Clinical Infectious Diseases

IDSA GUIDELINES

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

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The Infectious Diseases Society of America (IDSA) is committed to providing up-to-date guidance on the treatment of antimicrobial-resistant (AMR) infections. This guidance document focuses on infections caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E), AmpC β-lactamase-producing Enterobacterales (AmpC-E), carbapenem-resistant Enterobacterales (CRE), *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR *P. aeruginosa*), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Stenotrophomonas maltophilia*. This updated document replaces previous versions of the guidance document. A panel of 6 infectious diseases specialists with expertise in managing antimicrobial-resistant infections formulated questions about the treatment of infections caused by ESBL-E, AmpC-E, CRE, DTR *P. aeruginosa*, CRAB, and *S. maltophilia*. Because of differences in the epidemiology of AMR and availability of specific anti-infectives internationally, this document focuses on the treatment of AMR infections in the United States. Preferred and alternative suggested treatment approaches are provided with accompanying rationales, assuming the causative organism has been identified and antibiotic susceptibility results are known. Approaches to empiric treatment, transitioning to oral therapy, duration of therapy, and other management considerations are discussed briefly. Suggested approaches apply for both adult and pediatric populations, although suggested antibiotic dosages are provided only for adults. The field of AMR is highly dynamic. Consultation with an infectious diseases specialist is recommended for the treatment of AMR infections. This document is current as of December 31, 2023 and will be updated periodically. The most current version of this document, including date of publication, is available at www.idsociety.org/practice-guideline/amr-guidance/.

Keywords. ESBL; *Pseudomonas aeruginosa*; CRAB; *Stenotrophomonas maltophilia*.

Antimicrobial-resistant (AMR) infections are a global crisis. Internationally, approximately 1.3 million deaths were estimated to be directly attributable to AMR pathogens in 2019 [1]. In the United States, AMR pathogens caused more than 2.8 million infections and over 35 000 deaths annually from 2012 through 2017, according to the Centers for Disease Control and Prevention (CDC) Antibiotic Resistance Threats in the United States Report [2].

As an alternative to practice guidelines, the Infectious Diseases Society of America (IDSA) has endorsed developing more narrowly focused guidance documents for the treatment of infections where data may not be very robust and continue to rapidly evolve – such as with AMR. Guidance documents are prepared by a small team of experts, who answer questions about treatment based on a comprehensive (but not necessarily systematic) review of the literature, clinical experience, and expert opinion. Documents are made available online and updated annually.

In the present document, guidance is provided on the treatment of infections caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E), AmpC β-lactamase-producing Enterobacterales (AmpC-E), carbapenem-resistant Enterobacterales (CRE), *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR *P. aeruginosa*), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Stenotrophomonas maltophilia*. Many of these pathogens have been designated urgent or serious threats by the CDC [2]. Each pathogen causes a wide range of infections that are encountered in United States hospitals of

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all sizes, and that carry with them significant morbidity and mortality.

Guidance is presented in the form of answers to a series of clinical questions for each pathogen. Although brief descriptions of notable clinical trials, resistance mechanisms, and antimicrobial susceptibility testing (AST) methods are included, the document does not provide a comprehensive review of these topics. GRADE methodology (ie, Grading of Recommendations, Assessment, Development, and Evaluations) are not employed. Due to differences in the molecular epidemiology of resistance and availability of specific antibiotics internationally, treatment suggestions are geared toward AMR infections in the United States. This guidance document applies to both adult and pediatric populations. Suggested antibiotic dosing for adults with AMR infections, assuming normal renal and hepatic function, are provided in Table 1. Pediatric dosing is not provided. The content of this document is current as of 31 December 2023. The most current version of this IDSA guidance document and corresponding date of publication is available at: www.idsociety.org/practice-guideline/amr-guidance.

GENERAL MANAGEMENT RECOMMENDATIONS

Suggested treatment approaches in this guidance document assume that the causative organism has been identified and that in vitro activity of antibiotics is demonstrated. If 2 antibiotics are equally effective, important considerations in selecting a specific agent include safety, cost, convenience, and local formulary availability.

Complicated Urinary Tract Infection Definition

In this document, the term complicated urinary tract infections (cUTI) refers to UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in an adolescent or adult male. In general, the panel suggests cUTI be treated with similar agents and for similar treatment durations as pyelonephritis. For cUTI where the source has been controlled (eg, removal of a Foley catheter) and ongoing concerns for urinary stasis or indwelling urinary hardware are no longer present, it is reasonable to select antibiotic agents and treatment durations similar to those that would be selected for uncomplicated cystitis, with day 1 of therapy being the day source control occurred.

Empiric Therapy

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

For all organisms, but for DTR *P. aeruginosa*, CRAB, and *S. maltophilia* in particular, a distinction between bacterial colonization and infection is important because unnecessary antibiotic therapy will only further the development of resistance and may cause unnecessary antibiotic related harm to patients. Commonly selected empiric antibiotic regimens are generally not active against CRAB and *S. maltophilia* infections. The decision to target treatment for CRAB and/or *S. maltophilia* in empiric antibiotic regimens should involve a careful risk-benefit analysis after reviewing previous culture results, clinical presentation, individual host risk factors, and antibiotic-specific adverse event profiles.

Duration of Therapy and Transitioning to Oral Therapy

Recommendations on durations of therapy are not provided, but clinicians are advised that the duration of therapy should not differ for infections caused by organisms with resistant phenotypes compared to infections caused by more susceptible phenotypes [4]. After AST results are available, it may become apparent that inactive antibiotic therapy was initiated empirically. This may impact the duration of therapy. For example, uncomplicated cystitis is typically a mild infection [5]. If an antibiotic not active against the causative organism was administered empirically for uncomplicated cystitis, but clinical improvement nonetheless occurred, it is generally not necessary to repeat a urine culture, change the antibiotic regimen, or extend the planned treatment course. However, for all other infections, if AST results indicate a potentially inactive agent was initiated empirically, a change to an active regimen for a full treatment course (dated from the start of active therapy) is suggested. 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 AMR infections, as with the treatment of any bacterial infection. Finally, whenever possible, transitioning to oral therapy should be considered (assuming intravenous [IV] therapy was initially prescribed), 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 [6].

Table 1. Suggested Dosing of Antibiotics for the Treatment of Antimicrobial-resistant Infections in Adults, Assuming Normal Renal and Hepatic function[a,b]

