

Infectious Diseases Society of America Guidance on the Treatment of AmpC β -lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

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Abstract

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

Methods: A panel of six 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.

Results: 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.

Conclusions: The field of antimicrobial resistance is highly dynamic. Consultation with an infectious diseases specialist is recommended for the treatment of antimicrobial-resistant infections. *This document is current as of September 17, 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/.

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Introduction

The rise in antimicrobial resistance (AMR) continues to be a global crisis. Collectively, antimicrobial-resistant pathogens caused more than 2.8 million infections and over 35,000 deaths annually from 2012 through 2017, according to the 2019 Centers for Disease Control and Prevention (CDC) Antibiotic Resistance Threats in the United States Report [1]. The Infectious Diseases Society of America (IDSA) identified the development and dissemination of clinical practice guidelines and other guidance products for clinicians as a top initiative in its 2019 Strategic Plan [2]. IDSA acknowledged that the ability to address rapidly evolving topics such as AMR was limited by prolonged timelines needed to generate new or updated clinical practice guidelines, which are based on systematic literature reviews and employ rigorous GRADE (Grading of Recommendations Assessment, Development, and Evaluation) 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 β -lactamase-producing Enterobacterales (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 β -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 U.S. 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 September 17, 2021; updates will be provided periodically. The most current version of this IDSA guidance document and corresponding dates of publication is available at: www.idsociety.org/practice-guideline/amr-guidance-2.0/.

Methodology

IDSA convened a panel of six actively practicing infectious diseases specialists with clinical and research expertise in the treatment of antimicrobial-resistant bacterial infections. Through a series of 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](#).

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

Agent	Adult Dosage (assuming normal renal and liver function ^a)	Target Organisms ^{b,c}
Amikacin	Cystitis: 15 mg/kg/dose ^d IV once All other infections: 20 mg/kg/dose ^d IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation	ESBL-E, AmpC-E, CRE, DTR- <i>P. aeruginosa</i>
Ampicillin-sulbactam	9 g IV q8h over 4 hours OR 27 g 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 preclude 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>S. 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 <u>PLUS</u> 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	ESBL-E or AmpC infections: 400 mg IV q8h-q12h OR 500 – 750 mg PO q12h	ESBL-E, AmpC-E
Colistin	Refer to international consensus guidelines on polymyxins ^e	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	ESBL-E, AmpC-E
Fosfomycin	Cystitis: 3 g PO x 1 dose	ESBL- <i>E. coli</i> cystitis

Agent	Adult Dosage (assuming normal renal and liver function ^a)	Target Organisms ^{b,c}
Gentamicin	Cystitis: 5 mg/kg/dose ^d IV once All other infections: 7 mg/kg/dose ^d IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation	ESBL-E, AmpC-E, CRE, DTR- <i>P. aeruginosa</i>
Imipenem-cilastatin	Cystitis (standard infusion): 500 mg IV q6h, infused over 30 minutes All other ESBL-E 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	ESBL-E, 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	ESBL-E, AmpC-E, <i>S. maltophilia</i>
Meropenem	Cystitis (standard infusion): 1 g IV q8h, infused over 30 minutes All other ESBL-E 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	ESBL-E, 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	ESBL-E cystitis, AmpC-E cystitis
Plazomicin	Cystitis: 15 mg/kg ^d IV x 1 dose All other infections: 15 mg/kg ^d IV x 1 dose, subsequent doses and dosing interval based on pharmacokinetic evaluation	ESBL-E, AmpC-E, CRE, DTR- <i>P. aeruginosa</i>
Polymyxin B	Refer to international consensus guidelines on polymyxins ^e	DTR- <i>P. aeruginosa</i> , CRAB
Tigecycline	200 mg IV x 1 dose, then 100 mg IV q12h	CRE, CRAB, <i>S. maltophilia</i>

Agent	Adult Dosage (assuming normal renal and liver function ^a)	Target Organisms ^{b,c}
Tobramycin	Cystitis: 5 mg/kg/dose ^d IV x 1 dose All other infections: 7 mg/kg/dose ^d IV x 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation	ESBL-E, AmpC-E, CRE, DTR- <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)	ESBL-E, AmpC-E, <i>S. maltophilia</i>

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

Explanations/References

- Dosing suggested for several agents differs from U.S. Food and Drug Administration-recommended dosing.
- Target organisms limited to the following organisms and generally only after susceptibility has been demonstrated: ESBL-E, AmpC-E, CRE, DTR-*P. aeruginosa*, CRAB, and *Stenotrophomonas maltophilia*.
- For additional guidance on the treatment of ESBL-E, CRE, and DTR-*P. aeruginosa*, refer to: <https://www.idsociety.org/practice-guideline/amr-guidance/>.
- Use adjusted body weight for patients >120% of ideal body weight for aminoglycoside dosing.
- Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). *Pharmacotherapy* **2019**; 39(1): 10-39.

General Management Recommendations

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

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: (1) previous organisms identified from the patient and associated antibiotic susceptibility data in the last six months, (2) antibiotic exposures within the past 30 days, and (3) local susceptibility patterns for the most likely pathogens. Empiric decisions should be refined based on the identity and susceptibility profile of the pathogen, as well as based on the identification of any prominent β -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 to infections caused by the same bacterial species with a more susceptible phenotype. After antibiotic susceptibility results are available, it may become apparent that inactive antibiotic therapy was initiated empirically. This may impact the duration of therapy. For example, cystitis is typically a mild infection [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 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 β -Lactamase-Producing Enterobacterales

AmpC β -lactamases are class C serine β -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 one of three 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 MICs and result in ceftriaxone and ceftazidime resistance. In this scenario, an Enterobacterales isolate that initially tests as susceptible to ceftriaxone may exhibit non-susceptibility 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 two mechanisms (i.e., 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 non-susceptible 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 two mechanisms, some Enterobacterales isolates (e.g., 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 (e.g., *bla*_{CMY}, *bla*_{FOX}, *bla*_{DHA}, *bla*_{ACT}, *bla*_{MIR}) 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 β -lactam agents (e.g., ceftriaxone or ceftazidime) that, on subsequent isolation (and after β -lactam exposure), become resistant, with genotyping and expression studies to confirm that the same organism was recovered and that AmpC production significantly increased. Unfortunately, such studies are not available.

Commonly used acronyms to denote organisms at risk for AmpC production such as “SPACE” or “SPICE” obscure the wide range of *ampC* induction potential among Gram-negative organisms and ignore variance within bacterial genera [12, 13]. For example, *Citrobacter 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 *P. vulgaris* and *P. penneri*, which generally do not contain chromosomal *ampC* genes. The terminology “indole positive *Proteus* species” previously included *Proteus rettgeri* and *Proteus morganii* (since renamed *Providencia rettgeri* and *Morganella morganii*, respectively) [22], making the inclusion of “indole-positive *Proteus* spp.” in mnemonics for organisms at high risk of AmpC production no longer accurate.

The emergence of clinically relevant *ampC* expression during antibiotic treatment has been most frequently described for *E. cloacae*, *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*, *Morganella morganii*, and *Providencia* species, are unlikely to overexpress *ampC* based on both *in vitro* analysis [28] and clinical reports [16, 23]. Studies indicate that clinically significant AmpC production occurs in less than 5% of these organisms. When *S. marcescens*, *M. morganii*, 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 (e.g., *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 (e.g., administer ceftriaxone if susceptible to ceftriaxone). When treating infections caused by these less commonly recovered organisms (or caused by *S. marcescens*, *M. morganii*, or *Providencia* spp.) with a high bacterial burden and limited source control (e.g., 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 β -lactam antibiotics are at relatively high risk of inducing *ampC* genes. Both the ability to induce *ampC* genes and the inability to withstand AmpC hydrolysis should inform antibiotic decision-making.

Rationale

β -lactam antibiotics fall within a spectrum of potential for inducing *ampC*. Aminopenicillins (i.e., amoxicillin, ampicillin), narrow-spectrum (i.e., first generation) cephalosporins, and cephamycins are potent AmpC inducers [32, 33]. However, organisms at moderate to high risk for clinically significant *ampC* induction (e.g., *Enterobacter cloacae*) hydrolyze these antibiotics even at basal *ampC* expression levels. Therefore, such AmpC-E isolates will generally test as non-susceptible to these drugs, averting treatment dilemmas. Imipenem is also a potent *ampC* inducer but it generally remains 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 minimum inhibitory concentrations (MICs) [35-38].

Cefepime has the advantage of both being a weak inducer of AmpC production and of withstanding hydrolysis by AmpC β -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 (i.e., *E. cloacae*, *K. aerogenes*, and *C. freundii*) when the cefepime MIC is ≤ 2 mcg/mL. A carbapenem is recommended when the cefepime MIC is ≥ 4 mcg/mL, 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 use of cefepime leads to similar clinical outcomes as carbapenem therapy [27, 48, 49]. Furthermore, a meta-analysis including seven studies comparing clinical outcomes of patients receiving cefepime *versus* carbapenems for *Enterobacter* spp., *Citrobacter* spp., and *Serratia* spp. bloodstream infections did not find differences in clinical outcomes between these treatment regimens, although considerable heterogeneity between studies exist, ill appearing patients were more likely to receive carbapenem therapy, and 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 ≤ 2 mcg/mL ([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 mcg/mL have a high likelihood of producing ESBLs; in one study, 89% of *E. cloacae* isolate with cefepime MICs of 4-8 mcg/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 mcg/mL who received cefepime died within 30 days; in contrast, none of the six patients who received cefepime for infections caused by non-ESBL-producing cefepime isolates with MICs of 4-8 mcg/mL died within 30 days [51]. In light of these data, we suggest preferentially administering carbapenem therapy (i.e., ertapenem, meropenem, imipenem-cilastatin), for infections caused by *E. cloacae*, *K. aerogenes*, and *C. freundii* with cefepime MICs of 4-8 mcg/mL (i.e., 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. Firstly, there are no CLSI-endorsed criteria for AmpC detection in clinical isolates, making their accurate identification difficult. Secondly, these organisms may display ceftriaxone non-susceptibility for other reasons (e.g., ESBL production); however, such mechanisms are rarely investigated in clinical studies for organisms other than *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *P. mirabilis*. Thirdly, studies often report combined estimates for organisms at low risk for significant AmpC production (e.g., *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]. Fourthly, studies that evaluate the proportion of isolates exhibiting ceftriaxone non-susceptibility after ceftriaxone exposure do not include confirmation of genetic relatedness of index and subsequent isolates. Additionally, most AmpC clinical studies use pre-2010 CLSI ceftriaxone breakpoints (i.e., ceftriaxone MICs ≤ 8 mcg/mL), making translation of prevalence estimates to current CLSI ceftriaxone susceptibility breakpoints of ≤ 1 mcg/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 to alternate agents (i.e., 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 (i.e., 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 to 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 β -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 eight 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 (i.e., ill appearing patients were more likely to be prescribed carbapenems). In two observational studies included in this meta-analysis, 30-day mortality among patients treated with piperacillin-tazobactam was numerically higher than among patients treated with carbapenems (15% [6/41 patients] 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. morganii*, *Providencia* spp., or *S. marcescens* randomized to piperacillin-tazobactam (4.5 grams every 6 hours as a standard infusion) or meropenem (1 gram 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=0.13); clinical failure (21% vs. 12%, p=0.29); microbiological failure (13% vs. 0), p=0.03), and microbiological relapse (0% vs. 9%, p=0.06), 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 definitely 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 two 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 β -lactam and β -lactam- β -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 β -lactams (i.e., cefiderocol) and β -lactam- β -lactamase inhibitor combination agents (i.e., 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 β -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 β -lactam- β -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 one 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; a 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 recognized 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- β -lactam therapy for the treatment of infections caused by Enterobacterales at moderate to high risk of clinically significant AmpC production due to an inducible *ampC* gene?

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

Secondly, 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- β -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); β -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 two 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, 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 precludes the use of higher ampicillin-sulbactam dosages ([Table 1](#)). Alternate treatment options for mild CRAB infections include minocycline, tigecycline, polymyxin B (colistin for cystitis), or cefiderocol as described in [Question 4](#), [Question 5](#), and [Question 6](#). When non-susceptibility 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 two 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 one of seven 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 B-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 two 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 (e.g., osteomyelitis), step-down therapy to a single active agent can be considered. *In vitro* and animal studies have had conflicting findings but several investigations indicate increased bacterial killing with various combination regimens [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 makes interpretation of a number of these studies challenging.

