

# Infectious Diseases Society of America Guidance on the Treatment of AmpC $\beta$ -Lactamase–Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

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The Infectious Diseases Society of America (IDSA) is committed to providing up-to-date guidance on the treatment of antimicrobial-resistant infections. A previous guidance document focused on infections caused by extended-spectrum  $\beta$ -lactamase–producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). Here, guidance is provided for treating AmpC  $\beta$ -lactamase–producing Enterobacterales (AmpC-E), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Stenotrophomonas maltophilia* infections. A panel of 6 infectious diseases specialists with expertise in managing antimicrobial-resistant infections formulated questions about the treatment of AmpC-E, CRAB, and *S. maltophilia* infections. Answers are presented as suggested approaches and corresponding rationales. In contrast to guidance in the previous document, published data on the optimal treatment of AmpC-E, CRAB, and *S. maltophilia* infections are limited. As such, guidance in this document is provided as “suggested approaches” based on clinical experience, expert opinion, and a review of the available literature. 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. Preferred and alternative treatment suggestions are provided, assuming the causative organism has been identified and antibiotic susceptibility results are known. Approaches to empiric treatment, duration of therapy, and other management considerations are also discussed briefly. Suggestions apply for both adult and pediatric populations. 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 17 September 2021 and will be updated annually. The most current version of this document, including date of publication, is available at [www.idsociety.org/practice-guideline/amr-guidance-2.0/](http://www.idsociety.org/practice-guideline/amr-guidance-2.0/).

**Keywords.** AmpC; *Enterobacter cloacae*; *Stenotrophomonas maltophilia*; CRAB; non-fermenter.

The rise in antimicrobial resistance (AMR) continues to be a global crisis. Collectively, antimicrobial-resistant pathogens caused more than 2.8 million infections and over 35 000 deaths annually from 2012 through 2017, according to the 2019 Centers for Disease Control and Prevention (CDC) Antibiotic Resistance Threats in the United States Report [1]. The Infectious Diseases Society of America (IDSA) identified the development and dissemination of clinical practice guidelines and other guidance products for clinicians as a top initiative in its 2019 Strategic Plan [2]. IDSA acknowledged that the ability to address rapidly

evolving topics such as AMR was limited by prolonged timelines needed to generate new or updated clinical practice guidelines, which are based on systematic literature reviews and use rigorous GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria. 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 difficult-to-manage infections where data continue to evolve. Guidance documents will be prepared by a small team of experts, who will answer questions about treatment based on a comprehensive (but not necessarily systematic) review of the literature, clinical experience, and expert opinion. Documents will not include formal grading of evidence and will be updated at least annually online. The first guidance document addressed the treatment of infections by extended-spectrum  $\beta$ -lactamase–producing Enterobacterales

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(ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*) [3].

In the present document, guidance is provided on the treatment of infections caused by AmpC  $\beta$ -lactamase-producing Enterobacterales (AmpC-E), carbapenem-resistant *Acinetobacter baumannii* species (CRAB), and *Stenotrophomonas maltophilia*. Each pathogen causes a wide range of serious infections that are encountered in US hospitals of all sizes, and that carry with them significant morbidity and mortality. These organisms pose different management challenges for clinicians. Several well-studied antibiotics are available for treating AmpC-E infections, but there is often confusion about which species are at greatest risk for clinically significant AmpC production and the optimal treatment. In contrast, there are few therapeutic options and limited clinical data for the treatment of CRAB and *S. maltophilia* infections. Moreover, distinguishing colonization from invasive infections by CRAB and *S. maltophilia* can be difficult.

Guidance is presented in the form of answers to a series of clinical questions for each pathogen. Although brief descriptions of notable clinical trials, resistance mechanisms, and susceptibility testing methods are included, the document does not provide a comprehensive review of these topics. Due to differences in the molecular epidemiology of resistance and availability of specific anti-infectives internationally, treatment recommendations are geared toward antimicrobial-resistant infections in the United States. The content of this document is current as of 17 September 2021; updates will be provided periodically. The most current version of this guidance document is available at [www.idsociety.org/practice-guideline/amr-guidance-2.0/](http://www.idsociety.org/practice-guideline/amr-guidance-2.0/).

## METHODOLOGY

IDSA convened a panel of 6 actively practicing infectious diseases specialists with clinical and research expertise in the treatment of antimicrobial-resistant bacterial infections. Through a series of web-based meetings, the panel developed commonly encountered treatment questions and corresponding answers for each pathogen group. Because robust data on the treatment of AmpC-E, CRAB, and *S. maltophilia* infections are relatively scarce and somewhat conflicting, the panel elected to provide informed suggestions in place of recommendations. This guidance document applies to both adult and pediatric populations. Suggested antibiotic dosing for adults with antimicrobial-resistant infections, assuming normal renal and hepatic function, is provided in Table 1.

## GENERAL MANAGEMENT RECOMMENDATIONS

Treatment recommendations in this guidance document assume that the causative organism has been identified and that in vitro activity of antibiotics is demonstrated. Assuming 2

antibiotics are equally effective, safety, cost, convenience, and local formulary availability are important considerations in selecting a specific agent. The panel recommends that infectious diseases specialists and physician or pharmacist members of the local antibiotic stewardship program are involved in the management of patients with infections caused by antimicrobial-resistant organisms.

### Empiric Therapy

Empiric treatment decisions should be guided by the most likely pathogens, severity of illness of the patient, the likely source of the infection, and any additional patient specific factors (e.g., severe penicillin allergy, chronic kidney disease). When determining empiric treatment for a given patient, clinicians should also consider the following: (1) previous organisms identified from the patient and associated antibiotic susceptibility data in the last 6 months, (2) antibiotic exposures within the past 30 days, and (3) local susceptibility patterns for the most likely pathogens. Empiric decisions should be refined based on the identity and susceptibility profile of the pathogen, as well as based on the identification of any prominent  $\beta$ -lactamase genes.

For 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 [4]. 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 [5-9].

### Duration of Therapy and Transitioning to Oral Therapy

Recommendations on durations of therapy are not provided, but clinicians are advised that prolonged treatment courses are not necessary against infections caused by antimicrobial-resistant pathogens per se, compared with infections caused by the same bacterial species with a more susceptible phenotype. After antibiotic susceptibility results are available, it may become apparent that inactive antibiotic therapy was initiated empirically. This may impact the duration of therapy. For example, cystitis is typically a mild infection [10]. If an antibiotic not active against the causative organism was administered empirically for cystitis, but clinical improvement nonetheless occurred, the panelists agree that it is generally not necessary to repeat a urine culture, change the antibiotic regimen, or extend the planned treatment course. However, for all other infections, if antibiotic susceptibility data indicate a potentially inactive agent was initiated empirically, a change to an effective regimen for a full treatment course (dated from the start of active therapy) is recommended. Additionally, important host

**Table 1. Suggested Dosing of Antibiotics for the Treatment of Infections Caused by Antimicrobial-Resistant Organisms<sup>a</sup>**