Amikacin	**Uncomplicated cystitis**: 15 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 15 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Ampicillin-sulbactam	**Administer a total daily dose of 9 grams of sulbactam via 1 of the following regimens:** 9 grams of ampicillin-sulbactam (6 grams ampicillin, 3 grams sulbactam) IV every 8 h, infused over 4 h **OR** 27 grams of ampicillin-sulbactam (18 grams ampicillin, 9 grams sulbactam) IV as a continuous infusion over 24 h Additional information in Supplementary Material.
Cefepime	**Uncomplicated cystitis:** 1 gram IV every 8 h, infused over 30 min **All other infections:** 2 grams IV every 8 h, infused over 3 h
Cefiderocol	2 grams IV every 8 h, infused over 3 h CrCL ≥120 mL/min: 2 grams IV every 6 h, infused over 3 h
Ceftazidime-avibactam	2.5 grams IV every 8 h, infused over 3 h
Ceftazidime-avibactam PLUS aztreonam	**Ceftazidime-avibactam:** 2.5 grams IV every 8 h, infused over 3 h **PLUS** (administered simultaneously via Y-site administration) **Aztreonam:** 2 grams IV every 8 h, infused over 3 h Additional information in Supplementary Material.
Ceftolozane-tazobactam	**Uncomplicated Cystitis:** 1.5 grams IV every 8 h, infused over 1 h **All other infections:** 3 grams IV every 8 h, infused over 3 h
Ciprofloxacin	**Uncomplicated cystitis:** 400 milligrams IV every 12 h or 500 milligrams PO every 12 h **All other infections:** 400 milligrams IV every 8 h **OR** 750 milligrams PO every 12 h
Colistin	Refer to international consensus guidelines on polymyxins (Tsuji BT, et al Pharmacotherapy. 2019; 39:10–39).
Eravacycline	1 mg/kg per dose IV every 12 h
Ertapenem	1 gram IV every 24 h, infused over 30 min Additional information in Supplementary Material.
Fosfomycin	**Uncomplicated cystitis:** 3 grams PO as a single dose
Gentamicin	**Uncomplicated cystitis**: 5 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 7 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Imipenem-cilastatin	**Uncomplicated cystitis**: 500 mg IV every 6 h, infused over 30 min **All other infections:** 500 mg IV every 6 h, infused over 3 h (if feasible) Additional information in Supplementary Material.
Imipenem-cilastatin-relebactam	1.25 grams IV every 6 h, infused over 30 min Additional information in Supplementary Material.
Levofloxacin	**All infections:** 750 milligrams IV/PO every 24 h
Meropenem	**Uncomplicated cystitis:** 1 grams IV every 8 h, infused over 30 min **All other infections:** 2 grams IV every 8 h, infused over 3 h (if feasible) Additional information in Supplementary Material.
Meropenem-vaborbactam	4 grams IV every 8 h, infused over 3 h
Minocycline	200 milligrams IV/PO every 12 h
Nitrofurantoin	**Macrocrystal/monohydrate (Macrobid®)**: 100 mg PO every 12 h **Oral suspension**: 50 milligrams PO every 6 h
Plazomicin	**Uncomplicated cystitis:** 15 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 15 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Polymyxin B	Refer to international consensus guidelines on polymyxins (Tsuji BT, et al Pharmacotherapy. 2019;39:10–39).
Sulbactam-durlobactam	Sulbactam 1 gram/durlobactam 1 gram (2 grams total) IV every 6 h, infused over 3 h CrCL ≥130 mL/min**:** Sulbactam 1 gram/durlobactam 1 gram (2 grams total) IV every 4 h, infused over 3 h Additional information in Supplementary Material.
Tigecycline	200 mg IV as a single dose, then 100 mg IV every 12 h
Tobramycin	**Uncomplicated cystitis**: 5 mg/kg and the AST profile of the pathogen, IV as a single dose **Pyelonephritis or complicated urinary tract infections**: 7 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplementary Material.
Trimethoprim-sulfamethoxazole	**Uncomplicated cystitis**: 160 mg (trimethoprim component) IV/PO every 12 h **Other infections**: 10–15 mg/kg/day (trimethoprim component) IV/PO divided every 8 to 12 h Additional information in Supplementary Material.

Abbreviations: CrCl, creatinine clearance; IV, intravenous; PO, enterally.

[a]Dosing suggestions limited to organisms and infectious syndromes discussed in the IDSA AMR Treatment Guidance document.

[b]Dosing suggested for several agents may differ from dosing recommended by the United States Food and Drug Administration.

IDSA DISCLAIMER

It is important to realize that guidance cannot always account for individual variation among patients. The contents of this guidance are assessments of current scientific and clinical information provided as an educational service. They are not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read). They should not be considered inclusive of all available treatment approaches or as a statement of the standard of care. They are not intended to supplant clinician judgment with respect to particular patients or special clinical situations. Whether and the extent to which to follow guidance is voluntary, with the ultimate determination regarding their application to be made by the treating clinician in light of each patient's individual circumstances. Although IDSA makes every effort to present accurate, complete, and reliable information, this guidance is presented "as is" without any warranty, either express or implied. IDSA (and its officers, directors, members, employees, and agents) assume no responsibility for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with this guidance or reliance on the information presented.

SECTION 1: EXTENDED-SPECTRUM β-LACTAMASE-PRODUCING ENTEROBACTERALES

ESBLs are enzymes that inactivate most penicillins, cephalosporins, and aztreonam. EBSL-E generally remain susceptible to carbapenems. ESBLs do not inactivate non-β-lactam agents (eg, ciprofloxacin, trimethoprim-sulfamethoxazole [TMP-SMX], gentamicin, doxycycline). However, organisms carrying ESBL genes often harbor additional genes or mutations in genes expanding their resistance to a broad range of antibiotics.

Any gram-negative organism has the potential to harbor ESBL genes; however, they are most prevalent in *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* [7–9]. CTX-M enzymes, particularly CTX-M-15, are the most common ESBLs in the United States [9]. ESBLs other than CTX-M with unique hydrolyzing abilities are also present, including variants of TEM and SHV β-lactamases with amino acid substitutions, but they have undergone less rigorous clinical investigation than CTX-M enzymes [10–14]. Routine EBSL testing is not performed by most clinical microbiology laboratories [15, 16]. Rather, non-susceptibility to ceftriaxone (ie, ceftriaxone minimum inhibitory concentrations [MICs] ≥2 μg/mL), is often used as a proxy for ESBL production, although this threshold has limitations with specificity as organisms not susceptible to ceftriaxone for reasons other than ESBL production may be falsely presumed to be ESBL-producers [17, 18]. For this guidance document, ESBL-E refers to presumed or confirmed ESBL-producing *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*.

Treatment suggestions for ESBL-E infections assume that in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 1.1: What Are Preferred Antibiotics for the Treatment of Uncomplicated Cystitis Caused by ESBL-E?

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

Rationale

Nitrofurantoin and TMP-SMX have been shown to be effective options for uncomplicated cystitis, including uncomplicated ESBL-E cystitis [5, 19–21]. Although carbapenems and the fluoroquinolones ciprofloxacin or levofloxacin are effective agents against ESBL-E cystitis [22, 23], their use for uncomplicated cystitis is discouraged when other effective options are available. Limiting use of these agents preserves their activity for future infections when treatment options may be more restricted. Moreover, limiting their use reduces the risk of associated toxicities, particularly with the fluoroquinolones, which have been associated with an increased risk for prolonged QT intervals, tendinitis and tendon rupture, aortic dissections, seizures, peripheral neuropathy, and *Clostridioides difficile* infections [24–27].

Treatment with a single IV dose of an aminoglycoside is an alternative treatment option for uncomplicated ESBL-E cystitis. Aminoglycosides are nearly exclusively eliminated by the renal route. A single IV dose is generally effective for uncomplicated cystitis, with minimal toxicity, but robust clinical trial data are lacking [28]. Oral fosfomycin is an alternative treatment option exclusively for uncomplicated ESBL-E cystitis caused by *E. coli*. Susceptibility of *E. coli* to fosfomycin is not routinely tested by most clinical microbiology laboratories but *E. coli* resistance to fosfomycin remains rare in the United States [29, 30]. Among gram-negative species, Clinical and Laboratory Standards Institute (CLSI) breakpoints are only available for *E. coli* for fosfomycin. Fosfomycin is not suggested for the treatment of infections caused by *K. pneumoniae* and several other gram-negative organisms, which frequently carry *fosA* hydrolase genes that may lead to clinical failure [31, 32]. A randomized open-label trial indicated that a single dose of oral fosfomycin is associated with higher clinical failure than a 5-day course of nitrofurantoin for uncomplicated cystitis [19]. Although this trial was not limited to *E. coli* cystitis, in a subgroup analysis exclusively of *E. coli* infections, outcomes remained poor in the fosfomycin group

with day 14 clinical failure at 50% in the fosfomycin group vs 22% in the nitrofurantoin group [19]. The additive benefit of additional doses of oral fosfomycin for uncomplicated cystitis is not known but may be a reasonable option as has been suggested for cUTI [33] (Question 1.2).

Amoxicillin-clavulanic is not suggested for the treatment of ESBL-E cystitis. A randomized clinical trial compared a 3-day regimen of amoxicillin-clavulanic acid (500 mg/125 mg twice daily) to a 3-day course of ciprofloxacin (250 mg twice daily) for 370 women with uncomplicated *E. coli* cystitis [22]. Clinical cure was observed in 58% and 77% of the women randomized to the amoxicillin-clavulanic and ciprofloxacin arms, respectively. The higher failure rates with amoxicillin-clavulanic acid appear to be associated with persistent vaginal bacterial colonization, which occurred in 45% and 10% of patients in the amoxicillin-clavulanic acid and ciprofloxacin arms, respectively [22]. The proportion of women in the trial infected with ESBL-E strains is not available. Of note, both agents were administered at dosages lower than generally suggested (Table 1). Even though data indicate that clavulanic acid is effective against ESBLs in vitro [34, 35], this may not translate to clinical efficacy [36]. Robust data indicating that oral amoxicillin-clavulanic acid is effective for ESBL-E uncomplicated cystitis are lacking. Although amoxicillin-clavulanic acid is not a preferred agent for uncomplicated ESBL-producing cystitis, if it is prescribed because resistance or toxicities preclude use of alternative oral antibiotics and there is a preference to avoid IV antibiotics, caution should be given to patients about the potential increased risk of recurrent infection if amoxicillin-clavulanic acid is administered.