Seven RCTs have investigated the role of combination therapy for CRAB infections and only one of the seven 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 seven 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 seven 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, not reaching statistical significance. A third study randomized nine patients with colistin-resistant *A. baumannii* (carbapenem susceptibility status not described) and found no difference in clinical response between the colistin and colistin plus rifampin arms (80% vs. 67%, respectively) [108]. In all three of these trials, optimally-dosed colistin was not administered. The small sample size of the latter two study 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% vs. 47% and clinical failure was 45% vs. 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 to colistin in combination with meropenem [103]. The 28-day mortality was 46% vs. 42% and clinical failure was 70% vs. 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 CRAB pneumonia patients, with clinical isolates demonstrating susceptibility to both colistin and sulbactam. Patients were randomized to

colistin monotherapy vs. colistin in combination with high-dose sulbactam (total daily dosage of 24 g of ampicillin-sulbactam [4 g ampicillin and 2 g sulbactam intravenously q6h] [96]. Clinical improvement by day five was observed in 16% and 70% of patients in the colistin *versus* colistin-sulbactam arms, respectively, $p < 0.01$; however, investigators were unblinded to treatment assignment. Patients were allowed to transition to other antibiotics after day five, precluding an accurate comparison of 28-day mortality or clinical failure between the groups.

Although only one of seven 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](#), [Question 4](#), [Question 5](#), [Question 6](#), [Question 7](#), [Question 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 one 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 ([Question 3](#), [Question 4](#), [Question 5](#), [Question 6](#), [Question 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 two 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 β -lactam agents, with supportive data for this

combination generally limited to *in vitro* studies [92]. 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 β -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 β -lactamase inhibitors (e.g., 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 precludes 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 1,835 patients and found that ampicillin-sulbactam (ampicillin-sulbactam total daily dosages of at least 18 grams 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 2,118 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 CRAB pneumonia patients (with clinical isolates susceptible to both colistin and sulbactam) identified clinical improvement by day 5 in 16% and 70% of patients randomized to colistin monotherapy vs. colistin in combination with high-dose sulbactam (total daily dosage of 24 g of ampicillin-sulbactam [4 g ampicillin and 2 g sulbactam q6h] [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 CRAB pneumonia patients to colistin monotherapy vs. ampicillin-sulbactam monotherapy (total daily dosage of 27 g of ampicillin-sulbactam [6 g ampicillin and 3 g sulbactam intravenously q8h] [101]. Neither differences in 28-day mortality or 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% vs. 15%, comparing the two 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 non-susceptibility to ampicillin-sulbactam is demonstrated, the panel believes ampicillin-sulbactam may still remain an effective treatment option based on the potential for sulbactam to saturate altered PBP targets [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 one 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 grams of ampicillin-sulbactam is comprised of 2 grams of ampicillin and 1 gram of sulbactam. Ampicillin-sulbactam

total daily dosages of 27 grams (equivalent to 9 grams of sulbactam) as extended or continuous infusions are suggested (e.g., 9 grams [3 grams 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 grams, equivalent to 6 grams 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 one 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 [132, 150-152]. Polymyxin-based regimens were identified as more effective than tetracycline-based regimens in two meta-analysis, 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 [153-157].

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 >2 mcg/mL [158].

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 one agent in a treatment regimen has activity against CRAB, in light of four major issues with the polymyxins. Firstly, concentrations of polymyxins in serum achieved with conventional dosing strategies are highly variable and may be inadequate for effective bactericidal activity [145].

Secondly, dosages required to treat systemic infections approach the threshold for nephrotoxicity making the therapeutic window very narrow (i.e., ~2 mcg/mL may be required to achieve 1-log₁₀ reduction in bacterial growth, but this is also the threshold associated with nephrotoxicity) [159]. Thirdly, the activity of intravenous polymyxins in pulmonary epithelial lining fluid is suboptimal and generally does not result in adequate bacterial killing in the lungs [160-162]. Finally, there are several reports of clinical failure and resistance emergence during polymyxin monotherapy [158, 163-166].

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 one 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 [167, 168]. 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 [169, 170]. 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 [171]. It is commercially available in both oral and intravenous formulations. International surveillance data suggest minocycline is active against approximately 60-80% of CRAB isolates [172, 173]. *In vitro* pharmacodynamic data suggest high-dose minocycline (700 mg loading dose followed by 350 mg every 12 hours) may be more effective than standard minocycline dosages for the treatment of CRAB infections, particularly when used in combination with high-dose 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 [174-178]. Drawing conclusions on the effectiveness of minocycline from these observational reports

is challenging as they have important limitations (e.g., small sample sizes, selection bias, inadequate distinctions between colonization and infection, heterogeneous sites of infection). Despite the limitations of available data, the panel considers minocycline a reasonable treatment option for CRAB infections (dosed at 200 mg twice daily either 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 U.S. Food and Drug Administration 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 [179]. 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, 180-182]. Subsequent investigations have demonstrated that when high-dose tigecycline is prescribed (200 mg intravenously as a single dose followed 100 by mg intravenously q12h) mortality differences between tigecycline and comparator agents are no longer evident [183-185]. 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 one 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 [186-188]. 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 [179, 189, 190], 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 [191, 192] and post-marketing clinical reports describing its efficacy for the treatment of CRAB infections are virtually non-existent. 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 suggests reduced potency relative to other tetracycline derivatives and an unfavorable pharmacokinetic and pharmacodynamic profile [193-196]. 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](#), two large trials evaluated the role of colistin monotherapy *versus* colistin plus optimally dosed meropenem (i.e., 2 grams intravenously every 8 hours as an extended-infusion) [103, 104]. In the first study, amongst 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% vs. 42% and clinical failure was 70% vs. 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 one 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 [197-199]. 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 monitored closely 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 β -lactam agent with *in vitro* activity against CRAB isolates. International surveillance studies indicate that approximately 95% of CRAB isolates are susceptible to cefiderocol using the CLSI susceptibility criteria ≤ 4 mcg/mL [200-205]. At doses approximating human exposure to cefiderocol, bacterial stasis was achieved in an *A. baumannii* infected mouse thigh and lung models for cefiderocol MICs of ≤ 4 mcg/mL [203, 206]. A RCT including 54 patients with CRAB infections identified mortality at the end of study to be 49% vs. 18% in the cefiderocol *versus* best available therapy arms (largely composed of polymyxin-based regimens), respectively [207]. Poor outcomes with cefiderocol were observed in patients with pneumonia and bloodstream infections. A second randomized trial specifically evaluating patients with pneumonia randomized to cefiderocol or high-dose extended-infusion meropenem found no difference in clinical outcomes between the two treatment regimens, including among 36 patients with CRAB pneumonia [208].

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 [209]. 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 one 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 [210]. 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 [211-213]. 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 [212].

Three randomized trials compared the clinical outcomes of CRAB patients 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, not achieving statistical significance. A third study randomized nine patients with colistin-resistant *A. baumannii* and found no difference in clinical response between the colistin (80%) and colistin plus rifampin arms (67%) [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 [214]. In light of the known toxicities and drug interactions associated with

the rifamycins [215] 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 [216-243]. Three RCTs compared the outcomes of patients with Gram-negative ventilator-associated pneumonia comparing nebulized antibiotics *versus* placebo. All three trials allowed for the use of systemic antibiotics, at the discretion of the treating clinician. In brief, one trial compared the outcomes of 100 adults with pneumonia (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 three clinical trials demonstrated improved clinical outcomes or a survival benefit with the use of nebulized antibiotics compared with placebo for the treatment of ventilator-associated pneumonia, including in subgroup analyses of drug-resistant pathogens [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 epithelial lining fluid of the lungs [244]. 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 [245-247]. 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 [248-250]. Although generally believed to be less pathogenic than many other nosocomial organisms, *S. maltophilia* produces biofilm and virulence factors that can enable colonization or infection in vulnerable hosts, such as those with underlying lung disease and hematological malignancies [251, 252].

S. maltophilia infections pose management challenges very similar to those of CRAB infections. Firstly, 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 [253-257]. *S. maltophilia* is often recovered as a component of a polymicrobial infection – further challenging the need for targeted *S. maltophilia* therapy [248, 258]. 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, 259-264].

Second, treatment selection is hampered by the impressive number of antimicrobial resistance genes and gene mutations carried by *S. maltophilia* isolates [248, 250]. An L1 metallo β -lactamase and L2 serine β -lactamase render most conventional β -lactams ineffective against *S. maltophilia*. L1 hydrolyzes penicillins, cephalosporins, and carbapenems, but not aztreonam. L2 has extended cephalosporin activity as well as the ability to hydrolyze aztreonam [248]. *S. maltophilia* exhibits intrinsic resistance to aminoglycosides via chromosomal aminoglycoside acetyl transferase enzymes [265]. Furthermore, *S. maltophilia* can accumulate multidrug efflux pumps that reduce the activity of tetracyclines and fluoroquinolones, and chromosomal *Smqnr* genes that further reduce the effectiveness of fluoroquinolones [266].

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 seven agents against *S. maltophilia*: TMP-SMX, ticarcillin-clavulanate, ceftazidime, cefiderocol, levofloxacin, minocycline, and chloramphenicol. Ticarcillin-clavulanate manufacturing has been discontinued and chloramphenicol is rarely used in the United States due to significant toxicities [267], leaving five 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 methods that are commonly used in clinical laboratories [268, 269], 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, 270]. Incomplete *S. maltophilia* growth inhibition often occurs in polymyxin wells, suggestive of heteroresistance. Challenges exist in both the accuracy and reproducibility of polymyxin MICs [271, 272]. 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 β -lactamases produced by *S. maltophilia* likely to render ceftazidime ineffective. For moderate to severe infections, any of three 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](#), [Question 3](#), [Question 4](#), [Question 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 [273-275], 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 β -lactamases and L2 serine β -lactamases intrinsic to *S. maltophilia* [250] ([Question 7](#)).

In situations where *S. maltophilia* is causing moderate to severe disease, any of three approaches are suggested: (1) the use of combination therapy with at least two 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 ([Question 2](#), [Question 3](#), [Question 4](#), [Question 5](#)), or 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 [276-279]. 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 [280-282].

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* [283, 284], although there is an increasing recognition of *S. maltophilia* isolates resistant to TMP-SMX [278, 285]. 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 [282]. 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 [275, 286-288]; 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, one of two approaches are suggested: the use of combination therapy with a second agent added to TMP-SMX (e.g., 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* [276, 289]; 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 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 [279, 290-293]. 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 [290].

Surveillance studies report that minocycline and tigecycline have activity against approximately 70-90% of *S. maltophilia* isolates, with a lower MIC₉₀ generally observed for minocycline [279, 290-293]. 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 q12h compared to approximately 75% target attainment with tigecycline dosed at 100 mg intravenously q12h [291]. Both minocycline and tigecycline have extensive penetration into lung tissue [294-297].

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 [287]. Another observational study evaluating 119 patients with *S. maltophilia* infections who received

minocycline reported clinical success in approximately 80% of patients [298]; 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 [288]. 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 [174, 299, 300] ([Table 1](#)). At higher dosages (i.e., 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 [186-188]. 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 [250, 266]. Fluoroquinolone MICs may increase further as a result of overexpression of multidrug-resistant efflux pumps [283, 301-303]. Baseline susceptibility percentages of *S. maltophilia* to levofloxacin vary from approximately 30% to 80% in surveillance studies [278, 279, 293, 304]. Several studies have shown that *S. maltophilia* isolates that test susceptible to levofloxacin can develop elevated levofloxacin MICs during therapy [273-275, 305]. CLSI susceptibility criteria exist for levofloxacin against *S. maltophilia*, but not for ciprofloxacin or moxifloxacin [52].

Time-kill curves evaluating ciprofloxacin, levofloxacin, and moxifloxacin monotherapy generally indicate that these agents are inadequate at sustained inhibition of *S. maltophilia* growth [291, 306-309], but suggest that levofloxacin and moxifloxacin may have sufficient activity as components of combination therapy [278, 279]. 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 [291]. Levofloxacin and moxifloxacin were both associated with improved survival compared to 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 mcg/mL [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 [286]. When evaluated separately, there was no difference in mortality between ciprofloxacin or levofloxacin in combination with TMP-SMX. However, when pooling the fluoroquinolones, they appeared to be marginally significant in protecting against mortality compared to TMP-SMX, with mortality reported in 26% vs. 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 [275]. 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 amongst the fluoroquinolones. Adverse events related to fluoroquinolone use and the potential for the emergence of resistant *S. maltophilia* isolates during levofloxacin therapy should be considered when prescribing this agent [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 susceptibility of *S. maltophilia* isolates approaches 100%, even against isolates resistant to other commonly prescribed agents [200, 278, 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 [203, 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 five patients with *S. maltophilia* infections [207, 318]. All five patients were assigned to the cefiderocol arm, precluding comparisons between treatment regimens. Four out of five patients died, including two of three patients without CRAB co-infections. 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 post-licensure data become available to reexamine 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 or 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 β -lactamases intrinsic to *S. maltophilia* [250, 319-324]. The L1 metallo- β -lactamase hydrolyzes ceftazidime-avibactam but not aztreonam. The L2 serine β -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 β -lactamase genes intrinsic to *S. maltophilia* that are expected to render ceftazidime inactive.