Agent	Adult Dosage (Assuming Normal Renal and Liver Function)	Target Organisms <sup>b,c</sup>
Amikacin	Cystitis: 15 mg/kg/dose <sup>d</sup> IV once All other infections: 20 mg/kg/dose <sup>d</sup> IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation	ESBLE, AmpC-E, CRE, DTR- <i>Pseudomonas aeruginosa</i>
Ampicillin-sulbactam	9 g IV q8h over 4 hours or 27g IV q24h as a continuous infusion For mild infections caused by CRAB isolates susceptible to ampicillin-sulbactam, it is reasonable to administer 3g IV q4h—particularly if intolerance or toxicities precludes the use of higher dosages.	CRAB
Cefepime	Cystitis: 1 g IV q8h All other infections: 2 g IV q8h, infused over 3 hours	AmpC-E
Cefiderocol	2 g IV q8h, infused over 3 hours	CRE, DTR- <i>P. aeruginosa</i> , CRAB, <i>Stenotrophomonas maltophilia</i>
Ceftazidime-avibactam	2.5 g IV q8h, infused over 3 hours	CRE, DTR- <i>P. aeruginosa</i>
Ceftazidime-avibactam and aztreonam	Ceftazidime-avibactam: 2.5 g IV q8h, infused over 3 hours Plus Aztreonam: 2 g IV q8h, infused over 3 hours, administered at the same time as ceftazidime-avibactam, if possible	Metallo-β-lactamase-producing CRE, <i>S. maltophilia</i>
Ceftolozane-tazobactam	Cystitis: 1.5 g IV q8h, infused over 1 hour All other infections: 3 g IV q8h, infused over 3 hours	DTR- <i>P. aeruginosa</i>
Ciprofloxacin	ESBLE or AmpC infections: 400 mg IV q8h–q12h or 500–750 mg PO q12h	ESBLE, AmpC-E
Colistin	Refer to international consensus guidelines on polymyxins <sup>e</sup>	CRE cystitis, DTR- <i>P. aeruginosa</i> cystitis, CRAB cystitis
Eravacycline	1 mg/kg/dose IV q12h	CRE, CRAB
Ertapenem	1 g IV q24h, infused over 30 minutes	ESBLE, AmpC-E
Fosfomycin	Cystitis: 3 g PO × 1 dose	ESBLE, <i>coli</i> cystitis
Gentamicin	Cystitis: 5 mg/kg/dose <sup>d</sup> IV once All other infections: 7 mg/kg/dose <sup>d</sup> IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation	ESBLE, AmpC-E, CRE, DTR- <i>P. aeruginosa</i>
Imipenem-cilastatin	Cystitis (standard infusion): 500 mg IV q6h, infused over 30 minutes All other ESBLE or AmpC-E infections: 500 mg IV q6h, infused over 30 minutes All other CRE and CRAB infections: 500 mg IV q6h, infused over 3 hours	ESBLE, AmpC-E, CRE, CRAB
Imipenem-cilastatin-relebactam	1.25 g IV q6h, infused over 30 minutes	CRE, DTR- <i>P. aeruginosa</i>
Levofloxacin	750 mg IV/PO q24h	ESBLE, AmpC-E, <i>S. maltophilia</i>
Meropenem	Cystitis (standard infusion): 1 g IV q8h infused over 30 minutes All other ESBLE or AmpC-E infections: 1–2 g IV q8h, infused over 30 minutes All other CRE and CRAB infections: 2 g IV q8h, infused over 3 hours	ESBLE, AmpC-E, CRE, CRAB
Meropenem-vaborbactam	4 g IV q8h, infused over 3 hours	CRE
Minocycline	200 mg IV/PO q12h	CRAB, <i>S. maltophilia</i>
Nitrofurantoin	Cystitis: macrocrystal/monohydrate (Macrobid®) 100 mg PO q12h Cystitis: Oral suspension: 50 mg PO q6h	ESBLE cystitis, AmpC-E cystitis
Plazomicin	Cystitis: 15 mg/kg <sup>d</sup> IV × 1 dose All other infections: 15 mg/kg <sup>d</sup> IV × 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation	ESBLE, AmpC-E, CRE, DTR- <i>P. aeruginosa</i>
Polymyxin B	Refer to international consensus guidelines on polymyxins <sup>e</sup>	DTR- <i>P. aeruginosa</i> , CRAB
Tigecycline	200 mg IV × 1 dose, then 100 mg IV q12h	CRE, CRAB, <i>S. maltophilia</i>
Tobramycin	Cystitis: 5 mg/kg/dose <sup>d</sup> IV × 1 dose All other infections: 7 mg/kg/dose <sup>d</sup> IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation	ESBLE, AmpC-E, CRE, DTR- <i>P. aeruginosa</i>
Trimethoprim-sulfamethoxazole	Cystitis: 160 mg (trimethoprim component) IV/PO q12h Other infections: 8–12 mg/kg/day (trimethoprim component) IV/PO divided q8–12h (consider maximum dose of 960 mg trimethoprim component per day)	ESBLE, AmpC-E, <i>S. maltophilia</i>

Abbreviations: AmpC-E, AmpC-producing Enterobacteriales; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriales; DTR-*P. aeruginosa*, *Pseudomonas aeruginosa* with difficult-to-treat resistance; ESBLE, extended-spectrum β-lactamase-producing Enterobacteriales; IV, intravenous; MIC, minimum inhibitory concentration; PO, per os (by mouth); q4h, q6h, q8h, q12h, q24h, every 4, 6, 8, 12, and 24 hours, respectively.

<sup>d</sup>Dosing suggested for several agents differs from US Food and Drug Administration–recommended dosing.

<sup>b</sup>Target organisms limited to the following organisms and generally only after susceptibility has been demonstrated: ESBLE, AmpC-E, CRE, DTR-*P. aeruginosa*, CRAB, and *Stenotrophomonas maltophilia*.

<sup>c</sup>For additional guidance on the treatment of ESBLE, CRE, and DTR-*P. aeruginosa*, refer to: <https://www.idsociety.org/practice-guideline/amr-guidance/>.

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

<sup>e</sup>Reference [245].

factors related to immune status, ability to attain source control, and general response to therapy should be considered when determining treatment durations for antimicrobial-resistant infections, as with the treatment of any bacterial infection. Finally, whenever possible, oral step-down therapy should be considered, particularly if the following criteria are met: (1) susceptibility to an appropriate oral agent is demonstrated, (2) the patient is hemodynamically stable, (3) reasonable source control measures have occurred, and (4) concerns about insufficient intestinal absorption are not present [11]. Fulfilling these criteria can be admittedly challenging with CRAB and *S. maltophilia* infections.

## AMPC B-LACTAMASE-PRODUCING ENTEROBACTEREALES

AmpC  $\beta$ -lactamases are class C serine  $\beta$ -lactamase enzymes that can be produced by a number of Enterobacterales and glucose non-fermenting gram-negative organisms. AmpC production in Enterobacterales generally occurs by 1 of 3 mechanisms: inducible chromosomal resistance, stable chromosomal de-repression, or via plasmid-mediated *ampC* genes [12, 13]. 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 [14, 15]. 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 minimum inhibitory concentrations (MICs) and result in ceftriaxone and ceftazidime resistance. In this scenario, an Enterobacterales isolate that initially tests as susceptible to ceftriaxone may exhibit nonsusceptibility to this agent after treatment 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 or ceftazidime exposure [16].

For the other 2 mechanisms (ie, stable chromosomal de-repression or plasmid-mediated *ampC* genes), AmpC production is generally constitutive rather than induced. Isolates with constitutive *ampC* expression are expected to test nonsusceptible to ceftriaxone and 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 2 mechanisms, some Enterobacterales isolates (eg, certain *Escherichia coli* and *Shigella* spp.) contain mutations in promoters or attenuators of *ampC* or other regulatory genes, stably de-repressing gene expression [17]. For the second mechanism, constitutive expression of plasmid-borne *ampC* genes (eg, *bla*<sub>CMY</sub>, *bla*<sub>FOX</sub>, *bla*<sub>DHA</sub>, *bla*<sub>ACT</sub>, *bla*<sub>MIR</sub>) is most commonly observed in organisms such as *E. coli*, *Klebsiella pneumoniae*, and *Salmonella* spp. [18].

### Question 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*, *Klebsiella aerogenes*, and *Citrobacter freundii* are 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  $\beta$ -lactam agents (eg, ceftriaxone or ceftazidime) that, on subsequent isolation (and after  $\beta$ -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” or “SPICE” obscure the wide range of *ampC* induction potential among gram-negative organisms and ignore variance within bacterial genera [12, 13]. For example, *C. freundii* harbors a chromosomal *ampC*, whereas *Citrobacter koseri* does not [19–21]. Thus, with current acronyms, there is frequently 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 *Proteus vulgaris* and *Proteus penneri*, which generally do not contain chromosomal *ampC* genes. The terminology “indole-positive *Proteus* species” previously included *Proteus rettgeri* and *Proteus morgani* (since renamed *Providencia rettgeri* and *Morganella morgani*, respectively) [22], making the inclusion of “indole-positive *Proteus* species” 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*, *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 [16, 23–27]. These clinical observations mirror in vitro mutation rate analyses, which also suggest that these organisms are likely to overexpress *ampC* [28]. Therefore, when *E. cloacae*, *K. aerogenes*, or *C. freundii* are recovered in clinical cultures (other than those associated with uncomplicated cystitis), the panel suggests avoiding treatment with ceftriaxone or ceftazidime, even if an isolate initially tests susceptible to these agents (Question 2).

In contrast, other organisms historically presumed to be at risk for the development of clinically significant *ampC* expression, such as *Serratia marcescens*, *M. morgani*, and *Providencia*

spp., are unlikely to overexpress *ampC* based on both in vitro analysis [28] and clinical reports [6, 23]. 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 susceptibility testing results.

