. maltophilia* growth [671, 697-700], but suggest that levofloxacin and moxifloxacin may have sufficient activity as components of combination therapy [650, 651]. PK/PD modeling data suggest that fluoroquinolone monotherapy may be insufficient to achieve appropriate target attainment for *S. maltophilia* infections, even when administered at high dosages [671]. Levofloxacin and moxifloxacin were both associated with improved survival compared to placebo in a mouse model of hemorrhagic *S. maltophilia* pneumonia [701]. Neutropenic mouse models suggest that levofloxacin may be most effective against *S. maltophilia* isolates with MICs of ≤1 µg/mL [702].

Fluoroquinolone data for the treatment of *S. maltophilia* clinical infections mostly focus on levofloxacin. A meta-analysis including 663 patients from 14 observational studies compared mortality between fluoroquinolones and TMP-SMX, with approximately 50% of patients receiving fluoroquinolones (including, ciprofloxacin [34%] and levofloxacin [57%]) and 50% receiving TMP-SMX [660]. When evaluated separately, there was no difference in mortality between ciprofloxacin or levofloxacin in combination with TMP-SMX. However, when pooling the fluoroquinolones, they appeared to be marginally significant in protecting against mortality compared to TMP-SMX, with mortality reported in 26% versus 33% of patients, respectively. When limiting the analysis to patients with *S. maltophilia* bloodstream infections, where concerns related to distinguishing colonization and infection are less problematic, a benefit with fluoroquinolone use was not evident. An observational study comparing 31 patients receiving levofloxacin and 45 patients receiving TMP-SMX published after the aforementioned meta-analysis found comparable outcomes in both groups[661]. Similar to the meta-analysis, interpretation of the results is challenging since, amongst other limitations, all sites of infection were included without clear definitions distinguishing between colonization and infection. Another observational study compared 46 patients receiving standard-dose tigecycline and 36 patients receiving fluoroquinolones (levofloxacin or moxifloxacin) and found poorer outcomes in the standard-dose tigecycline arm[679]. There are a number of limitations to these studies including selection bias, small sample sizes, heterogeneity in host and microbial data, and the use of additional active agents.

As discussed in **Question 6.2**, an observational study of 1,581 patients with *S. maltophilia* identified in respiratory or blood cultures and treated with TMP-SMX or levofloxacin was undertaken using an administrative database[659]. Although this work suggested that levofloxacin may be protective against mortality in patients with *S. maltophilia* recovered from respiratory cultures and marginally protective against mortality regardless of the culture site, there are significant limitations to this study making its findings challenging to interpret.

Due to suboptimal results with fluoroquinolone monotherapy in in vitro studies, known mechanisms of resistance of *S. maltophilia* to fluoroquinolones, the emergence of resistance

during therapy, and inherent biases in the observational data, the panel suggests levofloxacin only be used as a component of combination therapy, when prescribed for the treatment of *S. maltophilia* infections. Because of the lack of susceptibility criteria for ciprofloxacin and moxifloxacin, the panel suggests preferentially administering levofloxacin amongst the fluoroquinolones. Adverse events related to fluoroquinolone use and the potential for the emergence of resistant *S. maltophilia* isolates during levofloxacin therapy should be considered when prescribing this agent [703].

Question 6.6: What is the role of ceftazidime-avibactam and aztreonam for the treatment of infections caused by *S. maltophilia*?

Suggested approach: The combination of ceftazidime-avibactam and aztreonam is suggested for *S. maltophilia* infections when critical illness is evident or intolerance or inactivity of other agents is observed.

Rationale

The combination of ceftazidime-avibactam and aztreonam can be used to overcome the activity of both the L1 and L2 β-lactamases intrinsic to *S. maltophilia* [621, 704-709]. The L1 metallo-β-lactamase hydrolyzes ceftazidime but not aztreonam. The L2 serine β-lactamase hydrolyzes ceftazidime and aztreonam but is inactivated by avibactam. Therefore, the combination of ceftazidime-avibactam and aztreonam enables aztreonam to bypass inactivation and successfully reach its target PBPs of *S. maltophilia.* Despite limited available clinical data with this combination for the treatment of *S. maltophilia* infections [706, 710, 711], the combination of ceftazidime-avibactam and aztreonam [267, 269] is a reasonable treatment option for moderate to severe infections, such as pneumonia or bloodstream infections in the hematologic malignancy population, as well as in situations where intolerance or resistance to other agents precludes their use. Strategies for administering the combination of ceftazidime-avibactam and aztreonam are reviewed in **Table 1 and Supplemental Material** [267-269]. Patients should be monitored closely for elevations in liver enzymes[270]. Although several groups have described methods used to test susceptibility with this combination of agents[259-266], the CLSI does not currently endorse a specific approach to test in vitro activity with this combination[16].