Rationale

The panel does not suggest prescribing ceftazidime for the treatment of *S. maltophilia* infections, as intrinsic L1 and L2 β -lactamases are expected to render it ineffective. Almost 30-40% of *S. maltophilia* isolates test susceptible to ceftazidime using CLSI interpretive criteria [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 ceftazidime is unable to substantively prevent *S. maltophilia* growth [279]. Comparative effectiveness studies evaluating the role of ceftazidime against *S. maltophilia* infections are virtually non-existent [328]. An additional concern potentially related to the presence of inactivating β -lactamases is that ceftazidime MICs against *S. maltophilia* may be inaccurate and non-reproducible using susceptibility methods commonly employed by clinical microbiology laboratories [268, 269].

Notes

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

Endowment; and served as an advisor for Rempex and Antimicrobial Resistance Services. **D.v.D.** serves as member of the advisory group for Qpex Biopharma, Shionogi, and Merck; receives honoraria from Shionogi and Pfizer; receives other remuneration from the British Society for Antimicrobial Chemotherapy; receives research grants from Shionogi; served as an advisory board member for Entasis, Roche, Allergan, Utility, and Achaogen; served as non-promotional speaker for Entasis and Pfizer; received research funding from the National Institutes of Health and Merck; serves as editor-in-chief for *JAC-Antimicrobial Resistance*; and is on the program committee for the European Society of Clinical Microbiology and Infectious Diseases. **C.J.C.** served on the advisory board for Merck, Qpex Biopharma, and Shionogi; serves as an advisory Board member for Astellas, Cidara, and Scynexis; serves as a consultant for Needham & Associates; and receives research funding from Astellas and Merck. All other authors: no disclosures reported. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019, **2019**.
2. Sears CL, File TM, Alexander BD, et al. Charting the Path Forward: Development, Goals and Initiatives of the 2019 Infectious Diseases of America Strategic Plan. *Clin Infect Dis* **2019**; 69(12): e1-e7.
3. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum beta-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P. *aeruginosa*). *Clin Infect Dis* **2021**; 72(7): e169-e83.
4. Kadri SS, Lai YL, Warner S, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. *Lancet Infect Dis* **2021**; 21(2): 241-51.
5. Al-Dorzi HM, Asiri AM, Shimemri A, et al. Impact of empirical antimicrobial therapy on the outcome of critically ill patients with *Acinetobacter* bacteremia. *Ann Thorac Med* **2015**; 10(4): 256-62.
6. O'Donnell JN, Putra V, Lodise TP. Treatment of patients with serious infections due to carbapenem-resistant *Acinetobacter baumannii*: How viable are the current options? *Pharmacotherapy* **2021**; 41: 762-80.
7. Karaba SM, Goodman KE, Amoah J, Cosgrove SE, Tamma PD. StenoSCORE: Predicting *Stenotrophomonas maltophilia* Bloodstream Infections in the Hematologic Malignancy Population. *Antimicrob Agents Chemother* **2021**; 65(8): e0079321.
8. Butler DA, Biagi M, Tan X, Qasmieh S, Bulman ZP, Wenzler E. Multidrug Resistant *Acinetobacter baumannii*: Resistance by Any Other Name Would Still be Hard to Treat. *Curr Infect Dis Rep* **2019**; 21(12): 46.
9. Wenzler E, Goff DA, Humphries R, Goldstein EJC. Anticipating the Unpredictable: A Review of Antimicrobial Stewardship and *Acinetobacter* Infections. *Infect Dis Ther* **2017**; 6(2): 149-72.
10. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* **2011**; 52(5): e103-20.
11. Heil EL, Bork JT, Abbo LM, et al. Optimizing the Management of Uncomplicated Gram-negative Bloodstream Infections: Consensus Guidance Using a Modified Delphi Process [In press]. *Open Forum Infect Dis* **2021**; 8: ofab434.

12. Jacoby GA. AmpC beta-lactamases. Clin Microbiol Rev **2009**; 22(1): 161-82, Table of Contents.
13. Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ, Antibacterial Resistance Leadership G. A Primer on AmpC beta-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. Clin Infect Dis **2019**; 69(8): 1446-55.
14. Eliopoulos GM. Induction of beta-lactamases. J Antimicrob Chemother **1988**; 22 Suppl A: 37-44.
15. Bennett PM, Chopra I. Molecular basis of beta-lactamase induction in bacteria. Antimicrob Agents Chemother **1993**; 37(2): 153-8.
16. Jacobson KL, Cohen SH, Inciardi JF, et al. The relationship between antecedent antibiotic use and resistance to extended-spectrum cephalosporins in group I beta-lactamase-producing organisms. Clin Infect Dis **1995**; 21(5): 1107-13.
17. Honore N, Nicolas MH, Cole ST. Inducible cephalosporinase production in clinical isolates of Enterobacter cloacae is controlled by a regulatory gene that has been deleted from Escherichia coli. EMBO J **1986**; 5(13): 3709-14.
18. Philippon A, Arlet G, Jacoby GA. Plasmid-determined AmpC-type beta-lactamases. Antimicrob Agents Chemother **2002**; 46(1): 1-11.
19. Lindberg F, Westman L, Normark S. Regulatory components in Citrobacter freundii ampC beta-lactamase induction. Proc Natl Acad Sci U S A **1985**; 82(14): 4620-4.
20. Underwood S, Avison MB. Citrobacter koseri and Citrobacter amalonaticus isolates carry highly divergent beta-lactamase genes despite having high levels of biochemical similarity and 16S rRNA sequence homology. J Antimicrob Chemother **2004**; 53(6): 1076-80.
21. Petrella S, Clermont D, Casin I, Jarlier V, Sougakoff W. Novel class A beta-lactamase Sed-1 from Citrobacter sedlakii: genetic diversity of beta-lactamases within the Citrobacter genus. Antimicrob Agents Chemother **2001**; 45(8): 2287-98.
22. Matsen JM, Blazevic DJ, Ryan JA, Ewing WH. Characterization of indole-positive Proteus mirabilis. Appl Microbiol **1972**; 23(3): 592-4.
23. Choi SH, Lee JE, Park SJ, et al. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC beta-lactamase: implications for antibiotic use. Antimicrob Agents Chemother **2008**; 52(3): 995-1000.
24. Chow JW, Fine MJ, Shlaes DM, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med **1991**; 115(8): 585-90.
25. Kaye KS, Cosgrove S, Harris A, Eliopoulos GM, Carmeli Y. Risk factors for emergence of resistance to broad-spectrum cephalosporins among Enterobacter spp. Antimicrob Agents Chemother **2001**; 45(9): 2628-30.

26. Hilty M, Sendi P, Seiffert SN, et al. Characterisation and clinical features of *Enterobacter cloacae* bloodstream infections occurring at a tertiary care university hospital in Switzerland: is cefepime adequate therapy? *Int J Antimicrob Agents* **2013**; 41(3): 236-49.
27. Tamma PD, Girdwood SC, Gopaul R, et al. The use of cefepime for treating AmpC beta-lactamase-producing *Enterobacteriaceae*. *Clin Infect Dis* **2013**; 57(6): 781-8.
28. Kohlmann R, Bahr T, Gatermann SG. Species-specific mutation rates for ampC derepression in *Enterobacteriales* with chromosomally encoded inducible AmpC beta-lactamase. *J Antimicrob Chemother* **2018**; 73(6): 1530-6.
29. Liu C, Wang X, Chen Y, et al. Three *Yersinia enterocolitica* AmpD Homologs Participate in the Multi-Step Regulation of Chromosomal Cephalosporinase, AmpC. *Front Microbiol* **2016**; 7: 1282.
30. Seoane A, Francia MV, Garcia Lobo JM. Nucleotide sequence of the ampC-ampR region from the chromosome of *Yersinia enterocolitica*. *Antimicrob Agents Chemother* **1992**; 36(5): 1049-52.
31. Girlich D, Naas T, Bellais S, Poirel L, Karim A, Nordmann P. Heterogeneity of AmpC cephalosporinases of *Hafnia alvei* clinical isolates expressing inducible or constitutive ceftazidime resistance phenotypes. *Antimicrob Agents Chemother* **2000**; 44(11): 3220-3.
32. Sanders CC, Bradford PA, Ehrhardt AF, et al. Penicillin-binding proteins and induction of AmpC beta-lactamase. *Antimicrob Agents Chemother* **1997**; 41(9): 2013-5.
33. Weber DA, Sanders CC. Diverse potential of beta-lactamase inhibitors to induce class I enzymes. *Antimicrob Agents Chemother* **1990**; 34(1): 156-8.
34. Livermore DM, Oakton KJ, Carter MW, Warner M. Activity of ertapenem (MK-0826) versus *Enterobacteriaceae* with potent beta-lactamases. *Antimicrob Agents Chemother* **2001**; 45(10): 2831-7.
35. Papp-Wallace KM, Bethel CR, Caillon J, et al. Beyond Piperacillin-Tazobactam: Cefepime and AAI101 as a Potent beta-Lactam-beta-Lactamase Inhibitor Combination. *Antimicrob Agents Chemother* **2019**; 63(5): e00105-19.
36. Endimiani A, Doi Y, Bethel CR, et al. Enhancing resistance to cephalosporins in class C beta-lactamases: impact of Gly214Glu in CMY-2. *Biochemistry* **2010**; 49(5): 1014-23.
37. Drawz SM, Papp-Wallace KM, Bonomo RA. New beta-lactamase inhibitors: a therapeutic renaissance in an MDR world. *Antimicrob Agents Chemother* **2014**; 58(4): 1835-46.
38. Bush K, Bradford PA. Interplay between beta-lactamases and new beta-lactamase inhibitors. *Nat Rev Microbiol* **2019**; 17(5): 295-306.
39. Hancock RE, Bellido F. Antibacterial in vitro activity of fourth generation cephalosporins. *J Chemother* **1996**; 8 Suppl 2: 31-6.
40. Negri MC, Baquero F. In vitro selective concentrations of cefepime and ceftazidime for AmpC beta-lactamase hyperproducer *Enterobacter cloacae* variants. *Clin Microbiol Infect* **1999**; 5 Suppl 1: S25-S8.

41. Harris PN, Wei JY, Shen AW, et al. Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by *Enterobacter*, *Citrobacter* or *Serratia* species: a systematic review with meta-analysis. *J Antimicrob Chemother* **2016**; 71(2): 296-306.
42. Hancock RE, Bellido F. Factors involved in the enhanced efficacy against gram-negative bacteria of fourth generation cephalosporins. *J Antimicrob Chemother* **1992**; 29 Suppl A: 1-6.
43. Fung-Tomc JC, Graderski E, Huczko E, Dougherty TJ, Kessler RE, Bonner DP. Differences in the resistant variants of *Enterobacter cloacae* selected by extended-spectrum cephalosporins. *Antimicrob Agents Chemother* **1996**; 40(5): 1289-93.
44. Barnaud G, Benzerara Y, Gravis J, et al. Selection during cefepime treatment of a new cephalosporinase variant with extended-spectrum resistance to cefepime in an *Enterobacter aerogenes* clinical isolate. *Antimicrob Agents Chemother* **2004**; 48(3): 1040-2.
45. Song W, Moland ES, Hanson ND, Lewis JS, Jorgensen JH, Thomson KS. Failure of cefepime therapy in treatment of *Klebsiella pneumoniae* bacteremia. *J Clin Microbiol* **2005**; 43(9): 4891-4.
46. Limaye AP, Gautam RK, Black D, Fritsche TR. Rapid emergence of resistance to cefepime during treatment. *Clin Infect Dis* **1997**; 25(2): 339-40.
47. Charrel RN, Pages JM, De Micco P, Mallea M. Prevalence of outer membrane porin alteration in beta-lactam-antibiotic-resistant *Enterobacter aerogenes*. *Antimicrob Agents Chemother* **1996**; 40(12): 2854-8.
48. Siedner MJ, Galar A, Guzman-Suarez BB, et al. Cefepime vs other antibacterial agents for the treatment of *Enterobacter* species bacteremia. *Clin Infect Dis* **2014**; 58(11): 1554-63.
49. Tan SH, Ng TM, Chew KL, et al. Outcomes of treating AmpC-producing Enterobacterales bacteraemia with carbapenems vs. non-carbapenems. *Int J Antimicrob Agents* **2020**; 55(2): 105860.
50. Tamma PD, Rodriguez-Bano J. The Use of Noncarbapenem beta-Lactams for the Treatment of Extended-Spectrum beta-Lactamase Infections. *Clin Infect Dis* **2017**; 64(7): 972-80.
51. Lee NY, Lee CC, Li CW, et al. Cefepime Therapy for Monomicrobial *Enterobacter cloacae* Bacteremia: Unfavorable Outcomes in Patients Infected by Cefepime-Susceptible Dose-Dependent Isolates. *Antimicrob Agents Chemother* **2015**; 59(12): 7558-63.
52. Clinical and Laboratory Standards Institute. M100: Performance Standards for Antimicrobial Susceptibility Testing. 31 ed. Wayne, PA, **2021**.
53. Cheng MP, Lee RS, Cheng AP, et al. Beta-Lactam/Beta-Lactamase Inhibitor Therapy for Potential AmpC-Producing Organisms: A Systematic Review and Meta-Analysis. *Open Forum Infect Dis* **2019**; 6(7): ofz248.