The panel suggests avoiding doxycycline for the treatment of ESBL-E uncomplicated cystitis. Two clinical outcomes studies, published nearly 50 years ago, demonstrated that oral tetracyclines may be effective for the treatment of UTIs [37, 38]. Both of these studies, however, primarily focused on *P. aeruginosa*, an organism not susceptible to oral tetracyclines, questioning the impact that antibiotic therapy had on clinical cure. Doxycycline is primarily eliminated through the intestinal tract with limited urinary excretion (35%–60%) [39]. Until more convincing data demonstrating the clinical effectiveness of oral doxycycline for the treatment of ESBL-E cystitis are available, the panel suggests against the use of doxycycline for this indication. The roles of piperacillin-tazobactam, cefepime, and the cephamycins for the treatment of uncomplicated cystitis are discussed in Question 1.4, Question 1.5, and Question 1.6, respectively.

Question 1.2: What Are Preferred Antibiotics for the Treatment of Pyelonephritis or cUTI Caused by ESBL-E?

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

Rationale

TMP-SMX, ciprofloxacin, and levofloxacin are preferred treatment options for patients with ESBL-E pyelonephritis or cUTIs, assuming in vitro susceptibility has been demonstrated, based on the ability of these agents to achieve adequate and sustained concentrations in the urine, clinical trial results, and clinical experience [40–42]. Carbapenems are also preferred agents, when resistance or toxicities prevent the use of TMP-SMX or fluoroquinolones, or early in the treatment course if a patient is critically ill (Question 1.3). If a carbapenem is initiated and susceptibility to TMP-SMX, ciprofloxacin, or levofloxacin is demonstrated, transitioning to oral formulations of these agents is preferred over completing a treatment course with a carbapenem. Limiting use of carbapenem exposure will preserve their activity for future AMR infections, which frequently arise in patients with cUTIs [43].

Aminoglycosides are alternative options for pyelonephritis and cUTI. Although expected to be effective, they are considered alternative agents because of their associated nephrotoxicity risk. Animal models suggest aminoglycosides concentrate in the renal parenchyma [44]. In a clinical trial of 609 adults receiving plazomicin for cUTI infections, clinical relapse occurred in 2% vs 7% and increases in serum creatinine levels of ≥0.5 mg above baseline occurred in 7% vs 4% of patients in the plazomicin and meropenem groups, respectively [45]. In general, higher percentages of Enterobacterales clinical isolates are susceptible to plazomicin compared to other aminoglycosides [46]. Other aminoglycosides are likely equally effective for the treatment of ESBL-E pyelonephritis or cUTI if susceptibility is demonstrated [45, 47, 48]. Of note, in 2023 the CLSI revised gentamicin, tobramycin, and amikacin breakpoints for the Enterobacterales [16] (Table 2). Aminoglycosides may be reasonable to consider for completing treatment courses (eg, transitioning from another agent for terminal doses) given their prolonged duration of activity in the renal cortex and the convenience of once daily dosing [47, 48] (Table 1, Supplementary Material). Duration-dependent risks of nephrotoxicity should be considered with all aminoglycosides [49, 50].

Fosfomycin is not suggested for the treatment of pyelonephritis or cUTI given its limited renal parenchymal concentrations. More data are needed to evaluate the role of oral fosfomycin for patients with pyelonephritis or cUTI, particularly when administered as a multidose regimen and after several days of preferred therapy. In a clinical trial of 97 women with *E. coli* pyelonephritis (approximately half of patients had associated bacteremia) who received up to 5 days of IV therapy, participants were subsequently transitioned to either once-daily 3 g

doses of oral fosfomycin or twice daily 500 mg doses of oral ciprofloxacin for 10 days of total antibiotic therapy [51]. Similar clinical cure percentages were identified in both groups (75% vs 65%, respectively). However, only approximately 6% of isolates were ESBL-producing, limiting generalizability to pyelonephritis caused by drug-resistant phenotypes [51]. Moreover, as 7 days is generally sufficient for the treatment of pyelonephritis, the attributable benefit of the additional days of oral fosfomycin or ciprofloxacin is unclear. Another clinical trial randomized 51 patients with cUTI to 3 g of fosfomycin daily or 750 mg of levofloxacin daily for 5–7 days, after up to 2 days of IV therapy [33]. Clinical cure at the end of therapy was similar in both treatment groups (69% vs 68%). In this study, 63% of infections were caused by *E. coli* but only 1 isolate in each arm was caused by an ESBL-producing isolate.

IV fosfomycin is not clinically available in the United States. Although some data suggest IV fosfomycin may have activity against organisms beyond *E. coli*, it is difficult to translate data from IV fosfomycin to oral fosfomycin given the limited oral bioavailability and lower daily dosages with oral fosfomycin [52]. Transitioning to daily oral fosfomycin needs further investigation before suggesting for or against this practice for the treatment of ESBL-E pyelonephritis or cUTI; however, it may be a reasonable option when other preferred or alternative oral options are not available.

Fosfomycin is an alternative option for the treatment of prostatitis caused by ESBL-producing *E. coli* when preferred options (ie, carbapenems, TMP-SMX, or fluoroquinolones) cannot be tolerated or do not test susceptible [53–59]. In an observational study, fosfomycin, dosed at 3 g orally daily for 1 week, followed by 3 g orally every 48 hours for 6–12 weeks, was associated with clinical cure in 36 (82%) of 44 males with chronic bacterial prostatitis [53]. Fosfomycin is not suggested for prostatitis caused by gram-negative organisms other than *E. coli* due to the likely presence of the *fosA* gene and its ability to inactive this agent (Question 1.1).

Nitrofurantoin does not achieve adequate concentrations in the renal parenchyma and is not advised for the treatment of pyelonephritis or cUTI. Doxycycline is also not advised for the treatment of ESBL-E pyelonephritis or cUTIs due to its limited urinary excretion (Question 1.1) [39]. The roles of piperacillin-tazobactam, cefepime, and the cephamycins for the treatment of pyelonephritis or cUTIs are discussed in Question 1.4, Question 1.5, and Question 1.6, respectively.

Question 1.3: What Are Preferred Antibiotics for the Treatment of Infections Outside of the Urinary Tract Caused by ESBL-E?

Suggested approach: Meropenem, imipenem-cilastatin, or ertapenem are preferred for the treatment of infections outside of the urinary tract caused by ESBL-E. For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem, or imipenem-cilastatin are the preferred carbapenems. After appropriate clinical response is achieved, transitioning to oral TMP-SMX, ciprofloxacin, or levofloxacin should be considered, if susceptibility is demonstrated.

Rationale

A carbapenem is recommended as first-line treatment of ESBL-E infections outside of the urinary tract, based primarily on data from a large clinical trial, as described below [60]. Meropenem, imipenem-cilastatin, or ertapenem are preferred agents; ertapenem offers a more convenient option for patients needing to continue carbapenem therapy in the outpatient setting when oral treatment options are not available.