A number of less commonly encountered pathogens (eg, *Hafnia alvei*, *Citrobacter youngae*, *Yersinia enterocolitica*) that carry inducible chromosomal *ampC* genes have not undergone significant investigation [28–31]. As such, descriptions of their potential for clinically significant AmpC production are very limited. It is reasonable to use antibiotic susceptibility testing results to guide treatment decisions if these organisms are recovered in clinical cultures (eg, 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 (eg, endocarditis, ventriculitis), 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: 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  $\beta$ -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**

$\beta$ -Lactam antibiotics fall within a spectrum of potential for inducing *ampC*. Aminopenicillins (ie, amoxicillin, ampicillin), narrow-spectrum (ie, first-generation) cephalosporins, and cephamycins are potent AmpC inducers [32, 33]. However, organisms at moderate to high risk for clinically significant *ampC* induction (eg, *E. cloacae*) hydrolyze these antibiotics even at basal *ampC* expression levels. Therefore, such AmpC-E isolates will generally test as nonsusceptible to these drugs, averting treatment dilemmas. Imipenem is also a potent *ampC* inducer, but it generally remains resistant to AmpC-E hydrolysis because of the formation of stable acyl enzyme complexes [32]. The induction potential of ertapenem and meropenem has not been formally investigated but, similar to imipenem, they are generally able to resist AmpC hydrolysis [34]. Piperacillin, ceftriaxone, ceftazidime, and aztreonam are relatively weak AmpC inducers [33]. Available evidence indicates that, despite

the limited ability of ceftriaxone and ceftazidime to induce AmpC production, 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 inducible AmpC production [12, 13]. Similarly, piperacillin, even with the addition of tazobactam, has the potential to be hydrolyzed in settings of sufficient AmpC production, translating to an increase in its MICs [35–38].

Cefepime has the advantage of both being a weak inducer of AmpC production and of withstanding hydrolysis by AmpC  $\beta$ -lactamases because of the formation of stable acyl enzyme complexes [39, 40]. Therefore, it is generally an effective agent for the treatment of AmpC-E infections [41]. Fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole (TMP-SMX), tetracycline, and other non- $\beta$ -lactam antibiotics do not induce *ampC* and are also not substrates for AmpC hydrolysis.

**Question 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 (ie, *E. cloacae*, *K. aerogenes*, and *C. freundii*) when the cefepime MIC is 2  $\mu\text{g}/\text{mL}$  or less. A carbapenem is recommended when the cefepime MIC is 4  $\mu\text{g}/\text{mL}$  or greater, assuming carbapenem susceptibility is demonstrated, as ESBL co-production may be present.

**Rationale**

Cefepime is an oxyminocephalosporin that is relatively stable against AmpC enzymes and that also has low *ampC* induction potential [39, 40, 42, 43]. However, several case reports of therapeutic failure of cefepime against infections caused by AmpC-E have led to hesitancy in prescribing this agent [44–46]. Understanding the contribution of AmpC production to cefepime clinical failure in these case reports is challenging as the drug was generally dosed every 12 hours, co-production of ESBL enzymes was rarely investigated, and the presence of outer membrane porin mutations that were identified in some of these reports may have contributed to cefepime treatment failure [43, 47]. Randomized controlled trials (RCTs) comparing clinical outcomes of patients with infections caused by AmpC-E treated with cefepime versus carbapenem therapy are not available. However, several observational studies suggest that the use of cefepime leads to similar clinical outcomes as carbapenem therapy [27, 48, 49]. Furthermore, a meta-analysis including 7 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 exist, ill-appearing patients were more likely to receive

carbapenem therapy, and the risk of AmpC production in these organisms varied by species [41]. 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 endorses cefepime as a preferred treatment option for *E. cloacae*, *K. aerogenes*, and *C. freundii* infections with cefepime MICs of 2 µg/mL or less (Table 1).

Although cefepime may be effective for the treatment of AmpC-E infections, it remains suboptimal against infections caused by ESBL-E [3, 50]. Enterobacterales isolates exhibiting cefepime MICs of 4–8 µg/mL have a high likelihood of producing ESBLs; in 1 study, 89% of *E. cloacae* isolates with cefepime MICs of 4–8 µg/mL were ESBL-producing [51]. 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 6 patients who received cefepime for infections caused by non-ESBL-producing cefepime isolates with MICs of 4–8 µg/mL died within 30 days [51]. In light of these data, we suggest preferentially administering carbapenem therapy (ie, ertapenem, meropenem, imipenem-cilastatin) for infections caused by *E. cloacae*, *K. aerogenes*, and *C. freundii* with cefepime MICs of 4–8 µg/mL (ie, the Clinical and Laboratory Standards Institute [CLSI] susceptible dose-dependent range) [52].

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

**Rationale**

Clinical reports differ on how frequently resistance to ceftriaxone emerges during 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 criteria for AmpC detection in clinical isolates, making their accurate identification difficult. Second, these organisms may display ceftriaxone nonsusceptibility for other reasons (eg, ESBL production); however, such mechanisms are rarely investigated in clinical studies for organisms other than *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*. Third, studies often report combined estimates for organisms at low risk for significant AmpC production (eg, *S. marcescens*, *M. morgannii*) with those posing a higher risk, obscuring our understanding

of how frequently resistance to ceftriaxone emerges for organisms truly at high risk for AmpC production [53]. Fourth, studies that evaluate the proportion of isolates exhibiting ceftriaxone nonsusceptibility 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 (ie, ceftriaxone MICs ≤8 µg/mL), making translation of prevalence estimates to current CLSI ceftriaxone susceptibility breakpoints of ≤1 µg/mL challenging [52, 53]. Finally, there is significant heterogeneity in sources of infections, severity of illness, pre-existing medical conditions, and ceftriaxone dosing and duration across studies, which complicates interpretation of clinical data.

These limitations notwithstanding, available data suggest that the emergence of resistance after ceftriaxone exposure occurs in approximately 8–40% of infections caused by *E. cloacae*, *K. aerogenes*, or *C. freundii* [16, 23–27]. 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. Randomized controlled trials have not compared the clinical outcomes of patients with presumed AmpC-E infections treated with ceftriaxone compared with alternate agents (ie, cefepime). Observational studies comparing clinical outcomes of patients with infections caused by *E. cloacae*, *K. aerogenes*, and *C. freundii* treated with ceftriaxone compared with other β-lactams are limited [24, 54, 55]. 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. [54]. 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, all of these studies had several of the limitations outlined above.

Nonetheless, since available data indicate a significant risk for the emergence of resistance when ceftriaxone is prescribed for infections caused by organisms at moderate to high risk of AmpC production (ie, infections caused by *E. cloacae*, *K. aerogenes*, *C. freundii*), the panel suggests generally avoiding ceftriaxone 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. Although ceftazidime is less commonly used for the treatment of Enterobacterales infections compared with ceftriaxone, ceftazidime should similarly be avoided for the treatment of infections caused by organisms at moderate to high risk of significant AmpC production, with the exception of uncomplicated cystitis. Preferred treatment options for AmpC-E cystitis are described in Question 7.

**Question 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 inhibiting AmpC hydrolysis than newer  $\beta$ -lactamase inhibitors, such as avibactam, relebactam, and vaborbactam [35, 37, 38, 56, 57]. 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 8 observational studies and did not identify a difference in mortality between patients treated with piperacillin-tazobactam and carbapenems for the treatment of bacteremia by *Enterobacter* spp., *Citrobacter* spp., or *Serratia* spp. [53]. However, significant heterogeneity across studies and confounding by indication likely existed (ie, ill-appearing patients were more likely to be prescribed carbapenems). In 2 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] vs 7% [3/41 patients] [58] and 45% [10/22 patients] vs 11% [5/45 patients], respectively) [55].

A pilot unblinded clinical trial compared the outcomes of 72 patients with bloodstream infections caused by *Enterobacter* spp., *K. aerogenes*, *C. freundii*, *M. morgani*, *Providencia* spp., or *S. marcescens* randomized to piperacillin-tazobactam (4.5 g every 6 hours as a standard infusion) or meropenem (1 g every 8 hours as a standard infusion) [59]. 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% vs 6%,  $P = .13$ ), clinical failure (21% vs 12%,  $P = .29$ ), microbiological failure (13% vs 0,  $P = .03$ ), and microbiological relapse (0% vs 9%,  $P = .06$ ) for the piperacillin-tazobactam and meropenem arms, respectively. The findings of this trial are challenging to interpret and a larger RCT 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 inhibit AmpC hydrolysis in vitro [35, 37, 38, 56] and at least 2 observational studies identifying increased mortality in patients prescribed piperacillin-tazobactam [55, 58], 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 6: What Is the Role of Newer  $\beta$ -Lactam and  $\beta$ -Lactam- $\beta$ -Lactamase Inhibitor Combinations 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**

Despite the increased potency of newer  $\beta$ -lactams (ie, cefiderocol) and  $\beta$ -lactam- $\beta$ -lactamase inhibitor combination agents (ie, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and meropenem-vaborbactam) against AmpC-E infections compared with piperacillin-tazobactam, the panel suggests that these agents be preferentially reserved for treating infections caused by organisms exhibiting carbapenem resistance.