54. Derrick C, Bookstaver PB, Lu ZK, et al. Multicenter, Observational Cohort Study Evaluating Third-Generation Cephalosporin Therapy for Bloodstream Infections Secondary to Enterobacter, Serratia, and Citrobacter Species. *Antibiotics (Basel)* **2020**; 9(5).
55. Chaubey VP, Pitout JD, Dalton B, Gregson DB, Ross T, Laupland KB. Clinical and microbiological characteristics of bloodstream infections due to AmpC beta-lactamase producing Enterobacteriaceae: an active surveillance cohort in a large centralized Canadian region. *BMC Infect Dis* **2014**; 14: 647.
56. Papp-Wallace KM, Mack AR, Taracila MA, Bonomo RA. Resistance to Novel beta-Lactam-beta-Lactamase Inhibitor Combinations: The "Price of Progress". *Infect Dis Clin North Am* **2020**; 34(4): 773-819.
57. Yahav D, Giske CG, Gramatniece A, Abodakpi H, Tam VH, Leibovici L. New beta-Lactam-beta-Lactamase Inhibitor Combinations. *Clin Microbiol Rev* **2020**; 34(1): e00115-20.
58. Cheng L, Nelson BC, Mehta M, et al. Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC beta-Lactamase-Producing Enterobacteriaceae. *Antimicrob Agents Chemother* **2017**; 61(6): e00276-17.
59. Stewart AG, Paterson DL, Young B, et al. Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC β -Lactamase-Producing Enterobacter spp, Citrobacter freundii, Morganella morganii, Providencia spp, or Serratia marcescens: A Pilot Multicenter Randomized Controlled Trial (MERINO-2). *Open Forum Infect Dis* **2021**; 8(8): ofab387.
60. Karlowsky JA, Biedenbach DJ, Kazmierczak KM, Stone GG, Sahm DF. Activity of Ceftazidime-Avibactam against Extended-Spectrum- and AmpC beta-Lactamase-Producing Enterobacteriaceae Collected in the INFORM Global Surveillance Study from 2012 to 2014. *Antimicrob Agents Chemother* **2016**; 60(5): 2849-57.
61. Zhanel GG, Lawrence CK, Adam H, et al. Imipenem-Relebactam and Meropenem-Vaborbactam: Two Novel Carbapenem-beta-Lactamase Inhibitor Combinations. *Drugs* **2018**; 78(1): 65-98.
62. Tselepis L, Langley GW, Aboklaish AF, et al. In vitro efficacy of imipenem-relebactam and cefepime-AAI101 against a global collection of ESBL-positive and carbapenemase-producing Enterobacteriaceae. *Int J Antimicrob Agents* **2020**; 56(1): 105925.
63. Isler B, Ezure Y, Romero JLG, Harris P, Stewart AG, Paterson DL. Is Ceftazidime/Avibactam an Option for Serious Infections Due to Extended-Spectrum-beta-Lactamase- and AmpC-Producing Enterobacteriales?: a Systematic Review and Meta-analysis. *Antimicrob Agents Chemother* **2020**; 65(1): e01052-20.
64. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections. *Clin Infect Dis* **2020**; 70(9): 1799-808.

65. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. *Infect Dis Ther* **2018**; 7(4): 439-55.
66. Tato M, Garcia-Castillo M, Bofarull AM, Canton R, Group CS. In vitro activity of ceftolozane/tazobactam against clinical isolates of *Pseudomonas aeruginosa* and Enterobacteriaceae recovered in Spanish medical centres: Results of the CENIT study. *International Journal of Antimicrobial Agents* **2015**; 46(5): 502-10.
67. Robin F, Auzou M, Bonnet R, et al. In Vitro Activity of Ceftolozane-Tazobactam against *Enterobacter cloacae* Complex Clinical Isolates with Different beta-Lactam Resistance Phenotypes. *Antimicrob Agents Chemother* **2018**; 62(9): e00675-18.
68. Stewart AG, Harris PNA, Chatfield MD, Littleford R, Paterson DL. Ceftolozane-tazobactam versus meropenem for definitive treatment of bloodstream infection due to extended-spectrum beta-lactamase (ESBL) and AmpC-producing Enterobacterales ("MERINO-3"): study protocol for a multicentre, open-label randomised non-inferiority trial. *Trials* **2021**; 22(1): 301.
69. Golden AR, Adam HJ, Baxter M, et al. In Vitro Activity of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacilli Isolated from Patients in Canadian Intensive Care Units. *Diagn Microbiol Infect Dis* **2020**; 97: 115012.
70. Karlowsky JA, Hackel MA, Tsuji M, Yamano Y, Echols R, Sahm DF. In Vitro Activity of Cefiderocol, a Siderophore Cephalosporin, Against Gram-Negative Bacilli Isolated by Clinical Laboratories in North America and Europe in 2015-2016: SIDERO-WT-2015. *Int J Antimicrob Agents* **2019**; 53(4): 456-66.
71. Kawai A, McElheny CL, Iovleva A, et al. Structural basis of reduced susceptibility to ceftazidime-avibactam and cefiderocol in *Enterobacter cloacae* due to AmpC R2 loop deletion. *Antimicrob Agents Chemother* **2020**; 64: e00198-20.
72. Shields RK, Iovleva A, Kline EG, Kawai A, McElheny CL, Doi Y. Clinical evolution of AmpC-mediated ceftazidime-avibactam and cefiderocol resistance in *Enterobacter cloacae* complex following exposure to cefepime. *Clin Infect Dis* **2020**; 71: 2713-6.
73. Tamma PD, Conley AT, Cosgrove SE, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. *JAMA Intern Med* **2019**; 179(3): 316-23.
74. Punjabi C, Tien V, Meng L, Deresinski S, Holubar M. Oral Fluoroquinolone or Trimethoprim-sulfamethoxazole vs. beta-lactams as Step-Down Therapy for Enterobacteriaceae Bacteremia: Systematic Review and Meta-analysis. *Open Forum Infect Dis* **2019**; 6(10): ofz364.
75. Procter and Gamble Pharmaceuticals, Inc. MACROBID - nitrofurantoin monohydrate and nitrofurantoin, macrocrystalline capsule [package insert]. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2009/020064s019lbl.pdf. Accessed 5 August 2020.

76. U.S. Food and Drug Administration. MONUROL (fosfomycin tromethamine) SACHET [package insert]. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2008/050717s005lbl.pdf. Accessed 5 August 2020.
77. Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. *JAMA* **2018**; 319(17): 1781-9.
78. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycyclines. *J Antimicrob Chemother* **2006**; 58(2): 256-65.
79. Fox MT, Melia MT, Same RG, Conley AT, Tamma PD. A Seven-Day Course of TMP-SMX May Be as Effective as a Seven-Day Course of Ciprofloxacin for the Treatment of Pyelonephritis. *Am J Med* **2017**; 130(7): 842-5.
80. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. *JAMA* **2000**; 283(12): 1583-90.
81. Goodlet KJ, Benhalima FZ, Nailor MD. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? *Antimicrob Agents Chemother* **2018**; 63(1): e02165-18.
82. Ito R, Mustapha MM, Tomich AD, et al. Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal fosA Gene. *mBio* **2017**; 8(4): e00749-17.
83. Elliott ZS, Barry KE, Cox HL, et al. The Role of fosA in Challenges with Fosfomycin Susceptibility Testing of Multispecies *Klebsiella pneumoniae* Carbapenemase-Producing Clinical Isolates. *J Clin Microbiol* **2019**; 57(10): e00634-19.
84. Vijayakumar S, Biswas I, Veeraraghavan B. Accurate identification of clinically important *Acinetobacter* spp.: an update. *Future Sci OA* **2019**; 5(6): FSO395.
85. Turton JF, Ward ME, Woodford N, et al. The role of ISAba1 in expression of OXA carbapenemase genes in *Acinetobacter baumannii*. *FEMS Microbiol Lett* **2006**; 258(1): 72-7.
86. Penwell WF, Shapiro AB, Giacobbe RA, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2015**; 59(3): 1680-9.
87. McLeod SM, Shapiro AB, Moussa SH, et al. Frequency and Mechanism of Spontaneous Resistance to Sulbactam Combined with the Novel beta-Lactamase Inhibitor ETX2514 in Clinical Isolates of *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2018**; 62(2): e01576-17.
88. Krizova L, Poirel L, Nordmann P, Nemec A. TEM-1 beta-lactamase as a source of resistance to sulbactam in clinical strains of *Acinetobacter baumannii*. *J Antimicrob Chemother* **2013**; 68(12): 2786-91.

89. Nemec A, Dolzani L, Brisse S, van den Broek P, Dijkshoorn L. Diversity of aminoglycoside-resistance genes and their association with class 1 integrons among strains of pan-European *Acinetobacter baumannii* clones. *J Med Microbiol* **2004**; 53(Pt 12): 1233-40.
90. Bonomo RA, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. *Clin Infect Dis* **2006**; 43 Suppl 2: S49-56.
91. Castanheira M, Deshpande LM, Woosley LN, Serio AW, Krause KM, Flamm RK. Activity of plazomicin compared with other aminoglycosides against isolates from European and adjacent countries, including Enterobacteriaceae molecularly characterized for aminoglycoside-modifying enzymes and other resistance mechanisms. *J Antimicrob Chemother* **2018**; 73(12): 3346-54.
92. Lenhard JR, Smith NM, Bulman ZP, et al. High-Dose Ampicillin-Sulbactam Combinations Combat Polymyxin-Resistant *Acinetobacter baumannii* in a Hollow-Fiber Infection Model. *Antimicrob Agents Chemother* **2017**; 61(3): e01268-16.
93. Beganovic M, Daffinee KE, Luther MK, LaPlante KL. Minocycline Alone and in Combination with Polymyxin B, Meropenem, and Sulbactam against Carbapenem-Susceptible and -Resistant *Acinetobacter baumannii* in an In Vitro Pharmacodynamic Model. *Antimicrob Agents Chemother* **2021**; 65(3).
94. Abdul-Mutakabbir JC, Yim J, Nguyen L, et al. In Vitro Synergy of Colistin in Combination with Meropenem or Tigecycline against Carbapenem-Resistant *Acinetobacter baumannii*. *Antibiotics (Basel)* **2021**; 10(7).
95. Rodriguez-Hernandez MJ, Cuberos L, Pichardo C, et al. Sulbactam efficacy in experimental models caused by susceptible and intermediate *Acinetobacter baumannii* strains. *J Antimicrob Chemother* **2001**; 47(4): 479-82.
96. Makris D, Petinaki E, Tsolaki V, et al. Colistin versus Colistin Combined with Ampicillin-Sulbactam for Multiresistant *Acinetobacter baumannii* Ventilator-associated Pneumonia Treatment: An Open-label Prospective Study. *Indian J Crit Care Med* **2018**; 22(2): 67-77.
97. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant *Acinetobacter baumannii*. *Scand J Infect Dis* **2007**; 39(1): 38-43.
98. Assimakopoulos SF, Karamouzou V, Lefkaditi A, et al. Triple combination therapy with high-dose ampicillin/sulbactam, high-dose tigecycline and colistin in the treatment of ventilator-associated pneumonia caused by pan-drug resistant *Acinetobacter baumannii*: a case series study. *Infez Med* **2019**; 27(1): 11-6.
99. Liu J, Shu Y, Zhu F, et al. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant *Acinetobacter baumannii* infections: A systematic review and network meta-analysis. *J Glob Antimicrob Resist* **2021**; 24: 136-47.

100. Jung SY, Lee SH, Lee SY, et al. Antimicrobials for the treatment of drug-resistant *Acinetobacter baumannii* pneumonia in critically ill patients: a systemic review and Bayesian network meta-analysis. *Crit Care* **2017**; 21(1): 319.
101. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *J Infect* **2008**; 56(6): 432-6.
102. Yilmaz GR, Guven T, Guner R, et al. Colistin alone or combined with sulbactam or carbapenem against *A. baumannii* in ventilator-associated pneumonia. *J Infect Dev Ctries* **2015**; 9(5): 476-85.
103. Kaye KS, University of Michigan. Trial for the Treatment of Extensively Drug-Resistant Gram-negative Bacilli. Available at: <https://clinicaltrials.gov/ct2/show/NCT01597973>. Accessed 14 August 2021.
104. Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis* **2018**; 18(4): 391-400.
105. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. *Antimicrob Agents Chemother* **2014**; 58(9): 5598-601.
106. Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. *Clin Infect Dis* **2013**; 57(3): 349-58.
107. Aydemir H, Akduman D, Piskin N, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Epidemiol Infect* **2013**; 141(6): 1214-22.
108. Park HJ, Cho JH, Kim HJ, Han SH, Jeong SH, Byun MK. Colistin monotherapy versus colistin/rifampicin combination therapy in pneumonia caused by colistin-resistant *Acinetobacter baumannii*: A randomised controlled trial. *J Glob Antimicrob Resist* **2019**; 17: 66-71.
109. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwinai N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria. *J Antimicrob Chemother* **2010**; 65(12): 2645-9.
110. Kollef MH, Ricard JD, Roux D, et al. A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia: IASIS Trial. *Chest* **2017**; 151(6): 1239-46.