For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenems. Ertapenem, in contrast to meropenem and imipenem, is highly protein bound leading to a relatively prolonged serum half-life [61]. In patients with hypoalbuminemia, the free fraction of ertapenem increases, leading to increased ertapenem clearance and a significant decrease in the serum half-life of this agent, which may not be optimal with daily dosing of this agent [62–64]. An observational study of 279 patients with Enterobacterales infections found that hypoalbuminemia (defined as serum albumin <2.5 g/dL) was associated with an approximately 5-times higher odds of 30-day mortality for patients receiving ertapenem compared to those receiving meropenem or imipenem-cilastatin [65]. Clinical literature regarding the use of ertapenem, relative to other carbapenems, in critically ill patients is limited and conflicting [64, 66]. However, given known pharmacokinetic (PK) alterations in patients with critical illness and limitations in the pharmacokinetic and pharmacodynamic (PK/PD) profile of ertapenem [67, 68], the panel suggests the use of meropenem or imipenem-cilastatin, rather than ertapenem, as initial therapy in critically ill patients with ESBL-E infections. Higher doses of ertapenem (eg, 1.5 grams) or more frequent dosing (eg, every 12 hours) may circumvent some of the probability of target attainment issues with ertapenem in obese and critically ill patients with hypoalbuminemia, respectively, but data for these alternative dosing strategies are limited [67, 69–71].

The clinical trial that established carbapenem therapy as the treatment of choice for ESBL-E bloodstream infections randomized 391 patients with ceftriaxone non-susceptible *E. coli* or *K. pneumoniae* (87% later confirmed to have ESBL genes) to piperacillin-tazobactam 4.5 g IV every 6 hours or meropenem 1 g IV every 8 hours, both as standard infusions (ie, over 30 minutes). The primary outcome of 30-day mortality occurred in 12% and 4% of patients receiving piperacillin-tazobactam and meropenem, respectively [60]. Trial data were subsequently reanalyzed only including patients with clinical isolates against which piperacillin-tazobactam MICs were ≤16 μg/mL by broth microdilution, the reference standard for AST [72]. Reanalyzing the data from 320 (82%) patients

with clinical isolates available for retesting, 30-day mortality occurred in 9% vs 4% of those in the piperacillin-tazobactam and meropenem arms, respectively. Although the absolute risk difference was attenuated and no longer significant in the reanalysis (ie, the 95% confidence interval ranged from −1% to 11%) [72], the panel still suggests carbapenem therapy as the preferred treatment of ESBL-producing bloodstream infections due to the notable direction of the risk difference. Limitations of piperacillin-tazobactam are further described in Question 1.4. Comparable clinical trial data are not available for ESBL-E infections from other body sites. Nevertheless, the panel suggests extrapolating evidence for ESBL-E bloodstream infections to other common sites of infection, such as intra-abdominal infections, skin and soft tissue infections, and pneumonia. Similarly, although the trial evaluated meropenem, the panel suggests extending the findings to imipenem-cilastatin and ertapenem, with the latter limited to patients with normal serum albumin and patients who are not critically ill.

Data from observational studies support the use of oral step-down therapy for Enterobacterales bloodstream infections, including those caused by AMR isolates, after appropriate clinical milestones are achieved [73, 74]. Based on the high bioavailability and sustained serum concentrations of oral TMP-SMX and fluoroquinolones, these agents should be treatment considerations for patients with ESBL-E infections if (1) susceptibility to 1 of these agents is demonstrated, (2) the patient is hemodynamically stable, (3) reasonable source control has occurred, and (4) concerns about insufficient intestinal absorption are not present [6].

Clinicians should avoid oral step-down to nitrofurantoin, fosfomycin, amoxicillin-clavulanic acid, omadacycline, or doxycycline for ESBL-E bloodstream infections. Nitrofurantoin

Table 2. 2024 Clinical and Laboratory Standards Institute Susceptible Breakpoints for Select Gram-Negative Organisms and Antibiotic Combinations as Suggested in the IDSA AMR Guidance Document[a]

Antibiotic	Enterobacterales (μg/mL)	*Pseudomonas aeruginosa* (μg/mL)	Carbapenem-Resistant *Acinetobacter baumannii* (μg/mL)	*Stenotrophomonas maltophilia* (μg/mL)
Amikacin	≤4	≤16[b]	…	…
Ampicillin-sulbactam	…	…	≤8/4	…
Aztreonam	≤4	≤8	…	…
Cefepime	≤2[c]	≤8	…	…
Cefiderocol	≤4	≤4	≤4	≤1
Ceftazidime	≤4	≤8	…	…
Ceftazidime-avibactam	≤8/4	≤8/4	…	…
Ceftolozane-tazobactam	≤2/4	≤4/4	…	…
Ciprofloxacin	≤0.25	≤0.5	…	…
Colistin or Polymyxin B	…[d]	…[d]	…[d]	…
Doxycycline	≤4	…	…	…
Ertapenem	≤0.5	…	…	…
Fosfomycin	≤64[e]	…	…	…
Gentamicin	≤2	…	…	…
Imipenem	≤1	≤2	…	…
Imipenem-relebactam	≤1/4	≤2/4	…	…
Levofloxacin	≤0.5	≤1	…	≤2
Meropenem	≤1	≤2	…	…
Meropenem-vaborbactam	≤4/8	…	…	…
Minocycline	≤4	…	≤4	≤1
Nitrofurantoin	≤32	…	…	…
Piperacillin-tazobactam	≤8/4[f]	≤16/4	…	…
Plazomicin	≤2	…	…	…
Sulbactam-durlobactam	…	…	≤4/4	…
Tigecycline	…[g]	…	…[h]	…[h]
Trimethoprim-sulfamethoxazole	≤2/38	…	…	≤2/38
Tobramycin	≤2	≤1	…	…

[a]For full details of antibiotic susceptibility testing interpretations refer to: Clinical and Laboratory Standards Institute. 2024. M100: Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. Wayne, PA. CLSI M100 document is updated annually; susceptibility criteria subject to changes in 2025.

[b]Breakpoints only available for infections originating from the urinary tract.

[c]Isolates with cefepime minimum inhibitory concentrations (MICs) of 4–8 μg/mL are susceptible dose-dependent.

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

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

[f]Isolates with piperacillin-tazobactam MICs of 16 μg/mL are considered susceptible dose-dependent.

[g]No Clinical and Laboratory Standards Institute (CLSI) breakpoint. Food and Drug Administration (FDA) defines susceptibility as MICs ≤2 μg/mL.

[h]Neither CLSI nor FDA breakpoints are available.

and fosfomycin achieve poor serum concentrations. Amoxicillin-clavulanic acid, omadacycline, and doxycycline have limited data to support their efficacy for ESBL-E bloodstream infections.

Question 1.4: Is There a Role for Piperacillin-tazobactam in the Treatment of Infections Caused by ESBL-E?

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

Rationale

Piperacillin-tazobactam often demonstrates in vitro activity against ESBL-E [75]. However, there are several concerns regarding tazobactam's ability to function as an effective β-lactamase inhibitor. First, piperacillin-tazobactam MIC testing may be inaccurate and/or poorly reproducible when ESBL enzymes are present, or in the presence of other β-lactamase enzymes such as OXA-1, making it unclear if an isolate that tests susceptible to this agent is reliably susceptible [72, 76–79]. Second, preclinical data indicate that with increased bacterial inoculum which may be present in certain clinical infections (eg, abscesses), regrowth of ESBL-E isolates appears significantly more likely in the setting of piperacillin-tazobactam compared with meropenem; the clinical implications of these findings are unclear [80–82]. Third, the effectiveness of tazobactam may be diminished for organisms with increased expression of ESBL enzymes or by the presence of multiple ESBL or other β-lactamases (eg, AmpC enzymes) [83]. This may in part be due to the low concentration of tazobactam relative to the amount of piperacillin. As an example, in a 4.5 g dose of piperacillin-tazobactam there is an 8:1 ratio of piperacillin to tazobactam (ie, 4 grams of piperacillin and 0.5 grams of tazobactam). In contrast, in a 3 g dose of ceftolozane there is a 2:1 ratio of ceftolozane to tazobactam. It is plausible that the lower dose of tazobactam in piperacillin-tazobactam may limit its abilities as an inhibitor [84]. Finally, the piperacillin-tazobactam breakpoint for Enterobacterales is primarily based on PK/PD considerations of piperacillin dosing strategies and not on whether a fixed concentration of 4 μg/mL of tazobactam in testing wells is reflective of the restorative ability of common tazobactam dosages to reestablish the activity of piperacillin in the setting of ESBL enzymes [84, 85].

If piperacillin-tazobactam was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary, as uncomplicated cystitis often resolves on its own. Determining the role of piperacillin-tazobactam for the treatment of ESBL-E pyelonephritis or cUTI is a more challenging.