**Rationale**

Tazobactam is less effective at inhibiting AmpC hydrolysis compared with newer  $\beta$ -lactamase inhibitors, such as avibactam, relebactam, and vaborbactam [35, 37, 38, 56, 57]. Surveillance studies indicate that ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam exhibit excellent in vitro activity against AmpC-E [60–62]. Available clinical outcomes studies have also reinforced in vitro data demonstrating the effectiveness of these newer  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations against Enterobacterales at moderate to high risk for clinically significant AmpC production [63–65].

Ceftolozane was developed to be more resistant to hydrolysis than earlier cephalosporins against *Pseudomonas*-derived AmpC cephalosporinases, but much less is known about its activity against AmpC-E. While some in vitro data suggest ceftolozane-tazobactam has reasonable activity against AmpC-E [66], in at least 1 investigation the agent was active against only 19% of *E. cloacae* isolates [67]. Clinical outcomes data for ceftolozane-tazobactam treatment of AmpC-E infections are limited; an RCT evaluating this question is underway [68]. In light of the concerns described for tazobactam inhibition in **Question 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.

Cefiderocol demonstrates in vitro activity against AmpC-E [69, 70] 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 [71, 72]. Similar observations have been made with ceftazidime-avibactam [71, 72]. Although ceftazidime-avibactam, imipenem-cilastatin-relebactam, meropenem-vaborbactam, 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 these agents exists.

**Question 7: What Is the Role of Non- $\beta$ -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**

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, either intravenously or as oral step-down therapy, as dictated by the clinical status, likely source of infection, and ability to consume and absorb oral antibiotics, after antibiotic susceptibility is demonstrated. Nitrofurantoin, TMP-SMX, or a single intravenous dose of an aminoglycoside can be considered for uncomplicated AmpC-E cystitis.

**Rationale**

The role of TMP-SMX or fluoroquinolones for the treatment of AmpC-E non-urinary tract infections has not been formally evaluated in clinical trials or robust observational studies. However, neither TMP-SMX nor fluoroquinolones are a substrate for AmpC hydrolysis. Oral step-down therapy with TMP-SMX or fluoroquinolones has been shown to be a reasonable treatment consideration for Enterobacterales bloodstream infections, including those caused by antimicrobial-resistant isolates, after appropriate clinical milestones are achieved [73, 74]. 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 [75–77]. Amoxicillin-clavulanate and doxycycline achieve unreliable serum concentrations [78].

Preferred treatment options for AmpC-E uncomplicated cystitis include nitrofurantoin [77], TMP-SMX [79, 80], or a single intravenous dose of an aminoglycoside [81]. Aminoglycosides are nearly exclusively eliminated by the renal route in their active form. A single intravenous dose is generally effective for uncomplicated cystitis, with minimal toxicity, but robust clinical outcomes data are limited [81]. The panel suggests limiting oral fosfomycin exclusively for the treatment of *E. coli* cystitis as the *fosA* gene, intrinsic to several other gram-negative organisms, including organisms at moderate to high risk of AmpC production, can hydrolyze the drug and may lead to clinical failure [82, 83].

**CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII**

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections pose significant challenges in healthcare settings [6, 8]. 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 [84].

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 (eg, 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 carbapenemases such as OXA-24/40-like carbapenemases and OXA-23-like carbapenemases mediates resistance to carbapenems [84, 85]. CRAB isolates may also produce metallo- $\beta$ -lactamases and additional serine carbapenemases, further limiting the utility of carbapenem agents. Sulbactam resistance is not completely understood but appears to be driven primarily via mutations targeting penicillin-binding proteins (PBPs);  $\beta$ -lactamase production may also contribute [86–88]. Aminoglycoside-modifying enzymes or 16S rRNA methyltransferases generally preclude aminoglycosides as treatment options for CRAB, including plazomicin [89–91]. Mutations in the chromosomally encoded quinolone resistance-determining regions upregulate efflux pumps and generally mediate resistance to fluoroquinolones [90].

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 remain incomplete.

**Question 1: What Is the General Approach for the Treatment of Infections Caused by CRAB?**

**Suggested Approach**

A single active agent may be sufficient for mild infections caused by CRAB. Of available options, the panel suggests ampicillin-sulbactam as a preferred agent. Combination therapy with at least 2 agents, with in vitro activity whenever possible, is suggested for the treatment of moderate to severe CRAB infections given the limited clinical data supporting the effectiveness of any single antibiotic agent.



### **Rationale**

A single active agent may be effective against mild infections caused by CRAB. Defining the severity of a CRAB infections is not always straightforward. Mild infections may include infections of the urinary tract, skin and soft tissue, and tracheitis, with appropriate clinical changes to indicate infection rather than colonization, but without evidence of hemodynamic instability. Of potential treatment options, the panel suggests ampicillin-sulbactam as the preferred agent, after susceptibility is demonstrated (Table 1). Sulbactam's unique activity against *A. baumannii* isolates has been observed through in vitro studies [92–94], animal models [95], and clinical outcomes data [96–100], as described in Question 3. Insufficient data exist to determine if standard-dose ampicillin-sulbactam and high-dose ampicillin-sulbactam have equivalent efficacy for mild CRAB infections caused by isolates susceptible to ampicillin-sulbactam. The panel favors high-dose ampicillin-sulbactam, however, acknowledging that standard dosing may also be reasonable for patients with mild infections caused by CRAB isolates susceptible to ampicillin-sulbactam, particularly if intolerance or toxicities preclude the use of higher ampicillin-sulbactam dosages (Table 1). Alternative treatment options for mild CRAB infections include minocycline, tigecycline, polymyxin B (colistin for cystitis), or cefiderocol as described in Questions 4–6. When nonsusceptibility to ampicillin-sulbactam is demonstrated, high-dose ampicillin-sulbactam may still remain an effective treatment option [97, 101, 102]. The panel suggests the addition of a second active agent if administering ampicillin-sulbactam to treat mild CRAB infections not susceptible to ampicillin-sulbactam.

Combination therapy with at least 2 agents, ideally with in vitro activity, is suggested for the treatment of moderate to severe CRAB infections, at least until an appropriate clinical response is observed, given the limited clinical data supporting the effectiveness of any single antibiotic agent. This recommendation is made despite the fact that only 1 of 7 clinical trials found improved clinical outcomes with the use of combination antibiotic therapy for CRAB infections [96, 103–108] (Question 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 [96].

High-dose ampicillin-sulbactam is suggested as a component of combination therapy (Table 1). Even if the CRAB isolate is not susceptible to ampicillin-sulbactam, the panel believes it may still be reasonable to consider high-dose ampicillin-sulbactam as a component of combination therapy for moderate to severe CRAB infections (Question 3). Because of the increased risk of toxicities with multiple  $\beta$ -lactam agents, if high-dose ampicillin-sulbactam is administered, preferred additional agents include minocycline, tigecycline, or polymyxin B.

Fosfomycin and rifampin are not suggested as components of combination therapy [105, 107, 108] (Question 2, Question 8).

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 [109–111], concerns regarding unequal distribution in infected lungs, and the potential for respiratory complications such as bronchoconstriction [112–115] (Question 9).

### **Question 2: What Is the Role of Combination Antibiotic Therapy for the Treatment of Infections Caused by CRAB?**

#### **Suggested Approach**

Combination therapy with at least 2 active agents, whenever possible, is suggested for the treatment of moderate to severe CRAB infections, at least until clinical improvement is observed, because of the limited clinical data supporting any single antibiotic agent. A single active agent can be considered for the treatment of mild CRAB infections.

### **Rationale**

Combination therapy is suggested for the treatment of moderate to severe infections, even if a single agent demonstrates activity. After clinical improvement has been demonstrated or in situations where prolonged durations of therapy may be needed (eg, 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 [116–124]. There are many observational studies evaluating the role of combination therapy versus monotherapy for the treatment of CRAB infections with differing results [102, 124–144]. The heterogeneity in patient populations, infectious sources, inclusion of colonizing isolates, variation in antibiotics and dosages used, small numbers, and imbalances between treatment arms make interpretation of a number of these studies challenging.