111. Niederman MS, Alder J, Bassetti M, et al. Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial. *Lancet Infect Dis* **2020**; 20(3): 330-40.
112. Maselli DJ, Keyt H, Restrepo MI. Inhaled Antibiotic Therapy in Chronic Respiratory Diseases. *Int J Mol Sci* **2017**; 18(5): 1062.
113. Rouby JJ, Bouhemad B, Monsel A, et al. Aerosolized antibiotics for ventilator-associated pneumonia: lessons from experimental studies. *Anesthesiology* **2012**; 117(6): 1364-80.
114. Wenzler E, Fraidenburg DR, Scardina T, Danziger LH. Inhaled Antibiotics for Gram-Negative Respiratory Infections. *Clin Microbiol Rev* **2016**; 29(3): 581-632.
115. Biagi M, Butler D, Tan X, Qasmieh S, Wenzler E. A Breath of Fresh Air in the Fog of Antimicrobial Resistance: Inhaled Polymyxins for Gram-Negative Pneumonia. *Antibiotics (Basel)* **2019**; 8(1).
116. Ku NS, Lee SH, Lim YS, et al. In vivo efficacy of combination of colistin with fosfomycin or minocycline in a mouse model of multidrug-resistant *Acinetobacter baumannii* pneumonia. *Sci Rep* **2019**; 9(1): 17127.
117. Yang YS, Lee Y, Tseng KC, et al. In Vivo and In Vitro Efficacy of Minocycline-Based Combination Therapy for Minocycline-Resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2016**; 60(7): 4047-54.
118. Bowers DR, Cao H, Zhou J, et al. Assessment of minocycline and polymyxin B combination against *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2015**; 59(5): 2720-5.
119. Montero A, Ariza J, Corbella X, et al. Antibiotic combinations for serious infections caused by carbapenem-resistant *Acinetobacter baumannii* in a mouse pneumonia model. *J Antimicrob Chemother* **2004**; 54(6): 1085-91.
120. Bernabeu-Wittel M, Pichardo C, Garcia-Curiel A, et al. Pharmacokinetic/pharmacodynamic assessment of the in-vivo efficacy of imipenem alone or in combination with amikacin for the treatment of experimental multiresistant *Acinetobacter baumannii* pneumonia. *Clin Microbiol Infect* **2005**; 11(4): 319-25.
121. Joly-Guillou ML, Wolff M, Farinotti R, Bryskier A, Carbon C. In vivo activity of levofloxacin alone or in combination with imipenem or amikacin in a mouse model of *Acinetobacter baumannii* pneumonia. *J Antimicrob Chemother* **2000**; 46(5): 827-30.
122. Zusman O, Avni T, Leibovici L, et al. Systematic review and meta-analysis of in vitro synergy of polymyxins and carbapenems. *Antimicrob Agents Chemother* **2013**; 57(10): 5104-11.
123. Mohammadi M, Khayat H, Sayehmiri K, et al. Synergistic Effect of Colistin and Rifampin Against Multidrug Resistant *Acinetobacter baumannii*: A Systematic Review and Meta-Analysis. *Open Microbiol J* **2017**; 11: 63-71.

124. Lenhard JR, Nation RL, Tsuji BT. Synergistic combinations of polymyxins. *Int J Antimicrob Agents* **2016**; 48(6): 607-13.
125. Falagas ME, Rafailidis PI, Ioannidou E, et al. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients. *Int J Antimicrob Agents* **2010**; 35(2): 194-9.
126. Ye JJ, Lin HS, Kuo AJ, et al. The clinical implication and prognostic predictors of tigecycline treatment for pneumonia involving multidrug-resistant *Acinetobacter baumannii*. *J Infect* **2011**; 63(5): 351-61.
127. Tseng YC, Wang JT, Wu FL, Chen YC, Chie WC, Chang SC. Prognosis of adult patients with bacteremia caused by extensively resistant *Acinetobacter baumannii*. *Diagn Microbiol Infect Dis* **2007**; 59(2): 181-90.
128. Hernandez-Torres A, Garcia-Vazquez E, Gomez J, Canteras M, Ruiz J, Yague G. Multidrug and carbapenem-resistant *Acinetobacter baumannii* infections: Factors associated with mortality. *Med Clin (Barc)* **2012**; 138(15): 650-5.
129. Poulakou G, Kontopidou FV, Paramythiotou E, et al. Tigecycline in the treatment of infections from multi-drug resistant gram-negative pathogens. *J Infect* **2009**; 58(4): 273-84.
130. Kalin G, Alp E, Akin A, Coskun R, Doganay M. Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Infection* **2014**; 42(1): 37-42.
131. Liang CA, Lin YC, Lu PL, Chen HC, Chang HL, Sheu CC. Antibiotic strategies and clinical outcomes in critically ill patients with pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. *Clin Microbiol Infect* **2018**; 24(8): 908 e1- e7.
132. Kim WY, Moon JY, Huh JW, et al. Comparable Efficacy of Tigecycline versus Colistin Therapy for Multidrug-Resistant and Extensively Drug-Resistant *Acinetobacter baumannii* Pneumonia in Critically Ill Patients. *PLoS One* **2016**; 11(3): e0150642.
133. Tasbakan MS, Pullukcu H, Sipahi OR, Tasbakan MI, Aydemir S, Bacakoglu F. Is tigecyclin a good choice in the treatment of multidrug-resistant *Acinetobacter baumannii* pneumonia? *J Chemother* **2011**; 23(6): 345-9.
134. Shields RK, Clancy CJ, Gillis LM, et al. Epidemiology, clinical characteristics and outcomes of extensively drug-resistant *Acinetobacter baumannii* infections among solid organ transplant recipients. *PLoS One* **2012**; 7(12): e52349.
135. Kuo LC, Lai CC, Liao CH, et al. Multidrug-resistant *Acinetobacter baumannii* bacteraemia: clinical features, antimicrobial therapy and outcome. *Clin Microbiol Infect* **2007**; 13(2): 196-8.
136. Simsek F, Gedik H, Yildirmak MT, et al. Colistin against colistin-only-susceptible *Acinetobacter baumannii*-related infections: Monotherapy or combination therapy? *Indian J Med Microbiol* **2012**; 30(4): 448-52.

137. Lim SK, Lee SO, Choi SH, et al. The outcomes of using colistin for treating multidrug resistant *Acinetobacter* species bloodstream infections. *J Korean Med Sci* **2011**; 26(3): 325-31.
138. Niu T, Luo Q, Li Y, Zhou Y, Yu W, Xiao Y. Comparison of Tigecycline or Cefoperazone/Sulbactam therapy for bloodstream infection due to Carbapenem-resistant *Acinetobacter baumannii*. *Antimicrob Resist Infect Control* **2019**; 8: 52.
139. Batirel A, Balkan, Il, Karabay O, et al. Comparison of colistin-carbapenem, colistin-sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections. *Eur J Clin Microbiol Infect Dis* **2014**; 33(8): 1311-22.
140. Amat T, Gutierrez-Pizarra A, Machuca I, et al. The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant *Acinetobacter baumannii*. *Clin Microbiol Infect* **2018**; 24(6): 630-4.
141. Lopez-Cortes LE, Cisneros JM, Fernandez-Cuenca F, et al. Monotherapy versus combination therapy for sepsis due to multidrug-resistant *Acinetobacter baumannii*: analysis of a multicentre prospective cohort. *J Antimicrob Chemother* **2014**; 69(11): 3119-26.
142. Dickstein Y, Lellouche J, Ben Dalak Amar M, et al. Treatment Outcomes of Colistin- and Carbapenem-resistant *Acinetobacter baumannii* Infections: An Exploratory Subgroup Analysis of a Randomized Clinical Trial. *Clin Infect Dis* **2019**; 69(5): 769-76.
143. Petrosillo N, Giannella M, Antonelli M, et al. Clinical experience of colistin-glycopeptide combination in critically ill patients infected with Gram-negative bacteria. *Antimicrob Agents Chemother* **2014**; 58(2): 851-8.
144. Freire MP, de Oliveira Garcia D, Garcia CP, et al. Bloodstream infection caused by extensively drug-resistant *Acinetobacter baumannii* in cancer patients: high mortality associated with delayed treatment rather than with the degree of neutropenia. *Clin Microbiol Infect* **2016**; 22(4): 352-8.
145. Sandri AM, Landersdorfer CB, Jacob J, et al. Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens. *Clin Infect Dis* **2013**; 57(4): 524-31.
146. Noguchi JK, Gill MA. Sulbactam: a beta-lactamase inhibitor. *Clin Pharm* **1988**; 7(1): 37-51.
147. Reddy T, Chopra T, Marchaim D, et al. Trends in antimicrobial resistance of *Acinetobacter baumannii* isolates from a metropolitan Detroit health system. *Antimicrob Agents Chemother* **2010**; 54(5): 2235-8.
148. Castanheira M, Mendes RE, Jones RN. Update on *Acinetobacter* species: mechanisms of antimicrobial resistance and contemporary in vitro activity of minocycline and other treatment options. *Clin Infect Dis* **2014**; 59 Suppl 6: S367-73.

149. Jaruratanasirikul S, Wongpoowarak W, Aeinlang N, Jullangkoon M. Pharmacodynamics modeling to optimize dosage regimens of sulbactam. *Antimicrob Agents Chemother* **2013**; 57(7): 3441-4.
150. Chuang YC, Cheng CY, Sheng WH, et al. Effectiveness of tigecycline-based versus colistin-based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis. *BMC Infect Dis* **2014**; 14: 102.
151. Ku K, Pogue JM, Moshos J, et al. Retrospective evaluation of colistin versus tigecycline for the treatment of *Acinetobacter baumannii* and/or carbapenem-resistant Enterobacteriaceae infections. *Am J Infect Control* **2012**; 40(10): 983-7.
152. Kwon SH, Ahn HL, Han OY, La HO. Efficacy and safety profile comparison of colistin and tigecycline on the extensively drug resistant *Acinetobacter baumannii*. *Biol Pharm Bull* **2014**; 37(3): 340-6.
153. Forrest A, Garonzik SM, Thamlikitkul V, et al. Pharmacokinetic/Toxicodynamic Analysis of Colistin-Associated Acute Kidney Injury in Critically Ill Patients. *Antimicrob Agents Chemother* **2017**; 61(11): e01367-17.
154. Horcajada JP, Sorli L, Luque S, et al. Validation of a colistin plasma concentration breakpoint as a predictor of nephrotoxicity in patients treated with colistin methanesulfonate. *Int J Antimicrob Agents* **2016**; 48(6): 725-7.
155. Dubrovskaya Y, Prasad N, Lee Y, Esaian D, Figueroa DA, Tam VH. Risk factors for nephrotoxicity onset associated with polymyxin B therapy. *J Antimicrob Chemother* **2015**; 70(6): 1903-7.
156. Pogue JM, Lee J, Marchaim D, et al. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. *Clin Infect Dis* **2011**; 53(9): 879-84.
157. Wagenlehner F, Lucenteforte E, Pea F, et al. Systematic review on estimated rates of nephrotoxicity and neurotoxicity in patients treated with polymyxins. *Clin Microbiol Infect* **2021**.
158. Qureshi ZA, Hittle LE, O'Hara JA, et al. Colistin-resistant *Acinetobacter baumannii*: beyond carbapenem resistance. *Clin Infect Dis* **2015**; 60(9): 1295-303.
159. Nation RL, Rigatto MHP, Falci DR, Zavascki AP. Polymyxin Acute Kidney Injury: Dosing and Other Strategies to Reduce Toxicity. *Antibiotics (Basel)* **2019**; 8(1): 24.
160. Cheah SE, Wang J, Nguyen VT, Turnidge JD, Li J, Nation RL. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in mouse thigh and lung infection models: smaller response in lung infection. *J Antimicrob Chemother* **2015**; 70(12): 3291-7.
161. Landersdorfer CB, Wang J, Wirth V, et al. Pharmacokinetics/pharmacodynamics of systemically administered polymyxin B against *Klebsiella pneumoniae* in mouse thigh and lung infection models. *J Antimicrob Chemother* **2018**; 73(2): 462-8.