Several observational studies have found similar clinical outcomes when comparing the efficacy of piperacillin-tazobactam and carbapenems for the treatment of ESBL-E pyelonephritis or cUTI [86–90]. A randomized, open-label clinical trial investigating this question was also conducted [91]. The trial included 66 patients with ESBL-producing *E. coli* pyelonephritis or cUTI (with confirmation of the presence of ESBL genes) randomized to either piperacillin-tazobactam 4.5 g IV every 6 hours or ertapenem 1 g IV every 24 hours. Clinical success was similar between the groups at 94% for piperacillin-tazobactam and 97% for ertapenem. These studies suggest noninferiority between piperacillin-tazobactam and carbapenems for pyelonephritis or cUTIs. In the subgroup of 231 patients with ESBL-E bloodstream infections from a urinary source in the aforementioned clinical trial (Question 1.3), higher mortality was identified in the piperacillin-tazobactam group (7% vs 3%) [60], although not achieving statistical significance. Evaluating the totality of the data, the panel prefers carbapenem therapy (or oral trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin, if susceptible) for the treatment of ESBL-E pyelonephritis or cUTIs but acknowledges it may be reasonable to prescribe piperacillin-tazobactam for these infections based on the results of available comparative effectiveness studies. If piperacillin-tazobactam was initiated as empiric therapy for pyelonephritis or cUTI caused by an organism later identified as an ESBL-E and clinical improvement occurs, the decision to continue piperacillin-tazobactam should be made with the understanding that theoretically there may be an increased risk for microbiological failure with this approach.

Observational studies have had conflicting results regarding the effectiveness of piperacillin-tazobactam for the treatment of ESBL-E bloodstream infections [91–103]. A clinical trial of ESBL-E bloodstream infections indicated inferior results with piperacillin-tazobactam compared to carbapenem therapy (Question 1.3) [60]. A second trial investigating the role of piperacillin-tazobactam for the treatment of ESBL-E bloodstream infections is ongoing [104].

In 2022, the CLSI lowered the piperacillin-tazobactam breakpoints for the Enterobacterales. MICs of ≤8/4 μg/mL are considered susceptible, and a MIC of 16 μg/mL is considered susceptible, dose-dependent (Table 2) [105]. In the clinical trial mentioned in Question 1.3, 94% of isolates would have been considered susceptible or susceptible dose-dependent to piperacillin-tazobactam if applying the revised piperacillin-tazobactam breakpoints, indicating that in the presence of ESBL production, susceptibility to piperacillin-tazobactam may not correlate with clinical success [60, 72].

Question 1.5: Is There a Role for Cefepime in the Treatment of Infections Caused by ESBL-E?

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

Rationale

ESBLs commonly hydrolyze cefepime [83, 106]. Furthermore, even if ESBL-producing isolates test susceptible to cefepime, cefepime MIC testing may be inaccurate and/or poorly reproducible with commercial AST methods [107]. Clinical trials designed to compare the outcomes of patients with ESBL-E bloodstream infections treated with cefepime or carbapenem have not been conducted.

If cefepime was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary, as uncomplicated cystitis often resolves on its own. Limited data are available evaluating the role of cefepime vs carbapenems for ESBL-E pyelonephritis and cUTI [89, 91, 108]. A clinical trial evaluating the treatment of molecularly confirmed ESBL-E pyelonephritis and cUTI terminated the cefepime arm early because of a high clinical failure signal with cefepime (2 g IV every 12 hours), despite all isolates having cefepime MICs of 1–2 μg/mL [91]. Until more robust comparative effectiveness studies are available to inform the role of cefepime, the panel suggests avoiding cefepime for the treatment of ESBL-E pyelonephritis or cUTI.

Clinical trials comparing cefepime to carbapenems for ESBL-E bloodstream infections have not been conducted. However, a randomized trial comparing cefepime (2 g IV every 8 hours) to imipenem-cilastatin (500 mg IV every 6 hours) for nosocomial pneumonia identified clinical failure in 4 of 13 patients (31%) with pneumonia due to ESBL-E in the cefepime arm, compared to none of 10 patients (0%) in the imipenem-cilastatin arm [109]. Observational studies that compare cefepime and carbapenems for the treatment of invasive ESBL-E infections demonstrated either no difference in outcomes or poorer outcomes with cefepime [110–113]. For these reasons, the panel suggests avoiding cefepime for the treatment of invasive ESBL-E infections.

Question 1.6: Is There a Role for the Cephamycins in the Treatment of Infections Caused by ESBL-E?

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

Rationale

The cephamycins are cephalosporins that are generally able to withstand hydrolysis from ESBL enzymes [114, 115]. The cephamycins available in the United States are cefoxitin and cefotetan, which are both IV agents. At least 10 observational studies have compared the clinical outcomes of patients with ESBL-E infections—generally UTIs or bloodstream infections from urinary sources—treated with cephamycins vs carbapenems [116–125]. Eight of the 10 investigations found no difference in clinical outcomes [116, 118–120, 122, 123]; 2 studies demonstrated poorer outcomes with cephamycins [117, 121]. One of the 2 studies included 57 patients with *K. pneumoniae* bloodstream infections; 14-day mortality was 55% and 39% in the cephamycin and carbapenem arms, respectively [117]. The second study was the largest published to date, including 380 patients with *E. coli* and *K. pneumoniae* bloodstream infections; 30-day mortality was 29% vs 13% in the cephamycin (ie, floxomef) and carbapenem arms, respectively [121]. Importantly, all 8 studies were observational, included diverse sources of infection, had notable selection bias, and used a variety of cephamycins with differences in dosing, duration, and frequency of administration.

The panel does not suggest cephamycins for the treatment of ESBL-E infections, including ESBL-E uncomplicated cystitis. Many of the cephamycins investigated in observational studies are not available in the United States. Limited numbers of patients received cefoxitin or cefotetan in published studies [119, 123, 126]. The panel believes more clinical data associated with these agents for the treatment of ESBL-E infections are necessary before advocating for their use—including optimal dosing and frequency of administration. Data suggest more favorable outcomes with high-dose, continuous infusion cefoxitin (ie, 6 g per day infused continuously) [123, 126], but this is challenging to administer. As both cefotetan and cefoxitin are only available IV and have relatively short half-lives, there does not appear to be a feasibility advantage with use of these agents over preferred agents for the treatment of ESBL-E infections.

Question 1.7: What Is the Role of Newer β-Lactam-β-Lactamase Inhibitor Combinations and Cefiderocol for the Treatment of Infections Caused by ESBL-E?

Suggested approach: The panel suggests that ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, ceftolozane-tazobactam, and cefiderocol be preferentially reserved for treating infections caused by organisms exhibiting carbapenem resistance.

Rationale

Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, ceftolozane-tazobactam, and cefiderocol exhibit activity against ESBL-E [127–129]. Avibactam is able to successfully protect ceftazidime against hydrolysis by binding

to and inhibiting the function of ESBL enzymes [9, 130]. Subgroup analysis of clinical trial data support ceftazidime-avibactam effectiveness against ESBL-E infections [131–135].

The carbapenem component of meropenem-vaborbactam and imipenem-cilastatin-relebactam provide sufficient activity against ESBL-E, even without the addition of a β-lactamase inhibitor.

Ceftolozane-tazobactam appears more potent against ESBL-E than piperacillin-tazobactam with ceftolozane MICs reducing several dilutions lower than piperacillin MICs, with the addition of tazobactam [136–141]. Moreover, ceftolozane appears to have greater stability to hydrolysis by common ESBL enzymes (eg, CTX-M-15) compared to piperacillin, making ceftolozane less reliant than piperacillin on tazobactam's inhibitory properties [142, 143]. Additionally, the ratio of β-lactam to tazobactam present in ceftolozane-tazobactam (2:1) results in greater concentration of tazobactam compared to piperacillin-tazobactam (8:1).