Seven RCTs have investigated the role of combination therapy for CRAB infections and only 1 of the 7 trials indicated a potential benefit with combination therapy [96, 103–108]. Of note, because of inconsistent and unclear colistin dosing reported in studies, the panel elected not to report colistin dosing used in individual studies. None of the 7 clinical trials that included a polymyxin arm investigated the role of polymyxin B, which has a more favorable pharmacokinetic profile than colistin [145]. Below is a summary of the 7 RCTs.

A trial including 210 intensive care unit (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 [106]. A second trial including 43 patients with CRAB pneumonia also compared colistin monotherapy and colistin in combination with rifampin [107]. In-hospital mortality was 73% in the colistin group and 62% in the colistin-rifampin group, which did not reach statistical significance. A third study

randomized 9 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% vs 67%, respectively) [108]. In all 3 of these trials, optimally dosed colistin was not administered. The small sample size of the latter 2 studies limits the interpretation of their findings.

A fourth trial including patients with various types of CRAB infections randomized 94 patients to receive colistin alone or colistin with fosfomycin [105]. Mortality within 28 days was 57% versus 47% and clinical failure was 45% versus 40% in the colistin monotherapy and colistin-fosfomycin arms, respectively. It is unknown if the statistical equivalence between the treatment arms is attributable to the relatively small sample size. Regardless, intravenous fosfomycin is not currently available in the United States, making it of limited relevance to this guidance document.

Two large trials evaluated the role of colistin monotherapy versus colistin in combination with meropenem [103, 104]. In the first study, 312 patients with CRAB bacteremia, pneumonia, or urinary tract infections were randomized to colistin alone versus colistin plus meropenem and no difference in 28-day mortality (46% vs 52%) or clinical failure (83% vs 81%) was observed between the groups [104]. The second trial, which has not been peer-reviewed at the time of publication of this guidance document, included 328 patients with drug-resistant *A. baumannii* bloodstream infections or pneumonia randomized to colistin alone compared with colistin in combination with meropenem [103]. The 28-day mortality was 46% versus 42% and clinical failure was 70% versus 64% in the colistin monotherapy and combination therapy arms, respectively. For both trials, the investigators concluded that the addition of meropenem to colistin did not improve clinical outcomes in patients with severe CRAB infections.

The seventh trial included 39 patients with CRAB pneumonia, 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 dosage of 24 g ampicillin-sulbactam [4 g ampicillin and 2 g sulbactam intravenously every 6 hours]) [96]. Clinical improvement by day 5 was observed in 16% and 70% of patients in the colistin versus colistin-sulbactam arms, respectively ( $P < .01$ ); however, investigators were unblinded to treatment assignment. Patients were allowed to transition to other antibiotics after day 5, precluding an accurate comparison of 28-day mortality or clinical failure between the groups.

Although only 1 of 7 clinical trials demonstrated any statistically significant benefit with combination therapy for CRAB infections, the panel favors the use of combination therapy for moderate to severe 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 (**Question 3–8**); (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; (3) patients susceptible to CRAB infections are generally chronically and critically ill with potentially impaired immune systems and the use of combination therapy, at least initially, may hasten recovery; and (4) antibiotics that initially appear active against CRAB may rapidly develop resistance so combination therapy increases the likelihood that at least 1 active agent is being administered.

Potential options for consideration as components of combination therapy include ampicillin-sulbactam (preferred), tetracycline derivatives (with the most experience available for minocycline, followed by tigecycline, and virtually no clinical data available for eravacycline or omadacycline), polymyxin B, extended-infusion meropenem, or cefiderocol (**Questions 3–7**) (**Table 1**). The panel suggests ampicillin-sulbactam as a component of combination therapy, even when resistance to this agent has been demonstrated (**Question 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 2 clinical trials [103, 104]; however, the combination of ampicillin-sulbactam, meropenem, and polymyxin B remains a consideration (keeping in mind the potential for toxicities from two high-dose  $\beta$ -lactam agents), with supportive data for this combination generally limited to *in vitro* studies [92]. As previously stated, because of the increased risk of toxicities with multiple  $\beta$ -lactam agents, if high-dose ampicillin-sulbactam is administered, minocycline, tigecycline, or polymyxin B are preferred as additional agents to choose amongst. The panel does not believe there is sufficient supportive evidence to suggest fosfomycin or rifampin as components of combination therapy (**Question 8**) [105, 107, 108].

### **Question 3: What Is the Role of Ampicillin-Sulbactam for the Treatment of Infections Caused by CRAB?**

#### **Suggested Approach**

High-dose ampicillin-sulbactam is a preferred therapy for CRAB infections when susceptibility has been demonstrated. High-dose ampicillin-sulbactam remains a treatment consideration as a component of combination therapy even when susceptibility has not been demonstrated.

#### **Rationale**

Sulbactam is a competitive, irreversible  $\beta$ -lactamase inhibitor that, in high doses, saturates PBPs (PBP1 and PBP3) of *A. baumannii* isolates [86, 146]. Sulbactam's unique activity against *A. baumannii* isolates has been demonstrated through *in vitro* studies [92–94], animal models [95], and clinical outcomes data [96–100]. The potent activity of sulbactam is not exhibited by

other  $\beta$ -lactamase inhibitors (eg, clavulanic acid). The panel suggests preferentially considering high-dose ampicillin-sulbactam monotherapy for mild CRAB infections. Insufficient data exist to determine if standard-dose ampicillin-sulbactam and high-dose ampicillin-sulbactam have equivalent efficacy for mild CRAB infections caused by isolates susceptible to ampicillin-sulbactam. The panel favors high-dose ampicillin-sulbactam, acknowledging that standard dosing is reasonable for patients with mild CRAB infections where intolerance or toxicities preclude the use of higher dosages (Table 1). The panel suggests high-dose ampicillin-sulbactam as a component of combination therapy for moderate to severe infections (Table 1).

Two meta-analyses have evaluated published observational and randomized clinical outcomes data for various treatment regimens against CRAB infections [99, 100]. A meta-analysis published in 2021 included 18 studies and 1835 patients and found that ampicillin-sulbactam (ampicillin-sulbactam total daily dosages of at least 18 g per day) in combination with a second agent was the most effective regimen to reduce mortality in critically ill patients infected with CRAB [99]. 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 2118 patients with CRAB infections [100]. This work 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 [100].

As described in **Question 2**, a clinical trial including 39 patients with CRAB pneumonia (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 dosage of 24 g ampicillin-sulbactam [4 g ampicillin and 2 g sulbactam every 6 hours]) [96]. This trial had a number of important limitations: the sample size was small, the open-label design may have led to biased outcome assignment, and an appropriate evaluation of long-term outcomes could not be undertaken. These limitations notwithstanding, this trial identified clinical improvement with a colistin-sulbactam combination for the treatment of CRAB infections. A separate trial randomized 28 patients with CRAB pneumonia to colistin monotherapy versus ampicillin-sulbactam monotherapy (total daily dosage of 27 g ampicillin-sulbactam [6 g ampicillin and 3 g sulbactam intravenously every 8 hours]) [101]. Neither differences in 28-day mortality nor clinical failure reached statistical significance (33% vs 30% and 33% vs 38%, among patients in the colistin and ampicillin-sulbactam arms, respectively). Nephrotoxicity was identified in 33% versus 15%, comparing the 2 groups. When evaluating the totality of in vitro, animal, and clinical data, the panel considers ampicillin-sulbactam a preferred option for the treatment of CRAB infections.

Fewer than 50% of CRAB isolates test susceptible to ampicillin-sulbactam [147, 148]. When nonsusceptibility 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 [92, 97, 101, 102]. The panel suggests the addition of a second agent if administering ampicillin-sulbactam to treat mild CRAB infections that are not susceptible to ampicillin-sulbactam and the addition of 1 or more additional agents to treat moderate to severe CRAB infections that are not susceptible to ampicillin-sulbactam.

Ampicillin-sulbactam uses 2:1 formulations; for example, 3 g of ampicillin-sulbactam is composed of 2 g of ampicillin and 1 g of sulbactam. Ampicillin-sulbactam total daily dosages of 27 g (equivalent to 9 g of sulbactam) as extended or continuous infusions are suggested (eg, 9 g [3 g of sulbactam] intravenously every 8 hours infused over 4 hours) [92, 93, 96, 97, 149]. As limited data on the safety and tolerability of high-dose ampicillin-sulbactam are available, particularly with long-term use and as a component of combination therapy, narrowing to a single active agent to complete the treatment course can be considered after sufficient clinical improvement is observed. Furthermore, as previously stated, ampicillin-sulbactam total daily dosages of 18 g, equivalent to 6 g of sulbactam, can be considered for mild, ampicillin-sulbactam-susceptible CRAB infections.