162. Montero A, Ariza J, Corbella X, et al. Efficacy of colistin versus beta-lactams, aminoglycosides, and rifampin as monotherapy in a mouse model of pneumonia caused by multiresistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2002**; 46(6): 1946-52.
163. Rojas LJ, Salim M, Cober E, et al. Colistin Resistance in Carbapenem-Resistant *Klebsiella pneumoniae*: Laboratory Detection and Impact on Mortality. *Clin Infect Dis* **2017**; 64(6): 711-8.
164. Marchaim D, Chopra T, Pogue JM, et al. Outbreak of colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae* in metropolitan Detroit, Michigan. *Antimicrob Agents Chemother* **2011**; 55(2): 593-9.
165. Lesho E, Yoon EJ, McGann P, et al. Emergence of colistin-resistance in extremely drug-resistant *Acinetobacter baumannii* containing a novel *pmrCAB* operon during colistin therapy of wound infections. *J Infect Dis* **2013**; 208(7): 1142-51.
166. Lopez-Rojas R, McConnell MJ, Jimenez-Mejias ME, Dominguez-Herrera J, Fernandez-Cuenca F, Pachon J. Colistin resistance in a clinical *Acinetobacter baumannii* strain appearing after colistin treatment: effect on virulence and bacterial fitness. *Antimicrob Agents Chemother* **2013**; 57(9): 4587-9.
167. Fluit AC, Florijn A, Verhoef J, Milatovic D. Presence of tetracycline resistance determinants and susceptibility to tigecycline and minocycline. *Antimicrob Agents Chemother* **2005**; 49(4): 1636-8.
168. Petersen PJ, Jacobus NV, Weiss WJ, Sum PE, Testa RT. In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936). *Antimicrob Agents Chemother* **1999**; 43(4): 738-44.
169. Montana S, Vilacoba E, Traglia GM, et al. Genetic Variability of AdeRS Two-Component System Associated with Tigecycline Resistance in XDR-*Acinetobacter baumannii* Isolates. *Curr Microbiol* **2015**; 71(1): 76-82.
170. Pournaras S, Koumaki V, Gennimata V, Kouskouni E, Tsakris A. In Vitro Activity of Tigecycline Against *Acinetobacter baumannii*: Global Epidemiology and Resistance Mechanisms. *Adv Exp Med Biol* **2016**; 897: 1-14.
171. Allen JC. Minocycline. *Ann Intern Med* **1976**; 85(4): 482-7.
172. Flamm RK, Castanheira M, Streit JM, Jones RN. Minocycline activity tested against *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* species complex isolates from a global surveillance program (2013). *Diagn Microbiol Infect Dis* **2016**; 85(3): 352-5.
173. Flamm RK, Shortridge D, Castanheira M, Sader HS, Pfaller MA. In Vitro Activity of Minocycline against U.S. Isolates of *Acinetobacter baumannii*-*Acinetobacter calcoaceticus* Species Complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* Complex: Results from the SENTRY Antimicrobial Surveillance Program, 2014 to 2018. *Antimicrob Agents Chemother* **2019**; 63(11): e01154-19.

174. Goff DA, Bauer KA, Mangino JE. Bad bugs need old drugs: a stewardship program's evaluation of minocycline for multidrug-resistant *Acinetobacter baumannii* infections. *Clin Infect Dis* **2014**; 59(Suppl 6): S381-7.
175. Chan JD, Graves JA, Dellit TH. Antimicrobial treatment and clinical outcomes of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *J Intensive Care Med* **2010**; 25(6): 343-8.
176. Ritchie DJ, Garavaglia-Wilson A. A review of intravenous minocycline for treatment of multidrug-resistant *Acinetobacter* infections. *Clin Infect Dis* **2014**; 59 Suppl 6: S374-80.
177. Pogue JM, Neelakanta A, Mynatt RP, Sharma S, Lephart P, Kaye KS. Carbapenem-resistance in gram-negative bacilli and intravenous minocycline: an antimicrobial stewardship approach at the Detroit Medical Center. *Clin Infect Dis* **2014**; 59(Suppl 6): S388-93.
178. Wood GC, Hanes SD, Boucher BA, Croce MA, Fabian TC. Tetracyclines for treating multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Intensive Care Med* **2003**; 29(11): 2072-6.
179. Livermore DM, Mushtaq S, Warner M, Woodford N. In Vitro Activity of Eravacycline against Carbapenem-Resistant Enterobacteriaceae and *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2016**; 60(6): 3840-4.
180. Lee YT, Wang YC, Kuo SC, et al. Multicenter Study of Clinical Features of Breakthrough *Acinetobacter* Bacteremia during Carbapenem Therapy. *Antimicrob Agents Chemother* **2017**; 61(9): e00931-17.
181. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J Antimicrob Chemother* **2011**; 66(9): 1963-71.
182. Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis* **2010**; 68(2): 140-51.
183. Zha L, Pan L, Guo J, French N, Villanueva EV, Tefsen B. Effectiveness and Safety of High Dose Tigecycline for the Treatment of Severe Infections: A Systematic Review and Meta-Analysis. *Adv Ther* **2020**; 37(3): 1049-64.
184. Chen Z, Shi X. Adverse events of high-dose tigecycline in the treatment of ventilator-associated pneumonia due to multidrug-resistant pathogens. *Medicine (Baltimore)* **2018**; 97(38): e12467.
185. De Pascale G, Montini L, Pennisi M, et al. High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. *Crit Care* **2014**; 18(3): R90.
186. Qvist N, Warren B, Leister-Tebbe H, et al. Efficacy of tigecycline versus ceftriaxone plus metronidazole for the treatment of complicated intra-abdominal infections: results from a randomized, controlled trial. *Surg Infect (Larchmt)* **2012**; 13(2): 102-9.

187. Towfigh S, Pasternak J, Poirier A, Leister H, Babinchak T. A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections. *Clin Microbiol Infect* **2010**; 16(8): 1274-81.
188. Fanning WL, Gump DW. Distressing side-effects of minocycline hydrochloride. *Arch Intern Med* **1976**; 136(7): 761-2.
189. Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible *Acinetobacter baumannii*. *Int J Antimicrob Agents* **2018**; 51(1): 62-4.
190. Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Quale J. Activity of eravacycline against Enterobacteriaceae and *Acinetobacter baumannii*, including multidrug-resistant isolates, from New York City. *Antimicrob Agents Chemother* **2015**; 59(3): 1802-5.
191. Solomkin J, Evans D, Slepavicius A, et al. Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. *JAMA Surg* **2017**; 152(3): 224-32.
192. Solomkin JS, Gardovskis J, Lawrence K, et al. IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs Meropenem in the Treatment of Complicated Intraabdominal Infections. *Clin Infect Dis* **2019**; 69(6): 921-9.
193. Pfaller MA, Huband MD, Shortridge D, Flamm RK. Surveillance of Omadacycline Activity Tested against Clinical Isolates from the United States and Europe as Part of the 2016 SENTRY Antimicrobial Surveillance Program. *Antimicrob Agents Chemother* **2018**; 62(4): e02327-17.
194. Pfaller MA, Huband MD, Shortridge D, Flamm RK. Surveillance of Omadacycline Activity Tested against Clinical Isolates from the United States and Europe: Report from the SENTRY Antimicrobial Surveillance Program, 2016 to 2018. *Antimicrob Agents Chemother* **2020**; 64(5): e02488-19.
195. Noel AR, Attwood M, Bowker KE, MacGowan AP. In vitro pharmacodynamics of omadacycline against *Escherichia coli* and *Acinetobacter baumannii*. *J Antimicrob Chemother* **2021**; 76(3): 667-70.
196. Dong D, Zheng Y, Chen Q, et al. In vitro activity of omadacycline against pathogens isolated from Mainland China during 2017-2018. *Eur J Clin Microbiol Infect Dis* **2020**; 39(8): 1559-72.
197. Lesho E, Wortmann G, Moran K, Craft D. Fatal *Acinetobacter baumannii* infection with discordant carbapenem susceptibility. *Clin Infect Dis* **2005**; 41(5): 758-9.
198. Jones RN, Sader HS, Fritsche TR, Rhomberg PR. Carbapenem susceptibility discords among *Acinetobacter* isolates. *Clin Infect Dis* **2006**; 42(1): 158.

199. Esterly JS, Qi C, Malczynski M, Scheetz MH. Predictability of doripenem susceptibility in *Acinetobacter baumannii* isolates based on other carbapenem susceptibilities and bla OXA gene status. *Pharmacotherapy* **2010**; 30(4): 354-60.
200. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against Carbapenem-Nonsusceptible and Multidrug-Resistant Isolates of Gram-Negative Bacilli Collected Worldwide in 2014 to 2016. *Antimicrob Agents Chemother* **2018**; 62(2): e01968-17.
201. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against a Recent Collection of Clinically Relevant Gram-Negative Bacilli from North America and Europe, Including Carbapenem-Nonsusceptible Isolates (SIDERO-WT-2014 Study). *Antimicrob Agents Chemother* **2017**; 61(9): e00093-17.
202. Dobias J, Denervaud-Tendon V, Poirel L, Nordmann P. Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens. *Eur J Clin Microbiol Infect Dis* **2017**; 36(12): 2319-27.
203. Nakamura R, Ito-Horiyama T, Takemura M, et al. In Vivo Pharmacodynamic Study of Cefiderocol, a Novel Parenteral Siderophore Cephalosporin, in Murine Thigh and Lung Infection Models. *Antimicrob Agents Chemother* **2019**; 63(9): e02031-18.
204. Ito A, Sato T, Ota M, et al. In Vitro Antibacterial Properties of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacteria. *Antimicrob Agents Chemother* **2018**; 62(1): e01454-17.
205. Ito A, Kohira N, Bouchillon SK, et al. In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria. *J Antimicrob Chemother* **2016**; 71(3): 670-7.
206. Monogue ML, Tsuji M, Yamano Y, Echols R, Nicolau DP. Efficacy of Humanized Exposures of Cefiderocol (S-649266) against a Diverse Population of Gram-Negative Bacteria in a Murine Thigh Infection Model. *Antimicrob Agents Chemother* **2017**; 61(11): e01022-17.
207. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis* **2021**; 21(2): 226-40.
208. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* **2021**; 21(2): 213-25.
209. McCreary EK, Heil EL, Tamma PD. New Perspectives on Antimicrobial Agents: Cefiderocol. *Antimicrob Agents Chemother* **2021**; 65(8): e0217120.
210. Wehrli W. Rifampin: mechanisms of action and resistance. *Rev Infect Dis* **1983**; 5 Suppl 3: S407-11.

211. Luna B, Trebosc V, Lee B, et al. A nutrient-limited screen unmasks rifabutin hyperactivity for extensively drug-resistant *Acinetobacter baumannii*. *Nat Microbiol* **2020**; 5(9): 1134-43.
212. Cheng J, Yan J, Reyna Z, et al. Synergistic Rifabutin and Colistin Reduce Emergence of Resistance When Treating *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2021**; 65(4): e02204-20.
213. Trebosc V, Schellhorn B, Schill J, et al. In vitro activity of rifabutin against 293 contemporary carbapenem-resistant *Acinetobacter baumannii* clinical isolates and characterization of rifabutin mode of action and resistance mechanisms. *J Antimicrob Chemother* **2020**; 75(12): 3552-62.
214. Phillips MC, Wald-Dickler N, Loomis K, Luna BM, Spellberg B. Pharmacology, Dosing, and Side Effects of Rifabutin as a Possible Therapy for Antibiotic-Resistant *Acinetobacter* Infections. *Open Forum Infect Dis* **2020**; 7(11): ofaa460.
215. Rothstein DM. Rifamycins, Alone and in Combination. *Cold Spring Harb Perspect Med* **2016**; 6(7).
216. Lu Q, Luo R, Bodin L, et al. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Anesthesiology* **2012**; 117(6): 1335-47.
217. Kwa AL, Loh C, Low JG, Kurup A, Tam VH. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Clin Infect Dis* **2005**; 41(5): 754-7.
218. Falagas ME, Siempos, II, Rafailidis PI, Korbila IP, Ioannidou E, Michalopoulos A. Inhaled colistin as monotherapy for multidrug-resistant gram (-) nosocomial pneumonia: a case series. *Respir Med* **2009**; 103(5): 707-13.
219. Choi HK, Kim YK, Kim HY, Uh Y. Inhaled colistin for treatment of pneumonia due to colistin-only-susceptible *Acinetobacter baumannii*. *Yonsei Med J* **2014**; 55(1): 118-25.
220. Hsieh TC, Chen FL, Ou TY, Jean SS, Lee WS. Role of aerosolized colistin methanesulfonate therapy for extensively-drug-resistant *Acinetobacter baumannii* complex pneumonia and airway colonization. *J Microbiol Immunol Infect* **2016**; 49(4): 523-30.
221. Kang CH, Tsai CM, Wu TH, et al. Colistin inhalation monotherapy for ventilator-associated pneumonia of *Acinetobacter baumannii* in prematurity. *Pediatr Pulmonol* **2014**; 49(4): 381-8.
222. Chen YM, Fang WF, Kao HC, et al. Influencing factors of successful eradication of multidrug-resistant *Acinetobacter baumannii* in the respiratory tract with aerosolized colistin. *Biomed J* **2014**; 37(5): 314-20.
223. Jean SS, Hsieh TC, Lee WS, Hsueh PR, Hsu CW, Lam C. Treatment outcomes of patients with non-bacteremic pneumonia caused by extensively drug-resistant *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex isolates: Is there any benefit of adding