Question 6.7: What is the role of ceftazidime for the treatment of infections caused by *S. maltophilia*?

Suggested approach: Ceftazidime is not a suggested treatment option for *S. maltophilia* infections due to the presence of β-lactamase genes intrinsic to *S. maltophilia* that are expected to render ceftazidime inactive.

Rationale

The panel does not suggest prescribing ceftazidime for the treatment of *S. maltophilia* infections, as intrinsic L1 and L2 β-lactamases are expected to render it ineffective. Almost 30-40% of *S. maltophilia* isolates test susceptible to ceftazidime using CLSI interpretive criteria; however, due to insufficient data to reevaluate ceftazidime breakpoints, "susceptibility" is likely not reflective of likely clinical success [673, 695]. Ceftazidime MICs against *S. maltophilia* may be inaccurate and non-reproducible using AST methods commonly employed by clinical microbiology laboratories, potentially related to the presence of inactivating β-lactamases [643, 644]. Avibactam (i.e., ceftazidime-avibactam) is not likely to expand the activity of ceftazidime against *S. maltophilia*, in the absence of aztreonam. In vitro models suggest ceftazidime is unable to substantively prevent *S. maltophilia* growth [651]. Comparative effectiveness studies evaluating the role of ceftazidime against *S. maltophilia* infections are virtually non-existent [712]. Local clinical microbiology laboratories and antibiotic stewardship teams are encouraged to convey the likely ineffectiveness of ceftazidime against *S. maltophilia* to clinicians, even when it tests susceptible.

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, AmpC-E, CRE, and DTR-*P. aeruginosa*, CRAB, and *S. maltophilia* will be updated approximately annually and is available at: https://www.idsociety.org/practice-guideline/amr-guidance/.

Notes

Acknowledgments: The authors express their sincere gratitude to the following infectious diseases specialists who provided input on antibiotic dosing suggestions: Julie Ann Justo, Erin K. McCreary, Thomas Lodise, Jason M. Pogue, Marc H. Scheetz, and Ryan K. Shields.

Conflict of Interest Summary: The following list includes 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). IDSA requests panel members to disclose activities and financial relationships/investments related to consultant/advisory roles, promotional speakers bureau, stocks/bonds, honoraria, expert testimony, ownership interest, research grants, organizational benefits, intellectual property, other numeration, activities with other organizations, and relevant financial interest of family members. Readers of this guidance should be mindful of this when the list of disclosures is reviewed. **S.L.A.** serves as a scientific advisor for Shionogi, Basilea Pharmaceutica, and GSK; served as a scientific advisor for Entasis Therapeutics, Merck, Paratek Pharmaceuticals, The Medicines Company, Zavante, Shionogi, Cempra, Theravance, bioMérieux, F2G, and AstraZeneca; received research funding from Melinta Therapeutics and Merck; served as a speaker at a non-branded CME-accredited satellite symposium at the MAD-ID meeting funded by an unrestricted educational grant from Melinta Therapeutics; serves as President-Elect for the Society of Infectious Diseases Pharmacists (SIDP); served as Chair for the SIDP Guidelines Committee and as a faculty member for the Infectious Diseases Board Certification Preparatory Course-American Society of Health-System Pharmacists; serves as