In a subgroup analysis of 72 patients with ESBL-E intra-abdominal infections in a randomized clinical trial, ceftolozane-tazobactam was associated with similar clinical cure as meropenem [144]. In a randomized clinical trial comparing ceftolozane-tazobactam vs meropenem for pneumonia, 28-day mortality in the subgroup of patients with ESBL-E pneumonia was similar between the 84 patients receiving ceftolozane-tazobactam (21%) and the 73 patients receiving meropenem (29%) [145, 146]. Clinical cure and microbiologic eradication rates were also similar between the ceftolozane-tazobactam and meropenem arms.

Although ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, ceftolozane-tazobactam, and cefiderocol are expected to be effective against ESBL-E infections, the panel suggests that these agents be preferentially reserved for treating carbapenem-resistant organisms or polymicrobial infections including organisms exhibiting carbapenem resistance (eg, ceftolozane-tazobactam for coinfection with DTR *P. aeruginosa* and ESBL-E).

SECTION 2: AMPC β-LACTAMASE-PRODUCING ENTEROBACTERALES

AmpC β-lactamases are enzymes that are produced at basal levels by a number of Enterobacterales and glucose non-fermenting gram-negative organisms. Their primary function is to assist with cell wall recycling [147]. AmpC β-lactamases are capable of hydrolyzing a number of β-lactam agents (to a level that makes the agents ineffective), some in settings of basal AmpC production (eg, cefazolin) and others in settings of increased AmpC production (eg, ceftriaxone). Increased AmpC production by Enterobacterales generally occurs by 1 of 3 mechanisms: (1) inducible chromosomal gene expression, (2) stable chromosomal gene de-repression, or (3) constitutively expressed *ampC* genes (frequently carried on plasmids, but sometimes integrated into the bacterial chromosome) [147–149].

Increased AmpC enzyme production resulting from inducible *ampC* expression can occur in the presence of specific antibiotics and results in sufficient AmpC enzyme in the periplasmic space to increase MICs to certain antibiotics (ie, ceftriaxone, cefotaxime, ceftazidime, aztreonam, and piperacillin-tazobactam). In this scenario, an Enterobacterales isolate that initially tests susceptible to ceftriaxone may exhibit non-susceptibility to this agent after treatment with ceftriaxone is initiated. In this guidance document, such organisms are described as having a moderate risk for clinically significant AmpC production. Resistance due to *ampC* induction can be observed after even a few doses of ceftriaxone, cefotaxime, or ceftazidime [150].

For the other 2 mechanisms (ie, stable chromosomal de-repression or constitutively overexpressed *ampC* genes), AmpC production is always increased. Isolates with either of these 2 mechanisms typically test non-susceptible to ceftriaxone, cefotaxime, and/or ceftazidime. As such, infections by organisms with these resistance mechanisms generally pose less of a treatment dilemma than infections caused by isolates with inducible *ampC* expression. Regarding the first of these 2 mechanisms, some Enterobacterales isolates (eg, certain *Escherichia coli* and *Shigella* spp.) contain mutations in promoter or attenuator regions of *ampC* or other related genes (eg, *ampD*, *ampR*, *ampG*), stably de-repressing gene expression [151]. For the second mechanism, constitutive expression of *ampC* genes (eg, *bla*CMY, *bla*FOX, *bla*DHA, *bla*ACT, *bla*MIR) occurs [152]. These *ampC* genes can be found either on plasmids (eg, *bla*CMY in *E. coli*) or be integrated into the bacterial chromosome (eg, *bla*CMY in *Citrobacter freundii*). In this document, we will focus on the treatment of infections by Enterobacterales species with a moderate likelihood of inducible *ampC* gene expression (ie, the first of the 3 mechanisms) [153, 154].

Question 2.1: Which Commonly Identified Enterobacterales Species Should Be Considered at Moderate Risk for Clinically Significant Inducible *ampC* Production?

Suggested approach: *Enterobacter cloacae* complex, *Klebsiella aerogenes*, and *Citrobacter freundii* are the most common Enterobacterales at moderate risk for clinically significant inducible 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 (eg, ceftriaxone) that, on subsequent isolation (and after β-lactam exposure), become resistant, with genotyping and expression studies to confirm that the same organism was recovered and that AmpC production significantly increased. Unfortunately, such studies are not available.

Commonly used acronyms to denote organisms at risk for AmpC production (eg, SPACE, SPICE, ESCPM) obscure the wide range of *ampC* induction potential among gram-negative organisms and ignore variance within bacterial genera [147, 148]. For example, *C. freundii* harbors a chromosomal *ampC*, whereas *Citrobacter koseri* does not [155–157]. Thus, current acronyms may be overly simplistic and associated with both an "undercalling" and "overcalling" of the likelihood of clinically significant AmpC production among individual bacterial species. As another example, "indole positive *Proteus* species" are often included in existing acronyms. Indole-positive *Proteus* spp. currently refers to organisms such as *P. vulgaris*, which generally does not contain a chromosomal *ampC* gene. The terminology "indole positive *Proteus* species" previously included *Proteus rettgeri* and *Proteus morganii* (since renamed *Providencia rettgeri* and *Morganella morganii*, respectively) [158], making the inclusion of "indole-positive *Proteus* spp." in mnemonics for organisms at moderate risk of AmpC production no longer accurate.

The emergence of clinically relevant *ampC* expression during antibiotic treatment has been most frequently described for *E. cloacae* complex (herein referred to as *E. cloacae* for simplicity), *K. aerogenes* (formerly *Enterobacter aerogenes*), and *C. freundii.* Clinical reports suggest that the emergence of resistance after exposure to an agent like ceftriaxone may occur in approximately 20% of infections caused by these organisms [150, 159–163]. These clinical observations mirror in vitro mutation rate analyses, which also suggest that these organisms are likely to overexpress *ampC* [164]. Therefore, when *E. cloacae*, *K. aerogenes*, or *C. freundii* are recovered in clinical cultures (other than urine cultures in uncomplicated cystitis), the panel suggests generally avoiding treatment with ceftriaxone, cefotaxime, or ceftazidime, even if an isolate initially tests susceptible to these agents (Question 2.2). Even without upregulation of AmpC production, basal production of AmpC β-lactamases in these organisms leads to intrinsic resistance to ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, and first- and second-generation cephalosporins [16].

In contrast, other organisms historically presumed to be at moderate risk for the development of clinically significant *ampC* expression, such as *Serratia marcescens, Morganella morganii, and Providencia* spp., are significantly less likely to overexpress *ampC* based on both in vitro analysis [164, 165] and clinical reports [150, 159, 166]. Available data suggest that clinically significant AmpC production occurs in less than 5% of these organisms. When *S. marcescens*, *M. morgannii*, or *Providencia* spp. are recovered from clinical cultures, the panel suggests selecting antibiotic treatment according to AST results. Basal production of AmpC β-lactamase renders these organisms intrinsically resistant to ampicillin, amoxicillin-clavulanate, and first- and second-generation cephalosporins [16].

A number of less common clinical pathogens (eg, *Hafnia alvei, Citrobacter youngae, Yersinia enterocolitica*) that carry inducible chromosomal *ampC* genes have not undergone significant investigation [164, 167–169]. As such, descriptions of their potential for clinically significant AmpC production are very limited. It is reasonable to use AST results to guide treatment decisions if these organisms are recovered in clinical cultures (eg, administer ceftriaxone if susceptible to ceftriaxone). When treating infections caused by these less commonly recovered organisms (or caused by *S. marcescens*, *M. morgannii*, or *Providencia* spp.) with a high bacterial burden and limited source control (eg, endocarditis, central nervous system infections), it is alternatively reasonable to consider treatment with cefepime instead of ceftriaxone, even if the organism tests susceptible to ceftriaxone. As with all infections, if an adequate clinical response is not observed after appropriately dosed antibiotic therapy is initiated and necessary source control measures are taken, clinicians should consider the possibility of the emergence of resistance to the initially prescribed agent.

Question 2.2: What Features Should Be Considered in Selecting Antibiotics for Infections Caused by Organisms at Moderate Risk of Clinically Significant AmpC Production Due to an Inducible *ampC* Gene?

Suggested approach: Several β-lactam antibiotics are at moderate risk of inducing *ampC* genes. Both the ability to induce *ampC* genes and the relative stability of the agent against hydrolysis by AmpC should inform antibiotic decision-making.