#### **Question 4: What Is the Role of the Polymyxins for the Treatment of Infections Caused by CRAB?**

##### *Suggested Approach*

Polymyxin B can be considered as monotherapy for mild CRAB infections and in combination with at least 1 other agent for the treatment of moderate to severe CRAB infections. Colistin is suggested rather than polymyxin B for urinary CRAB infections.

##### *Rationale*

Ampicillin-sulbactam-based regimens remain a preferred agent for the treatment of CRAB infections as described in **Question 3**; evidence is not as robust to preferentially select between polymyxin-based regimens or tetracycline-based regimens [53, 132, 150, 151]. Polymyxin-based regimens were identified as more effective than tetracycline-based regimens in 2 meta-analyses, although nephrotoxicity was generally higher with the former [99, 100]. Selecting between polymyxins and tetracycline derivatives should be based on individualized patient risk factors. Patients should be closely monitored for potential nephrotoxicity and neurotoxicity when receiving polymyxin agents [152–156].

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 [93, 94]. The panel preferentially suggests using polymyxin B when considering polymyxin-based regimens, based on its more favorable

pharmacokinetic profile than that of colistin [145]. Colistin is favored for CRAB urinary tract infections 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 greater than 2 µg/mL [157].

The panel prefers that polymyxins be prescribed as a component of combination therapy for moderate to severe CRAB infections to increase the likelihood that at least 1 agent in a treatment regimen has activity against CRAB, in light of 4 major issues with the polymyxins. First, concentrations of polymyxins in serum achieved with conventional dosing strategies are highly variable and may be inadequate for effective bactericidal activity [145]. Second, dosages required to treat systemic infections approach the threshold for nephrotoxicity, making the therapeutic window very narrow (ie, ~2 µg/mL may be required to achieve 1-log<sub>10</sub> reduction in bacterial growth, but this is also the threshold associated with nephrotoxicity) [158]. Third, the activity of intravenous polymyxins in pulmonary epithelial lining fluid is suboptimal and generally does not result in adequate bacterial killing in the lungs [159–161]. Finally, there are several reports of clinical failure and resistance emergence during polymyxin monotherapy [157, 162–165].

#### **Question 5: What Is the Role of Tetracycline Derivatives for the Treatment of Infections Caused by CRAB?**

##### ***Suggested Approach***

Tetracycline derivatives can be considered as monotherapy for mild CRAB infections and in combination with at least 1 other agent for the treatment of moderate to severe CRAB infections. Of these agents, the panel prefers minocycline because of the long-standing clinical experience with this agent and the availability of CLSI susceptibility interpretive criteria. High-dose tigecycline is an alternative option. The panel does not suggest eravacycline for the treatment of CRAB infections until more clinical data are available.

##### ***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 [166, 167]. 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 [168, 169]. 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 [78].

There has been considerable clinical experience with the use of minocycline since its introduction in the 1960s [170]. It is commercially available in both oral and intravenous formulations. International surveillance data suggest that minocycline

is active against approximately 60–80% of CRAB isolates [171, 172]. In vitro pharmacodynamic data suggest that 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 sulbactam and polymyxin B [93]. Clinical data demonstrating the safety and efficacy of this dose of minocycline 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 report describing its use are available [173–177]. Drawing conclusions on the effectiveness of minocycline from these observational reports is challenging as they have important limitations (eg, 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 intravenously or orally) as there are no clear clinical failure signals with its use for treating CRAB infections and CLSI susceptibility criteria are available (Table 1).

Tigecycline is a tetracycline derivative only available as an intravenous formulation. Neither CLSI nor US Food and Drug Administration (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 [178]. Several observational studies and a meta-analysis of 15 randomized 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 [131, 179–181]. Subsequent investigations have demonstrated that, when high-dose tigecycline is prescribed (200 mg intravenously as a single dose followed 100 mg intravenously every 12 hours), mortality differences between tigecycline and comparator agents are no longer evident [182–184]. If tigecycline is prescribed for the treatment of CRAB infections, the panel recommends that high doses be used (Table 1).

While minocycline or tigecycline monotherapy may be sufficient for mild CRAB infections, the panel suggests prescribing either agent in combination with at least 1 additional agent for moderate to severe CRAB infections. Both agents are associated with nausea in 20–40% of patients, and this is likely more common with higher dosages [185–187]. When used as components of a combination regimen, transitioning to a single active agent can be considered after an appropriate clinical response is observed to limit the development of antibiotic-associated adverse events.

Although eravacycline MICs are generally 2- to 8-fold lower than tigecycline MICs against CRAB [178, 188, 189], the clinical relevance of the differences in MIC distributions between these

agents is unclear due to differences in the pharmacodynamic profile of tigecycline and eravacycline. As with tigecycline, no CLSI susceptibility interpretive criteria exist for eravacycline. Patients with CRAB infections were not included in clinical trials that investigated the efficacy of eravacycline [190, 191] and postmarketing clinical reports describing its efficacy for the treatment of CRAB infections are virtually nonexistent. In light of the insufficient clinical data for eravacycline, the panel recommends limiting its use to situations when minocycline and tigecycline are either not active or unable to be tolerated. The limited in vitro data evaluating the activity of omadacycline, a tetracycline derivative with both an intravenous and oral formulation, against CRAB suggest reduced potency relative to other tetracycline derivatives and an unfavorable pharmacokinetic and pharmacodynamic profile [192–195]. The panel does not endorse the use of omadacycline to treat CRAB infections.

**Question 6: What Is the Role of Extended-Infusion Meropenem for the Treatment of Infections Caused by CRAB?**

*Suggested Approach*

High-dose, extended-infusion meropenem can be considered as a component of combination therapy for the treatment of moderate to severe CRAB infections. The combination of a polymyxin and meropenem, without a third agent, is not suggested 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 bacterial eradication against CRAB [92–94]. As described in **Question 2**, 2 large trials evaluated the role of colistin monotherapy versus colistin plus optimally dosed meropenem (ie, 2 g intravenously every 8 hours as an extended-infusion) [103, 104]. In the first study, among 312 patients with CRAB infections there were no differences in 28-day mortality (46% vs 52%) or clinical failure (83% vs 81%) between the groups in the colistin monotherapy and colistin-meropenem arms, respectively [104]. In the second trial of 328 patients with CRAB bloodstream infections or pneumonia, 28-day mortality was 46% versus 42% and clinical failure was 70% versus 64% in the colistin monotherapy and colistin-meropenem arms, respectively [103]. The panel does not suggest the combination of colistin-meropenem (without the addition of at least 1 more agent) as neither clinical trial demonstrated a benefit with this combination for the treatment of CRAB infections.

Imipenem-cilastatin can be used as an alternative to meropenem (Table 1) and may retain activity against some meropenem-resistant isolates [196–198]. As both ampicillin-sulbactam and meropenem (or imipenem-cilastatin) would be administered at high doses for the treatment of CRAB infections, there is the potential for additive  $\beta$ -lactam toxicity,

particularly neurologic adverse events, which should be closely monitored if used in combination.

**Question 7: 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 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  $\beta$ -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 of 4  $\mu$ g/mL or less [199–204]. At doses approximating human exposure to cefiderocol, bacterial stasis was achieved in *A. baumannii*-infected mouse thigh and lung models for cefiderocol MICs of 4  $\mu$ g/mL or less [202, 205]. An RCT including 54 patients with CRAB infections identified mortality at the end of study to be 49% versus 18% in the cefiderocol versus best-available-therapy arms (largely composed of polymyxin-based regimens), respectively [206]. 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 2 treatment regimens, including among 36 patients with CRAB pneumonia [207].

Because of the heterogeneity of regimens used in the best-available-therapy arm in the first trial, the relatively small numbers of patients with CRAB when combining both trials, and the difficulty with distinguishing between respiratory tract colonization and infection, contextualizing the results is challenging [208]. However, if cefiderocol is prescribed for the treatment of invasive CRAB infections, it should be used with caution. The panel suggests prescribing cefiderocol as a component of a combination regimen until and if more favorable clinical data on cefiderocol's activity as monotherapy are available, to increase the likelihood that at least 1 effective agent is included as part of the treatment regimen. The panel also suggests limiting consideration of cefiderocol for moderate to severe CRAB infections after other regimens have been exhausted.