Associate Editor for Open Forum Infectious Diseases for Infectious Diseases of America. **R.A.B**. receives research funding from Shionogi, Venatorx Pharmaceuticals, Merck, Entasis Therapeutics, Wockhardt, NIH, and VA; received research funding from Allecra Therapeutics, AstraZeneca, Harrington Family Foundation, Tetraphase Pharmaceuticals, Steris, and Melinta Therapeutics; receives a research grant from NIH regarding a patent held by Case Western Reserve University; served scientific expert testimony on behalf of Case Western Reserve University; received an honoraria from Unilab; served on the editorial board for Antimicrobial Agents and Chemotherapy; served as Treasurer for VA Society for Prevention ID; and serves as an editorial board member for mBio. **A.J.M.** serves as a scientific advisor for Merck, Qpex Biopharma, Venatorx Pharmaceuticals, Melinta Therapeutics, Cephied, DayZeroDiagnositics, and OpGen; served as a scientific advisor for Shionogi, Accelerate Diagnostics, Rempex Pharmaceuticals, and Antimicrobial Resistance Services; receives research funding from CDC, NIH, and FDA; receives an organizational benefit from the University of Virginia Strategic Investment Fund; serves as Vice Chair of the Antimicrobial Susceptibility Testing Committee for Clinical Laboratory and Standards Institute; and serves as an elected member to the Council on Microbial Sciences for American Society of Microbiology. **D.v.D.** serves as a scientific advisor for Roche; served as a scientific advisor for Utility, Shionogi, Allergan, Achaogen, Qpex Biopharma, Union Therapeutics, and Entasis Therapeutics; served as an advisory board member for Merck, T2 Biosystems, and Karius; received honoraria from Shionogi and Pfizer; receives research grants from NIH and Merck; received research funding from Shionogi; served as a non-promotional speaker for Entasis Therapeutics and Pfizer; serves as an ongoing speaker for educational talks with Clinical Care Options; serves as a "selective pressure" member of the ECCMID Program Committee, ESCMID; and serves as editor in chief for JAC Antimicrobial Resistance. **C.J.C.** serves as a scientific advisor for Merck, Qpex Biopharma, Astellas Pharma, Cidara Therapeutics, Scynexsis, and Shionogi; serves as a scientific consultant for Needham & Associates; serves as a speaker for T2 Biosystems; receives research funding from NIH, VA, Astellas Pharma, and Merck. No disclosures reported: **P.D.T**.

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.

Table 2. 2023 Clinical and Laboratory Standards Institute Susceptibility Interpretive Criteria for Select Gram-Negative Organisms and Select Antibiotic Combinations as Suggested in the IDSA AMR Guidance Document[1]

Antibiotic	Enterobacterales (µg/mL)	*Pseudomonas aeruginosa* (µg/mL)	*Acinetobacter baumannii* (µg/mL)	*Stenotrophomonas maltophilia* (µg/mL)
Amikacin	≤4	≤16[2]	--	--
Ampicillin-sulbactam	--	--	≤8/4	--
Aztreonam	≤4	≤8	--	--
Cefepime	≤2[3]	≤8	--	--
Cefiderocol	≤4	≤4	≤4	≤1
Ceftazidime	≤4	≤8	--	--
Ceftazidime-avibactam	≤8/4	≤8/4	--	--
Ceftolozane-tazobactam	≤2/4	≤4/4	--	--
Ciprofloxacin	≤0.25	≤0.5	--	--
Colistin or Polymyxin B	--[4]	--[4]	--[4]	--
Doxycycline	≤4	--	--	--
Ertapenem	≤0.5	--	--	--
Fosfomycin	≤64[5]	--	--	--
Gentamicin	≤2	--	--	--
Imipenem	≤1	≤2	--	--
Imipenem-relebactam	≤1/4	≤2/4	--	--
Levofloxacin	≤0.5	≤1	--	≤2[9]
Meropenem	≤1	≤2	--	--
Meropenem-vaborbactam	≤4/8	--	--	--
Minocycline	≤4	--	≤4	≤4
Nitrofurantoin	≤32	--	--	--
Piperacillin-tazobactam	≤8/4[6]	≤16/4	--	--
Plazomicin	≤2	--	--	--
Tigecycline	--[7]	--	--[8]	--[8]
Trimethoprim-sulfamethoxazole	≤2/38	--	--	≤2/38
Tobramycin	≤2	≤1	--	--

[1] Only includes antibiotic and organism combinations suggested in the IDSA Guidance document. For full details of antibiotic susceptibility testing interpretations refer to: Clinical and Laboratory Standards Institute. 2023. M100: Performance Standards for Antimicrobial Susceptibility Testing. 33 ed. Wayne, PA. CLSI M100 document is updated annually; susceptibility criteria subject to changes in 2024.

[2] Susceptibility criteria only available for infections originating from the urinary tract.

[3] Cefepime MICs of 4-8 µg/mL are susceptible dose-dependent.

[4] No susceptible category for colistin or polymyxin B; MICs ≤2 µg/mL considered intermediate.

[5] Applies to *Escherichia coli* urinary tract isolates only.

[6] Piperacillin-tazobactam MICs of 16 µg/mL are considered susceptible dose-dependent.

[7] No CLSI breakpoint. FDA defines susceptibility as MICs ≤2 µg/mL.

[8] Neither CLSI nor FDA susceptibility criteria are available.

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