Rationale

β-lactam antibiotics fall within a spectrum of potential for inducing *ampC* genes. Aminopenicillins (ie, amoxicillin, ampicillin), narrow-spectrum (ie, first-generation) cephalosporins, and cephamycins are potent *ampC* inducers [170, 171]. However, both organisms at low risk (eg, *S. marcescens*) and at moderate risk (eg, *E. cloacae*) for clinically significant *ampC* induction hydrolyze these antibiotics even at basal *ampC* expression levels. Therefore, such AmpC-E isolates will generally test as resistant to these drugs, averting treatment dilemmas.

Imipenem is also a potent *ampC* inducer but it generally remains stable to AmpC-E hydrolysis because of the formation of stable acyl enzyme complexes [170]. The induction potential of ertapenem and meropenem has not been formally investigated but, similar to imipenem, they are generally stable to AmpC hydrolysis [172, 173]. Ceftriaxone, cefotaxime, ceftazidime, piperacillin-tazobactam, and aztreonam are relatively weak *ampC* inducers [171, 174]. Available evidence indicates that despite their limited ability to induce *ampC*, the susceptibility of these agents to hydrolysis makes them less likely to be effective for the treatment of infections by organisms at moderate risk for clinically significant AmpC production [173, 175–177]. They remain, however, reasonable treatment options for

Enterobacterales at lower risk for clinically significant AmpC production (eg, *S. marcescens*).

Cefepime has the advantage of both being a weak inducer of *ampC* and of withstanding hydrolysis by AmpC β-lactamases because of the formation of stable acyl enzyme complexes [178, 179]. Therefore, cefepime is generally an effective agent for the treatment of AmpC-E infections [180]. TMP-SMX, fluoroquinolones, aminoglycosides, tetracyclines, and other non-β-lactam antibiotics do not induce *ampC* and are also not substrates for AmpC hydrolysis.

Question 2.3: What Is the Role of Cefepime for the Treatment of Infections Caused by Enterobacterales at Moderate 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 risk of significant AmpC production (ie, *E. cloacae* complex, *K. aerogenes*, and *C. freundii)*.

Rationale

Cefepime is an oxyimino-cephalosporin that is relatively stable against AmpC enzymes and that also has low *ampC* induction potential [178, 179, 181, 182]. Clinical trials comparing clinical outcomes of patients with AmpC-E infections treated with cefepime vs carbapenem therapy are not available. However, several observational studies suggest cefepime is associated with similar clinical outcomes as carbapenem therapy [163, 183–186]. Furthermore, a meta-analysis including seven studies comparing clinical outcomes of patients receiving cefepime vs carbapenems for *Enterobacter* spp., *Citrobacter* spp., and *Serratia* spp. bloodstream infections did not find differences in clinical outcomes between these treatment regimens [180]. However, considerable heterogeneity between studies existed, ill-appearing patients were more likely to receive carbapenem therapy, and risk of clinically significant AmpC production varied by the included species. In light of both the advantages of cefepime as a compound and no clear clinical failure signals in the literature when administered for the treatment of AmpC-E infections, the panel suggests cefepime as a preferred treatment option for *E. cloacae*, *K. aerogenes*, and *C. freundii* infections (Table 1).

Although cefepime may be effective for the treatment of AmpC-E infections, it remains suboptimal against infections caused by ESBL-E, which is a consideration if both enzymes may be produced by an Enterobacterales (Question 1.5). In a study from Taiwan, 89% of *E. cloacae* isolates with cefepime MICs of 4–8 μg/mL (ie, susceptible dose-dependent) were ESBL-producing [111]. The same study evaluated 217 patients with *E. cloacae* bloodstream infections and found that all 10 patients with infections caused by ESBL-producing isolates with cefepime MICs of 4–8 μg/mL who received cefepime died within 30 days. In contrast, none of the 6 patients who received cefepime for infections caused by non-ESBL-producing cefepime isolates with MICs of 4–8 μg/mL died within 30 days [111].

Data are incomplete on the frequency of ESBL production by Enterobacterales at moderate risk of clinically significant AmpC production in the United States. An evaluation of 211 consecutive *E. cloacae* isolates from 66 United States hospitals from 2019 to 2020 indicated that 3% contained a *bla*CTX-M gene [8]. A study from Pittsburgh found that 15 of 45 (33%) *E. cloacae* bloodstream isolates collected between 2003 and 2005 produced SHV-type ESBLs [187]. There was no association between ESBL production and the cefepime MIC. A study from Baltimore found that ESBL genes were identified in 22% of *K. aerogenes* (4/18), 14% of *E. cloacae* (7/51), and in no *C. freundii* (0/8 [0%]) bloodstream isolates collected between 2018–2021 [188]. There was no correlation between the presence of an ESBL gene and the cefepime MIC; none of the ESBL-producing isolates had cefepime MICs of 4–8 μg/mL [188].

Contemporary data specific to the United States are needed to better understand how frequently ESBLs are produced by Enterobacterales at moderate risk of clinically significant AmpC production. Available data do not suggest there is a clear association between cefepime susceptible dose-dependent MICs (ie, MICs 4–8 μg/mL) and ESBL production. Cefepime susceptible dose-dependent MICs are based on cefepime dosages of 2 grams every 8 hours, infused over 3 hours and this dosing strategy is suggested to treat Enterobacterales infections with cefepime MICs in this range [16, 186] (Table 2).

Question 2.4: What Is the Role of Ceftriaxone for the Treatment of Infections Caused by Enterobacterales at Moderate Risk of Clinically Significant AmpC Production Due to an Inducible *ampC* Gene?

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

Rationale

Clinical reports differ on how frequently resistance to ceftriaxone emerges during the treatment of infections by Enterobacterales at moderate risk for clinically significant *ampC* induction. Several challenges exist when interpreting studies that have attempted to address this question. First, there are no CLSI-endorsed approaches for AmpC detection in clinical isolates, making quantifying their production difficult. Second, these organisms may display ceftriaxone resistance for other reasons (eg, ESBL production); however, such mechanisms are rarely investigated in clinical studies for organisms other than *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis*. Third, studies often

combine estimates for organisms at low risk for significant AmpC production (eg, *S. marcescens*, *M. morganii*) with those posing a higher risk (eg, *E. cloacae*, *C. freundii*), obscuring an understanding of how frequently resistance to ceftriaxone emerges for organisms at moderate risk for clinically significant AmpC production [189]. Fourth, studies that evaluate the proportion of isolates exhibiting ceftriaxone non-susceptibility after ceftriaxone exposure do not include confirmation of genetic relatedness of index and subsequent isolates. Additionally, many AmpC clinical studies used pre-2010 CLSI ceftriaxone breakpoints (ie, ceftriaxone MICs ≤8 μg/mL), making translation of prevalence estimates to current CLSI ceftriaxone susceptibility breakpoints of ≤1 μg/mL challenging [16, 189]. Finally, in addition to selection bias, there is significant heterogeneity in sources of infections, severity of illness, pre-existing medical conditions, co-administration of additional antibiotics, and ceftriaxone dosing and duration across studies, complicating the interpretation of clinical data.

These limitations notwithstanding, available data suggest that the emergence of resistance after ceftriaxone exposure occurs in approximately 20% of infections caused by *E. cloacae*, *K. aerogenes*, or *C. freundii* [150, 159–163, 190–192]. 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. No clinical trials have compared the outcomes of patients with presumed AmpC-E infections treated with ceftriaxone compared to alternate agents (eg, cefepime). A number of observational studies compared the clinical outcomes of patients with infections caused by *E. cloacae*, *K. aerogenes*, and *C. freundii* treated with ceftriaxone compared with other β-lactams [160, 190, 191, 193–197]. Most of these studies did not identify differences in clinical outcomes when comparing patients treated with ceftriaxone vs carbapenems, with the limitations outlined above.

Nonetheless, because available data indicate a reasonable risk for the emergence of resistance when ceftriaxone (or other third-generation cephalosporins) is prescribed for infections caused by organisms at moderate risk of AmpC production (ie, infections caused by *E. cloacae*, *K. aerogenes*, *C. freundii*), the panel suggests generally avoiding third-generation cephalosporins 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 uncomplicated cystitis. For other relatively uncomplicated infections it may be reasonable to transition to ceftriaxone after clear clinical improvement has been achieved and if there are no concerns for ongoing sources of infection (eg, abscesses, indwelling catheters), weighing the convenience of once-daily ceftriaxone dosing with the potentially increased risk of emergence of resistance.