**Question 8: What Is the Role of the Rifamycins for the Treatment of Infections Caused by CRAB?**

*Suggested Approach*

Despite promising in vitro and animal studies (particularly for rifabutin), the panel does not favor the use of rifabutin or other

rifamycins as a component of CRAB therapy, until a benefit is confirmed in clinical outcomes studies.

### **Rationale**

The rifamycin class of antibiotics includes agents such as rifampin, rifabutin, and rifapentine that inhibit bacterial RNA polymerase [209]. 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 [210–212]. 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 [211].

Three randomized trials compared the clinical outcomes of patients with CRAB receiving colistin alone versus colistin in combination with rifampin (**Question 2**) [106–108]. 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 [106]. A second trial including 43 patients with CRAB pneumonia also compared colistin monotherapy and colistin in combination with rifampin [107] and identified in-hospital mortality to be 73% in the colistin group and 62% in the colistin-rifampin group, which did not achieve statistical significance. A third study randomized 9 patients with colistin-resistant *A. baumannii* and found no difference in clinical response between the colistin (80%) and colistin plus rifampin arms (67%) [108].

Admittedly, there are limitations to all these trials, including suboptimal dosing of colistin and small sample sizes. Although there is enhanced in vitro and in vivo effect of rifabutin, it is unknown if a clinical benefit would have been observed if rifabutin had been used in place of rifampin [213]. In light of the known toxicities and drug interactions associated with the rifamycins [214] 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, until a benefit is confirmed in clinical outcomes studies.

### **Question 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 [215–242]. Three RCTs compared the outcomes of patients with gram-negative ventilator-associated pneumonia comparing nebulized antibiotics with placebo. All 3 trials allowed for the use of systemic

antibiotics, at the discretion of the treating clinician. In brief, 1 trial compared the outcomes of 100 adults with pneumonia (65% caused by *A. baumannii*) treated with nebulized colistin versus placebo [109]; a second trial compared the outcomes of 142 adults with pneumonia (20% caused by *A. baumannii*) treated with nebulized amikacin/fosfomycin versus placebo [110]; and the third trial compared the outcomes of 508 adults with pneumonia (29% caused by *A. baumannii*) treated with nebulized amikacin versus placebo [111]. None of the 3 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 [109–111].

Reasons for the lack of clinical benefit in these trials are unclear. In a pharmacokinetic-pharmacodynamic modeling study, aerosolized delivery of the prodrug of colistin to critically ill patients achieved high active drug levels in the epithelial lining fluid of the lungs [243]. However, it is likely that nebulized antibiotics do not achieve sufficient penetration and/or distribution throughout lung tissue to exert significant bactericidal activity [113], likely due, in part, to the use of parenteral formulations not specifically designed for inhalation in suboptimal delivery devices such as jet nebulizers [114, 115]. Professional societies have expressed conflicting views regarding the role of nebulized antibiotics as adjunctive therapy to intravenous antibiotics [244–246]. 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 in 10–20% of patients receiving aerosolized antibiotics [112].

### **STENOTROPHOMONAS MALTOPHILIA**

*Stenotrophomonas maltophilia* is an aerobic, glucose non-fermenting, gram-negative bacillus that is ubiquitous in water environments. The organism has a long history of changing nomenclatures and a complicated phylogeny [247–249]. 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 hematologic malignancies [250, 251].

*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 [252–256]. *S. maltophilia* is often recovered as a component of a polymicrobial infection—further challenging the need for targeted *S. maltophilia* therapy [247, 257]. 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 [7, 258–263].

Second, treatment selection is hampered by the impressive number of antimicrobial resistance genes and gene mutations carried by *S. maltophilia* isolates [247, 249]. An L1 metallo- $\beta$ -lactamase and L2 serine  $\beta$ -lactamase render most conventional  $\beta$ -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 [247]. *S. maltophilia* exhibits intrinsic resistance to aminoglycosides via chromosomal aminoglycoside acetyltransferase enzymes [264]. Furthermore, *S. maltophilia* can accumulate multidrug efflux pumps that reduce the activity of tetracyclines and fluoroquinolones and chromosomal *Smqnr* genes, which further reduces the effectiveness of fluoroquinolones [265].

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.

Last, *S. maltophilia* antibiotic susceptibility testing is problematic. The CLSI has established MIC interpretive criteria for 7 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 [266], leaving 5 agents for which interpretable antibiotic MIC data can be provided to clinicians. Confidence in MIC interpretive criteria is undermined by concerns about reproducibility of ceftazidime and levofloxacin MIC testing results using methods that are commonly used in clinical laboratories [267, 268], the limited pharmacokinetic-pharmacodynamic data used to inform breakpoints for most agents, and insufficient data to identify correlations between MICs and clinical outcomes.

There are no CLSI susceptibility criteria established for the polymyxins [52, 269]. Incomplete *S. maltophilia* growth inhibition often occurs in polymyxin wells, suggestive of heteroresistance. Challenges exist in both the accuracy and reproducibility of polymyxin MICs [270, 271]. The panel does not suggest polymyxins for the treatment of *S. maltophilia* infections.

#### **Question 1: What Is a General Approach for the Treatment of Infections Caused by *S. maltophilia*?**

##### **Suggested Approach**

For mild infections, TMP-SMX, minocycline, tigecycline, levofloxacin, or cefiderocol monotherapy are suggested

treatment options; of these, the panel suggests TMP-SMX and minocycline as the preferred agents. Ceftazidime is not suggested for the treatment of *S. maltophilia* regardless of the severity of infection, given the intrinsic  $\beta$ -lactamases produced by *S. maltophilia* likely to render ceftazidime ineffective. For moderate to severe infections, any of 3 approaches are suggested: (1) the use of combination therapy, with TMP-SMX and minocycline as the preferred combination; (2) the initiation of TMP-SMX monotherapy with the addition of a second agent (minocycline [preferred], tigecycline, levofloxacin, or cefiderocol) if there is a delay in clinical improvement with TMP-SMX alone; or (3) the combination of ceftazidime-avibactam and aztreonam, when intolerance or inactivity of other agents are anticipated.

##### **Rationale**

For mild infections and polymicrobial infections, where the role of *S. maltophilia* as a pathogen is unclear, TMP-SMX, minocycline, tigecycline, levofloxacin, or cefiderocol, all as monotherapy, can be considered (**Question 2–5**). TMP-SMX is traditionally regarded as the drug of choice for *S. maltophilia* infections (**Question 2**). Because of the potential for a combination of efflux pumps and *Smqnr* genes rendering levofloxacin inactive during therapy for *S. maltophilia* infections [272–274], the panel suggests administering levofloxacin with caution (**Question 4**). Similarly, despite promising in vitro and animal data, caution should be used when prescribing cefiderocol until more clinical data investigating its role for *S. maltophilia* infections are available (**Question 5**). Ceftazidime is not suggested for the treatment of *S. maltophilia* infections either as monotherapy or as a component of combination therapy as it not expected to be effective given the presence of L1 metallo- $\beta$ -lactamases and L2 serine  $\beta$ -lactamases intrinsic to *S. maltophilia* [249] (**Question 7**).

In situations where *S. maltophilia* is causing moderate to severe disease, any of 3 approaches are suggested: (1) the use of combination therapy with at least 2 of the above agents, at least until clinical improvement is observed, primarily because of the limited clinical data supporting any individual agent; (2) a sequential approach of initiating TMP-SMX and adding a second agent if an appropriate clinical response is not observed (**Questions 2–5**); or (3) in situations precluding the use of either TMP-SMX or minocycline, the combination of ceftazidime-avibactam and aztreonam can be considered (**Question 6**). In vitro data are conflicting, but several investigations suggest synergy between TMP-SMX and a second agent (including minocycline, fluoroquinolones, and cefiderocol) against *S. maltophilia* isolates [275–278]. 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 [279–281].

**Question 2: What Is the Role of Trimethoprim-Sulfamethoxazole for the Treatment of Infections Caused by *S. maltophilia*?**

**Suggested Approach**

TMP-SMX monotherapy is a preferred treatment agent for mild *S. maltophilia* infections. TMP-SMX either as monotherapy or, preferably, in combination with another active agent is suggested for moderate to severe *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* [282, 283], although there is an increasing recognition of *S. maltophilia* isolates resistant to TMP-SMX [277, 284]. 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 almost nonexistent. 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 [281]. 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 demonstrate similar outcomes [274, 285–287]; these studies have a number of significant limitations as further described in **Question 3** and **Question 4**. Acknowledging the paucity of clinical data supporting this recommendation, 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 1**, while TMP-SMX monotherapy is a reasonable option for mild *S. maltophilia* infections, for moderate to severe infections when TMP-SMX is initiated, 1 of 2 approaches are suggested: the use of combination therapy with a second agent added to TMP-SMX (eg, minocycline, tigecycline, levofloxacin, cefiderocol) at least until clinical improvement is observed or, alternatively in less severe infections, a sequential approach of initiating TMP-SMX and adding a second agent if an appropriate clinical response is not observed. Pharmacodynamic data for TMP-SMX are limited for *S. maltophilia* [275, 288]; suggestions for dosing are included in [Table 1](#).