- tigecycline to aerosolized colistimethate sodium? *Medicine (Baltimore)* **2018**; 97(39): e12278.
224. Tumbarello M, De Pascale G, Trecarichi EM, et al. Effect of aerosolized colistin as adjunctive treatment on the outcomes of microbiologically documented ventilator-associated pneumonia caused by colistin-only susceptible gram-negative bacteria. *Chest* **2013**; 144(6): 1768-75.
 225. Kofteridis DP, Alexopoulou C, Valachis A, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. *Clin Infect Dis* **2010**; 51(11): 1238-44.
 226. Korkmaz Ekren P, Toreyin N, Sayiner A, Bacakoglu F, Colistin Study G. The Role of Aerolized Colistin in the Treatment of Hospital-Acquired Pneumonia: Experience of Multicenter From Turkey. *Crit Care Med* **2016**; 44(5): e304.
 227. Demirdal T, Sari US, Nemli SA. Is inhaled colistin beneficial in ventilator associated pneumonia or nosocomial pneumonia caused by *Acinetobacter baumannii*? *Ann Clin Microbiol Antimicrob* **2016**; 15: 11.
 228. Abdellatif S, Trifi A, Daly F, Mahjoub K, Nasri R, Ben Lakhal S. Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial. *Ann Intensive Care* **2016**; 6(1): 26.
 229. Kim YK, Lee JH, Lee HK, et al. Efficacy of nebulized colistin-based therapy without concurrent intravenous colistin for ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. *J Thorac Dis* **2017**; 9(3): 555-67.
 230. Michalopoulos A, Fotakis D, Virtzili S, et al. Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: a prospective study. *Respir Med* **2008**; 102(3): 407-12.
 231. Kalin G, Alp E, Coskun R, Demiraslan H, Gundogan K, Doganay M. Use of high-dose IV and aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia: do we really need this treatment? *J Infect Chemother* **2012**; 18(6): 872-7.
 232. Naesens R, Vlieghe E, Verbrugghe W, Jorens P, Ieven M. A retrospective observational study on the efficacy of colistin by inhalation as compared to parenteral administration for the treatment of nosocomial pneumonia associated with multidrug-resistant *Pseudomonas aeruginosa*. *BMC Infect Dis* **2011**; 11: 317.
 233. Lin CC, Liu TC, Kuo CF, Liu CP, Lee CM. Aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* pneumonia: experience in a tertiary care hospital in northern Taiwan. *J Microbiol Immunol Infect* **2010**; 43(4): 323-31.
 234. Doshi NM, Cook CH, Mount KL, et al. Adjunctive aerosolized colistin for multi-drug resistant gram-negative pneumonia in the critically ill: a retrospective study. *BMC Anesthesiol* **2013**; 13(1): 45.

235. Mastoraki A, Douka E, Kriaras I, Stravopodis G, Manoli H, Geroulanos S. *Pseudomonas aeruginosa* susceptible only to colistin in intensive care unit patients. *Surg Infect (Larchmt)* **2008**; 9(2): 153-60.
236. Berlana D, Llop JM, Fort E, Badia MB, Jodar R. Use of colistin in the treatment of multiple-drug-resistant gram-negative infections. *Am J Health Syst Pharm* **2005**; 62(1): 39-47.
237. Korbila IP, Michalopoulos A, Rafailidis PI, Nikita D, Samonis G, Falagas ME. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. *Clin Microbiol Infect* **2010**; 16(8): 1230-6.
238. Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. *Crit Care* **2005**; 9(1): R53-9.
239. Ganapathy H, Pal SK, Teare L, Dziewulski P. Use of colistin in treating multi-resistant Gram-negative organisms in a specialised burns unit. *Burns* **2010**; 36(4): 522-7.
240. Falagas ME, Kasiakou SK, Kofteridis DP, Roditakis G, Samonis G. Effectiveness and nephrotoxicity of intravenous colistin for treatment of patients with infections due to polymyxin-only-susceptible (POS) gram-negative bacteria. *Eur J Clin Microbiol Infect Dis* **2006**; 25(9): 596-9.
241. Kuo SC, Lee YT, Yang SP, et al. Eradication of multidrug-resistant *Acinetobacter baumannii* from the respiratory tract with inhaled colistin methanesulfonate: a matched case-control study. *Clin Microbiol Infect* **2012**; 18(9): 870-6.
242. Motaouakkil S, Charra B, Hachimi A, et al. Colistin and rifampicin in the treatment of nosocomial infections from multiresistant *Acinetobacter baumannii*. *J Infect* **2006**; 53(4): 274-8.
243. Jang JY, Kwon HY, Choi EH, Lee WY, Shim H, Bae KS. Efficacy and toxicity of high-dose nebulized colistin for critically ill surgical patients with ventilator-associated pneumonia caused by multidrug-resistant *Acinetobacter baumannii*. *J Crit Care* **2017**; 40: 251-6.
244. Boisson M, Jacobs M, Gregoire N, et al. Comparison of intrapulmonary and systemic pharmacokinetics of colistin methanesulfonate (CMS) and colistin after aerosol delivery and intravenous administration of CMS in critically ill patients. *Antimicrob Agents Chemother* **2014**; 58(12): 7331-9.
245. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* **2016**; 63(5): e61-e111.
246. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy

- (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). *Pharmacotherapy* **2019**; 39(1): 10-39.
247. Rello J, Sole-Lleonart C, Rouby JJ, et al. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. *Clin Microbiol Infect* **2017**; 23(9): 629-39.
 248. Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. *Clin Microbiol Rev* **2012**; 25(1): 2-41.
 249. Groschel MI, Meehan CJ, Barilar I, et al. The phylogenetic landscape and nosocomial spread of the multidrug-resistant opportunist *Stenotrophomonas maltophilia*. *Nat Commun* **2020**; 11(1): 2044.
 250. Mojica MF, Rutter JD, Taracila M, et al. Population Structure, Molecular Epidemiology, and beta-Lactamase Diversity among *Stenotrophomonas maltophilia* Isolates in the United States. *mBio* **2019**; 10(4): e00405-19.
 251. Klimkaite L, Armalyte J, Skerniskyte J, Suziedeliene E. The Toxin-Antitoxin Systems of the Opportunistic Pathogen *Stenotrophomonas maltophilia* of Environmental and Clinical Origin. *Toxins (Basel)* **2020**; 12(10).
 252. Trifonova A, Strateva T. *Stenotrophomonas maltophilia* - a low-grade pathogen with numerous virulence factors. *Infect Dis (Lond)* **2019**; 51(3): 168-78.
 253. Paez JI, Costa SF. Risk factors associated with mortality of infections caused by *Stenotrophomonas maltophilia*: a systematic review. *J Hosp Infect* **2008**; 70(2): 101-8.
 254. Osawa K, Shigemura K, Kitagawa K, Tokimatsu I, Fujisawa M. Risk factors for death from *Stenotrophomonas maltophilia* bacteremia. *J Infect Chemother* **2018**; 24(8): 632-6.
 255. Falagas ME, Kastoris AC, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Dimopoulos G. Attributable mortality of *Stenotrophomonas maltophilia* infections: a systematic review of the literature. *Future Microbiol* **2009**; 4(9): 1103-9.
 256. Jeon YD, Jeong WY, Kim MH, et al. Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia. *Medicine (Baltimore)* **2016**; 95(31): e4375.
 257. Araoka H, Baba M, Yoneyama A. Risk factors for mortality among patients with *Stenotrophomonas maltophilia* bacteremia in Tokyo, Japan, 1996-2009. *Eur J Clin Microbiol Infect Dis* **2010**; 29(5): 605-8.
 258. Cho SY, Lee DG, Choi SM, et al. *Stenotrophomonas maltophilia* bloodstream infection in patients with hematologic malignancies: a retrospective study and in vitro activities of antimicrobial combinations. *BMC Infect Dis* **2015**; 15: 69.

259. Micozzi A, Venditti M, Monaco M, et al. Bacteremia due to *Stenotrophomonas maltophilia* in patients with hematologic malignancies. *Clin Infect Dis* **2000**; 31(3): 705-11.
260. Widmer AF, Kern WV, Roth JA, et al. Early versus late onset bloodstream infection during neutropenia after high-dose chemotherapy for hematologic malignancy. *Infection* **2019**; 47(5): 837-45.
261. Safdar A, Rolston KV. *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin Infect Dis* **2007**; 45(12): 1602-9.
262. Kim SH, Cha MK, Kang CI, et al. Pathogenic significance of hemorrhagic pneumonia in hematologic malignancy patients with *Stenotrophomonas maltophilia* bacteremia: clinical and microbiological analysis. *Eur J Clin Microbiol Infect Dis* **2019**; 38(2): 285-95.
263. Tada K, Kurosawa S, Hiramoto N, et al. *Stenotrophomonas maltophilia* infection in hematopoietic SCT recipients: high mortality due to pulmonary hemorrhage. *Bone Marrow Transplant* **2013**; 48(1): 74-9.
264. Araoka H, Fujii T, Izutsu K, et al. Rapidly progressive fatal hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in hematologic malignancy. *Transpl Infect Dis* **2012**; 14(4): 355-63.
265. Okazaki A, Avison MB. Aph(3')-IIc, an aminoglycoside resistance determinant from *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother* **2007**; 51(1): 359-60.
266. Gordon NC, Wareham DW. Novel variants of the Smqr family of quinolone resistance genes in clinical isolates of *Stenotrophomonas maltophilia*. *J Antimicrob Chemother* **2010**; 65(3): 483-9.
267. Barnhill AE, Brewer MT, Carlson SA. Adverse effects of antimicrobials via predictable or idiosyncratic inhibition of host mitochondrial components. *Antimicrob Agents Chemother* **2012**; 56(8): 4046-51.
268. Khan A, Pettaway C, Dien Bard J, Arias CA, Bhatti MM, Humphries RM. Evaluation of the Performance of Manual Antimicrobial Susceptibility Testing Methods and Disk Breakpoints for *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother* **2021**; 65: e02631-20.
269. Khan A, Arias CA, Abbott A, Dien Bard J, Bhatti MM, Humphries RM. Evaluation of the Vitek 2, Phoenix and Microscan for Antimicrobial Susceptibility Testing of *Stenotrophomonas maltophilia*. *J Clin Microbiol* **2021**; 59: e0065421.
270. Satlin MJ, Lewis JS, Weinstein MP, et al. Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing Position Statements on Polymyxin B and Colistin Clinical Breakpoints. *Clin Infect Dis* **2020**; 71(9): e523-e9.
271. Martinez-Servat S, Yero D, Huedo P, et al. Heterogeneous Colistin-Resistance Phenotypes Coexisting in *Stenotrophomonas maltophilia* Isolates Influence Colistin Susceptibility Testing. *Front Microbiol* **2018**; 9: 2871.

272. Moskowitz SM, Garber E, Chen Y, et al. Colistin susceptibility testing: evaluation of reliability for cystic fibrosis isolates of *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*. *J Antimicrob Chemother* **2010**; 65(7): 1416-23.
273. Cho SY, Kang CI, Kim J, et al. Can levofloxacin be a useful alternative to trimethoprim-sulfamethoxazole for treating *Stenotrophomonas maltophilia* bacteremia? *Antimicrob Agents Chemother* **2014**; 58(1): 581-3.
274. Baek JH, Kim CO, Jeong SJ, et al. Clinical factors associated with acquisition of resistance to levofloxacin in *Stenotrophomonas maltophilia*. *Yonsei Med J* **2014**; 55(4): 987-93.
275. Nys C, Cherabuddi K, Venugopalan V, Klinker KP. Clinical and Microbiologic Outcomes in Patients with Monomicrobial *Stenotrophomonas maltophilia* Infections. *Antimicrob Agents Chemother* **2019**; 63(11): e00788-19.
276. Zelenitsky SA, Iacovides H, Ariano RE, Harding GK. Antibiotic combinations significantly more active than monotherapy in an in vitro infection model of *Stenotrophomonas maltophilia*. *Diagn Microbiol Infect Dis* **2005**; 51(1): 39-43.
277. Yu VL, Felegie TP, Yee RB, Pasculle AW, Taylor FH. Synergistic interaction in vitro with use of three antibiotics simultaneously against *Pseudomonas maltophilia*. *J Infect Dis* **1980**; 142(4): 602-7.
278. Biagi M, Vialichka A, Jurkovic M, et al. Activity of Cefiderocol Alone and in Combination with Levofloxacin, Minocycline, Polymyxin B, or Trimethoprim-Sulfamethoxazole against Multidrug-Resistant *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother* **2020**; 64(9).
279. Wei C, Ni W, Cai X, Zhao J, Cui J. Evaluation of Trimethoprim/Sulfamethoxazole (SXT), Minocycline, Tigecycline, Moxifloxacin, and Ceftazidime Alone and in Combinations for SXT-Susceptible and SXT-Resistant *Stenotrophomonas maltophilia* by In Vitro Time-Kill Experiments. *PLoS One* **2016**; 11(3): e0152132.
280. Shah MD, Coe KE, El Boghdadly Z, et al. Efficacy of combination therapy versus monotherapy in the treatment of *Stenotrophomonas maltophilia* pneumonia. *J Antimicrob Chemother* **2019**; 74(7): 2055-9.
281. Araoka H, Baba M, Okada C, Abe M, Kimura M, Yoneyama A. Evaluation of trimethoprim-sulfamethoxazole based combination therapy against *Stenotrophomonas maltophilia*: in vitro effects and clinical efficacy in cancer patients. *Int J Infect Dis* **2017**; 58: 18-21.
282. Muder RR, Harris AP, Muller S, et al. Bacteremia due to *Stenotrophomonas* (*Xanthomonas*) *maltophilia*: a prospective, multicenter study of 91 episodes. *Clin Infect Dis* **1996**; 22(3): 508-12.
283. Chang YT, Lin CY, Chen YH, Hsueh PR. Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options. *Front Microbiol* **2015**; 6: 893.

284. Cai B, Tillotson G, Benjumea D, Callahan P, Echols R. The Burden of Bloodstream Infections due to *Stenotrophomonas maltophilia* in the United States: A Large, Retrospective Database Study. *Open Forum Infect Dis* **2020**; 7(5): ofaa141.
285. Al-Jasser AM. *Stenotrophomonas maltophilia* resistant to trimethoprim-sulfamethoxazole: an increasing problem. *Ann Clin Microbiol Antimicrob* **2006**; 5: 23.
286. Ko JH, Kang CI, Cornejo-Juarez P, et al. Fluoroquinolones versus trimethoprim-sulfamethoxazole for the treatment of *Stenotrophomonas maltophilia* infections: a systematic review and meta-analysis. *Clin Microbiol Infect* **2019**; 25(5): 546-54.
287. Hand E, Davis H, Kim T, Duhon B. Monotherapy with minocycline or trimethoprim/sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *J Antimicrob Chemother* **2016**; 71(4): 1071-5.
288. Tekce YT, Erbay A, Cabadak H, Sen S. Tigecycline as a therapeutic option in *Stenotrophomonas maltophilia* infections. *J Chemother* **2012**; 24(3): 150-4.
289. Brown GR. Cotrimoxazole - optimal dosing in the critically ill. *Ann Intensive Care* **2014**; 4: 13.
290. Biagi M, Tan X, Wu T, et al. Activity of Potential Alternative Treatment Agents for *Stenotrophomonas maltophilia* Isolates Nonsusceptible to Levofloxacin and/or Trimethoprim-Sulfamethoxazole. *J Clin Microbiol* **2020**; 58(2).
291. Wei C, Ni W, Cai X, Cui J. A Monte Carlo pharmacokinetic/pharmacodynamic simulation to evaluate the efficacy of minocycline, tigecycline, moxifloxacin, and levofloxacin in the treatment of hospital-acquired pneumonia caused by *Stenotrophomonas maltophilia*. *Infect Dis (Lond)* **2015**; 47(12): 846-51.
292. Looney WJ, Narita M, Muhlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. *Lancet Infect Dis* **2009**; 9(5): 312-23.
293. Farrell DJ, Sader HS, Jones RN. Antimicrobial susceptibilities of a worldwide collection of *Stenotrophomonas maltophilia* isolates tested against tigecycline and agents commonly used for *S. maltophilia* infections. *Antimicrob Agents Chemother* **2010**; 54(6): 2735-7.
294. Burkhardt O, Rauch K, Kaever V, Hadem J, Kielstein JT, Welte T. Tigecycline possibly underdosed for the treatment of pneumonia: a pharmacokinetic viewpoint. *Int J Antimicrob Agents* **2009**; 34(1): 101-2.
295. Watanabe A, Anzai Y, Niitsuma K, Saito M, Yanase K, Nakamura M. Penetration of minocycline hydrochloride into lung tissue and sputum. *Chemotherapy* **2001**; 47(1): 1-9.
296. De Pascale G, Lisi L, Ciotti GMP, et al. Pharmacokinetics of high-dose tigecycline in critically ill patients with severe infections. *Ann Intensive Care* **2020**; 10(1): 94.
297. Crandon JL, Kim A, Nicolau DP. Comparison of tigecycline penetration into the epithelial lining fluid of infected and uninfected murine lungs. *J Antimicrob Chemother* **2009**; 64(4): 837-9.

298. Jacobson S, Junco Noa L, Wallace MR, Bowman MC. Clinical outcomes using minocycline for *Stenotrophomonas maltophilia* infections. *J Antimicrob Chemother* **2016**; 71(12): 3620.
299. Falagas ME, Vardakas KZ, Tsiveriotis KP, Triarides NA, Tansarli GS. Effectiveness and safety of high-dose tigecycline-containing regimens for the treatment of severe bacterial infections. *Int J Antimicrob Agents* **2014**; 44(1): 1-7.
300. Lodise TP, Van Wart S, Sund ZM, et al. Pharmacokinetic and Pharmacodynamic Profiling of Minocycline for Injection following a Single Infusion in Critically Ill Adults in a Phase IV Open-Label Multicenter Study (ACUMIN). *Antimicrob Agents Chemother* **2021**; 65(3).
301. Zhang L, Li XZ, Poole K. Multiple antibiotic resistance in *Stenotrophomonas maltophilia*: involvement of a multidrug efflux system. *Antimicrob Agents Chemother* **2000**; 44(2): 287-93.
302. Wu CJ, Lu HF, Lin YT, Zhang MS, Li LH, Yang TC. Substantial Contribution of SmeDEF, SmeVWX, SmQnr, and Heat Shock Response to Fluoroquinolone Resistance in Clinical Isolates of *Stenotrophomonas maltophilia*. *Front Microbiol* **2019**; 10: 822.
303. Garcia-Leon G, Ruiz de Alegria Puig C, Garcia de la Fuente C, Martinez-Martinez L, Martinez JL, Sanchez MB. High-level quinolone resistance is associated with the overexpression of smeVWX in *Stenotrophomonas maltophilia* clinical isolates. *Clin Microbiol Infect* **2015**; 21(5): 464-7.
304. Hamdi AM, Fida M, Abu Saleh OM, Beam E. *Stenotrophomonas* Bacteremia Antibiotic Susceptibility and Prognostic Determinants: Mayo Clinic 10-Year Experience. *Open Forum Infect Dis* **2020**; 7(1): ofaa008.
305. Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *Antimicrob Agents Chemother* **2014**; 58(1): 176-82.
306. Grillon A, Schramm F, Kleinberg M, Jehl F. Comparative Activity of Ciprofloxacin, Levofloxacin and Moxifloxacin against *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* Assessed by Minimum Inhibitory Concentrations and Time-Kill Studies. *PLoS One* **2016**; 11(6): e0156690.
307. Ba BB, Feghali H, Arpin C, Saux MC, Quentin C. Activities of ciprofloxacin and moxifloxacin against *Stenotrophomonas maltophilia* and emergence of resistant mutants in an in vitro pharmacokinetic-pharmacodynamic model. *Antimicrob Agents Chemother* **2004**; 48(3): 946-53.
308. Bonfiglio G, Cascone C, Azzarelli C, Cafiso V, Marchetti F, Stefani S. Levofloxacin in vitro activity and time-kill evaluation of *Stenotrophomonas maltophilia* clinical isolates. *J Antimicrob Chemother* **2000**; 45(1): 115-7.
309. Giamarellos-Bourboulis EJ, Karnesis L, Galani I, Giamarellou H. In vitro killing effect of moxifloxacin on clinical isolates of *Stenotrophomonas maltophilia* resistant to trimethoprim-sulfamethoxazole. *Antimicrob Agents Chemother* **2002**; 46(12): 3997-9.

310. Imoto W, Kaneko Y, Yamada K, et al. A mouse model of rapidly progressive fatal haemorrhagic pneumonia caused by *Stenotrophomonas maltophilia*. *J Glob Antimicrob Resist* **2020**; 23: 450-5.
311. Fratoni AJ, Nicolau DP, Kuti JL. Levofloxacin pharmacodynamics against *Stenotrophomonas maltophilia* in a neutropenic murine thigh infection model: implications for susceptibility breakpoint revision. *J Antimicrob Chemother* **2021**.
312. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. *JAMA Intern Med* **2017**; 177(9): 1308-15.
313. Hsueh SC, Lee YJ, Huang YT, Liao CH, Tsuji M, Hsueh PR. In vitro activities of cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam and other comparative drugs against imipenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, all associated with bloodstream infections in Taiwan. *J Antimicrob Chemother* **2019**; 74(2): 380-6.
314. Yamano Y. In Vitro Activity of Cefiderocol Against a Broad Range of Clinically Important Gram-negative Bacteria. *Clin Infect Dis* **2019**; 69(Suppl 7): S544-S51.
315. Rolston KVI, Gerges B, Shelburne S, Aitken SL, Raad I, Prince RA. Activity of Cefiderocol and Comparators against Isolates from Cancer Patients. *Antimicrob Agents Chemother* **2020**; 64(5): e01955-19.
316. Kawaguchi N, Katsube T, Echols R, Wajima T. Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses of Cefiderocol, a Parenteral Siderophore Cephalosporin, in Patients with Pneumonia, Bloodstream Infection/Sepsis, or Complicated Urinary Tract Infection. *Antimicrob Agents Chemother* **2021**; 65(3): e01437-20.
317. Chen IH, Kidd JM, Abdelraouf K, Nicolau DP. Comparative In Vivo Antibacterial Activity of Human-Simulated Exposures of Cefiderocol and Ceftazidime against *Stenotrophomonas maltophilia* in the Murine Thigh Model. *Antimicrob Agents Chemother* **2019**; 63: e01558-19.
318. Heil EL, Tamma PD. Cefiderocol: the Trojan horse has arrived but will Troy fall? *Lancet Infect Dis* **2021**; 21(2): 153-5.
319. Biagi M, Lamm D, Meyer K, et al. Activity of Aztreonam in Combination with Avibactam, Clavulanate, Relebactam, and Vaborbactam against Multidrug-Resistant *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother* **2020**; 64(12): e00297-20.
320. Mojica MF, Papp-Wallace KM, Taracila MA, et al. Avibactam Restores the Susceptibility of Clinical Isolates of *Stenotrophomonas maltophilia* to Aztreonam. *Antimicrob Agents Chemother* **2017**; 61(10): e00777-17.
321. Mojica MF, Ouellette CP, Leber A, et al. Successful Treatment of Bloodstream Infection Due to Metallo-beta-Lactamase-Producing *Stenotrophomonas maltophilia* in a Renal Transplant Patient. *Antimicrob Agents Chemother* **2016**; 60(9): 5130-4.

322. Lin Q, Zou H, Chen X, et al. Avibactam potentiated the activity of both ceftazidime and aztreonam against *S. maltophilia* clinical isolates in vitro. *BMC Microbiol* **2021**; 21(1): 60.
323. Sader HS, Duncan LR, Arends SJR, Carvalhaes CG, Castanheira M. Antimicrobial Activity of Aztreonam-Avibactam and Comparator Agents When Tested against a Large Collection of Contemporary *Stenotrophomonas maltophilia* Isolates from Medical Centers Worldwide. *Antimicrob Agents Chemother* **2020**; 64(11): e01433-20.
324. Emeraud C, Escaut L, Boucly A, et al. Aztreonam plus Clavulanate, Tazobactam, or Avibactam for Treatment of Infections Caused by Metallo-beta-Lactamase-Producing Gram-Negative Bacteria. *Antimicrob Agents Chemother* **2019**; 63(5): e00010-19.
325. Diarra A, Pascal L, Carpentier B, et al. Successful use of avibactam and aztreonam combination for a multiresistant *Stenotrophomonas maltophilia* bloodstream infection in a patient with idiopathic medullary aplasia. *Infect Dis Now* **2021**; 51: 637-8.
326. Cowart MC, Ferguson CL. Optimization of Aztreonam in Combination With Ceftazidime/Avibactam in a Cystic Fibrosis Patient With Chronic *Stenotrophomonas maltophilia* Pneumonia Using Therapeutic Drug Monitoring: A Case Study. *Ther Drug Monit* **2021**; 43(2): 146-9.
327. Lodise TP, Smith NM, O'Donnell N, et al. Determining the optimal dosing of a novel combination regimen of ceftazidime/avibactam with aztreonam against NDM-1-producing Enterobacteriaceae using a hollow-fibre infection model. *J Antimicrob Chemother* **2020**; 75(9): 2622-32.
328. Falagas ME, Valkimadi PE, Huang YT, Matthaïou DK, Hsueh PR. Therapeutic options for *Stenotrophomonas maltophilia* infections beyond co-trimoxazole: a systematic review. *J Antimicrob Chemother* **2008**; 62(5): 889-94.