**Question 3: What Is the Role of Tetracycline Derivatives for the Treatment of Infections Caused by *S. maltophilia*?**

**Suggested Approach**

High-dose minocycline monotherapy is a treatment consideration for mild *S. maltophilia* infections. High-dose minocycline

in combination with a second active agent, at least until clinical improvement is observed, is suggested for the treatment of moderate to severe *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 treatment option for *S. maltophilia* infections.

**Rationale**

Tetracycline derivatives such as minocycline, tigecycline, and eravacycline generally have low MICs when tested against *S. maltophilia* in surveillance studies [278, 289–292]. Both in vitro and in vivo data on the role of eravacycline against *S. maltophilia* are scarce. Omadacycline, a tetracycline derivative with oral and intravenous formulations, has limited in vitro activity against *S. maltophilia* relative to other tetracycline derivatives [289].

Surveillance studies report that minocycline and tigecycline have activity against approximately 70–90% of *S. maltophilia* isolates, with a lower MIC<sub>90</sub> generally observed for minocycline [278, 289–292]. Amongst tetracycline derivatives, CLSI susceptibility criteria are only available for minocycline [52]. Greater than 90% target attainment is achieved with minocycline dosages of 100 mg intravenously every 12 hours compared with approximately 75% target attainment with tigecycline dosed at 100 mg intravenously every 12 hours [290]. Both minocycline and tigecycline have extensive penetration into lung tissue [293–296].

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 [286]. Another observational study evaluating 119 patients with *S. maltophilia* infections who received minocycline reported clinical success in approximately 80% of patients [297]; 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 [287]. 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 minocycline or tigecycline are not reasonable treatment options for *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. 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



[173, 298, 299] (Table 1). At higher dosages (ie, 200 mg twice daily) both intravenous and oral formulations of minocycline are expected to provide adequate drug levels.

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 [78]. Therefore, they are not suggested for *S. maltophilia* urinary tract infections, and they are endorsed only as a component of combination therapy for the treatment of *S. maltophilia* bloodstream infections, at least until clearance of blood cultures and after clinical improvement is observed. Nausea and emesis are reported in as many as 20–40% of patients receiving minocycline or tigecycline [185–187]. More data are necessary to evaluate the role of eravacycline or omadacycline for the treatment of *S. maltophilia* infections.

#### **Question 4: What Is the Role of Fluoroquinolones for the Treatment of Infections Caused by *S. maltophilia*?**

##### **Suggested Approach**

Levofloxacin monotherapy is a treatment option for mild *S. maltophilia* infections. The emergence of resistance during levofloxacin therapy is a concern. If administered for the treatment of moderate to severe *S. maltophilia* infections, levofloxacin should only be considered in combination with a second active agent (TMP-SMX, minocycline, tigecycline, cefiderocol).

##### **Rationale**

*S. maltophilia* isolates frequently harbor *Smqnr* resistance determinants in their chromosomes that interfere with fluoroquinolone binding to gyrase and topoisomerase, leading to increased fluoroquinolone MICs [249, 265]. Fluoroquinolone MICs may increase further as a result of overexpression of multidrug-resistant efflux pumps [282, 300–302]. Baseline susceptibility percentages of *S. maltophilia* to levofloxacin vary from approximately 30% to 80% in surveillance studies [277, 278, 292, 303]. Several studies have shown that *S. maltophilia* isolates that test susceptible to levofloxacin can develop elevated levofloxacin MICs during therapy [272–274, 304]. CLSI susceptibility criteria exist for levofloxacin against *S. maltophilia*, but not for ciprofloxacin or moxifloxacin [305].

Time-kill curves evaluating ciprofloxacin, levofloxacin, and moxifloxacin monotherapy generally indicate that these agents are inadequate at sustained inhibition of *S. maltophilia* growth [290, 306–309], but suggest that levofloxacin and moxifloxacin may have sufficient activity as components of combination therapy [277, 278]. Pharmacokinetic-pharmacodynamic modeling data also suggest that fluoroquinolone monotherapy may be insufficient at achieving appropriate target attainment for *S. maltophilia* infections, even when administered at high dosages [290]. Levofloxacin and moxifloxacin were both associated with improved survival compared with placebo in a mouse model of hemorrhagic *S. maltophilia* pneumonia [310]. Neutropenic mouse models suggest

that levofloxacin may be most effective against isolates with *S. maltophilia* isolates with MICs of 1 µg/mL or less [311].

Human data for the treatment of *S. maltophilia* infections are almost exclusively limited to ciprofloxacin and 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 [285]. 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 with 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 [274]. Similar to the meta-analysis, interpretation of the results is challenging since all sites of infection were included without clear definitions distinguishing between colonization and infection.

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 that fluoroquinolones be used with caution for the treatment of *S. maltophilia* infections. Although fluoroquinolones can be considered as monotherapy for mild infections, the panel suggests they only be used as a component of combination therapy, preferably with TMP-SMX, when prescribed for the treatment of moderate to severe *S. maltophilia* infections. Because of the lack of susceptibility criteria for ciprofloxacin and moxifloxacin, the panel suggests preferentially administering levofloxacin among 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 [312].

#### **Question 5: What Is the Role of Cefiderocol for the Treatment of Infections Caused by *S. maltophilia*?**

##### **Suggested Approach**

Cefiderocol monotherapy is a treatment option for mild *S. maltophilia* infections, acknowledging the limited clinical data available with this agent. Cefiderocol in combination with a second active agent, at least until clinical improvement is observed, is suggested for the treatment of moderate to severe *S. maltophilia* infections.

### **Rationale**

Cefiderocol is a novel siderophore-cephalosporin antibiotic. Surveillance studies indicate that susceptibility of *S. maltophilia* isolates approaches 100%, even against isolates resistant to other commonly prescribed agents [199, 277, 313–315], 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 [316]. 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 [202, 317].

Clinical data evaluating the role of cefiderocol for the treatment of *S. maltophilia* infections are scarce. A randomized trial evaluating the role of cefiderocol for carbapenem-resistant infections included 5 patients with *S. maltophilia* infections [206, 318]. All 5 patients were assigned to the cefiderocol arm, precluding comparisons between treatment regimens. Four out of 5 patients died, including 2 of 3 patients without CRAB coinfections. Despite the limited availability of clinical data, in vitro data and animal models are very encouraging for the use of cefiderocol in treating *S. maltophilia* infections. While cefiderocol monotherapy may be adequate for mild infections, the panel suggests using cefiderocol in combination with a second agent for the treatment of moderate to severe *S. maltophilia* infections, at least until clinical improvement is observed, and more postlicensure data become available to re-examine this need.

### **Question 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 moderate to severe *S. maltophilia* infections when neither TMP-SMX nor minocycline are considered viable treatment options.

### **Rationale**

The combination of ceftazidime-avibactam and aztreonam can be used to overcome the activity of both the L1 and L2  $\beta$ -lactamases intrinsic to *S. maltophilia* [249, 319–324]. The L1 metallo- $\beta$ -lactamase hydrolyzes ceftazidime-avibactam but not aztreonam. The L2 serine  $\beta$ -lactamase inactivates 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 penicillin-binding proteins of *S. maltophilia*. Despite limited available clinical data with this combination for the treatment of *S. maltophilia* infections [321, 325, 326], the panel believes the combination of ceftazidime-avibactam and

aztreonam (administered simultaneously) [327] 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.

### **Question 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  $\beta$ -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  $\beta$ -lactamases are expected to render it ineffective. Almost 30–40% of *S. maltophilia* isolates test susceptible to ceftazidime using CLSI interpretive criteria [293, 304]. 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.

In vitro models suggest that ceftazidime is unable to substantively prevent *S. maltophilia* growth [279]. Comparative effectiveness studies evaluating the role of ceftazidime against *S. maltophilia* infections are virtually nonexistent [328]. An additional concern potentially related to the presence of inactivating  $\beta$ -lactamases is that ceftazidime MICs against *S. maltophilia* may be inaccurate and nonreproducible using susceptibility methods commonly employed by clinical microbiology laboratories [267, 268].

### **Notes**

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