Question 2.5: What Is the Role of Piperacillin-Tazobactam for the Treatment of Infections Caused by Enterobacterales at Moderate Risk of Clinically Significant AmpC Production Due to an Inducible *ampC* Gene?

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

Rationale

Tazobactam is less effective at protecting β-lactams from AmpC hydrolysis than newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam [149, 173, 174, 198]. The role of piperacillin-tazobactam in treating Enterobacterales at moderate risk for clinically significant AmpC production remains uncertain. A 2019 meta-analysis summarized the findings of eight observational studies and did not identify a difference in mortality between patients treated with piperacillin-tazobactam and carbapenems for bacteremia caused by *Enterobacter* spp., *Citrobacter* spp., or *Serratia* spp. [189]. However, significant heterogeneity across studies and confounding by indication likely existed (ie, ill appearing patients were more likely to be prescribed carbapenems). In 2 observational studies included in this meta-analysis, 30-day mortality among patients treated with piperacillin-tazobactam was numerically higher than for patients treated with carbapenems (15% [6/41 patients] vs 7% [3/41 patients] [199] and 45% [10/22 patients] vs 11% [5/45 patients], respectively) [194]. At least 2 other observational studies including 103 and 81 patients, respectively, with bloodstream infections caused by Enterobacterales known to harbor chromosomal *ampC* genes indicated significantly poorer clinical outcomes for patients treated with piperacillin-tazobactam compared with cefepime or carbapenem therapy [192, 200].

A pilot unblinded clinical trial compared the outcomes of 72 patients with bloodstream infections caused by *Enterobacter* spp., *K. aerogenes, C. freundii*, *M. morganii*, *Providencia* spp., or *S. marcescens* randomized to piperacillin-tazobactam (4.5 grams IV every 6 hours as a standard infusion) or meropenem (1 gram IV every 8 hours as a standard infusion) [201]. 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 for individual components of this composite outcome: mortality (0% vs 6%, $P = .13$); clinical failure (21% vs 12%, $P = .29$); microbiological failure (13% vs 0%), $P = .03$), and microbiological relapse (0% vs 9%, $P = .06$), for the piperacillin-tazobactam and meropenem arms, respectively. The findings of this trial are challenging to interpret and a larger trial is needed to more definitively determine the role of piperacillin-tazobactam for the treatment of organisms at moderate risk for clinically significant *ampC* induction.

In light of the limited ability of tazobactam to protect piperacillin from AmpC hydrolysis in vitro and at least 4 observational studies identifying poorer clinical outcomes in patients prescribed piperacillin-tazobactam [191, 194, 199, 200], the panel suggests against 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 – although narrower-spectrum agents are generally preferred. For other relatively uncomplicated infections it may be reasonable to transition to piperacillin-tazobactam in settings of adverse events to preferred agents (eg, neurotoxicity associated with cefepime) or other patient-specific factors (eg, polymicrobial infections), after considering the potentially increased risk of treatment failure with piperacillin-tazobactam therapy. This practice is only advised after clinical improvement has been achieved and if there are no concerns for ongoing sources of infection (eg, abscesses, indwelling catheters).

Question 2.6: What Is the Role of Newer β-Lactam-β-Lactamase Inhibitor Combinations and Cefiderocol for the Treatment of Infections Caused by Enterobacterales at Moderate Risk of Clinically Significant AmpC Production Due to an Inducible *ampC* Gene?

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

Rationale

Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam generally exhibit in vitro activity against AmpC-E [130, 202–204]. Ceftazidime-avibactam is likely to be effective as a treatment for infections caused by AmpC-E [205]. Although the frequency is unknown, emergence of resistance of AmpC-E to ceftazidime-avibactam has been described, generally due to amino acid changes in the omega loop region of the AmpC enzyme [206–208]. Carbapenems are generally stable to hydrolysis by AmpC-E; by extension meropenem-vaborbactam and imipenem-cilastatin-relebactam are expected to be effective treatment options for AmpC-E.

Cefiderocol demonstrates in vitro activity against AmpC-E [129, 209] and it is likely to be effective in clinical practice, although some case reports indicate the potential for AmpC-E to develop resistance to this agent [206, 207]. Although ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are likely to be effective against AmpC-E infections, the panel suggests that these agents be preferentially reserved for treating infections caused by organisms exhibiting carbapenem resistance, where a greater need for them exists.

Ceftolozane was developed to be more resistant to hydrolysis than earlier cephalosporins against *Pseudomonas*-derived AmpC cephalosporinases; however, less is known about ceftolozane-tazobactam's activity against AmpC-E. Tazobactam is less effective at protecting β-lactams from AmpC hydrolysis compared with newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam [149, 173, 174, 198]. Although some in vitro data suggest ceftolozane-tazobactam has activity against AmpC-E [210], in at least 1 investigation the agent was active against only 19% of *E. cloacae* isolates producing moderate levels of AmpC enzymes [211]. Clinical outcomes data for ceftolozane-tazobactam for the treatment of AmpC-E infections are limited; a clinical trial evaluating this question is underway [212]. Based on the limited available data, the panel suggests against the use of ceftolozane-tazobactam as a treatment option for AmpC-E infections.

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

Question 2.7: What Is the Role of Non-β-Lactam Therapy for the Treatment of Infections Caused by Enterobacterales at Moderate Risk of Clinically Significant AmpC Production Due to an Inducible *ampC* Gene?

Suggested approach: Nitrofurantoin and TMP-SMX are preferred treatment options for uncomplicated cystitis caused by AmpC-E. Ciprofloxacin, levofloxacin, or an aminoglycoside (as a single dose) are alternative treatment options for AmpC-E uncomplicated cystitis. TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis or cUTIs caused by AmpC-E.

Aminoglycosides are alternative options for pyelonephritis or cUTI when resistance or toxicities preclude the use of TMP-SMX or fluoroquinolones. For AmpC-E infections outside of the urinary tract, transitioning from cefepime to oral TMP-SMX, ciprofloxacin, or levofloxacin should be considered, if susceptibility is demonstrated.

Rationale

Preferred treatment options for AmpC-E uncomplicated cystitis include nitrofurantoin [19] or TMP-SMX [21]. Ciprofloxacin, levofloxacin, or a single dose of IV aminoglycosides are alternative are alternative treatment options for AmpC-E uncomplicated cystitis, as described in Question 1.1.

TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis or cUTIs caused by AmpC-E [42, 213], as described in Question 1.2. Cefepime is a preferred agent for pyelonephritis or cUTI when resistance or toxicities preclude the use of TMP-SMX or fluoroquinolones. Aminoglycosides are alternative options for the

treatment of AmpC-E pyelonephritis or cUTI as discussed in Question 1.2.

The role of TMP-SMX or fluoroquinolones for the treatment of AmpC-E infections outside of the urinary tract has not been formally evaluated in clinical trials. However, neither TMP-SMX nor fluoroquinolones are substrates for AmpC hydrolysis. Transitioning to oral TMP-SMX or fluoroquinolones has been shown to be effective for Enterobacterales bloodstream infections, including those caused by AmpC-E, after appropriate clinical milestones are achieved [73, 74]. These agents are reasonable treatment options for patients with AmpC-E infections if the conditions described in the second to last paragraph of Question 1.3 are met.

SECTION 3: CARBAPENEM-RESISTANT ENTEROBACTERALES

CRE are defined as members of the Enterobacterales order resistant to at least 1 carbapenem antibiotic (ie, ertapenem, meropenem, imipenem, doripenem) or producing a carbapenemase enzyme [214]. Resistance to at least 1 carbapenem other than imipenem is required for bacteria intrinsically less susceptible to imipenem (eg, *Proteus* spp., *Morganella* spp., *Providencia* spp.) [214].

CRE comprise a heterogenous group of pathogens encompassing multiple mechanisms of resistance, broadly divided into those that are not carbapenemase-producing and those that are carbapenemase-producing. CRE that are not carbapenemase-producing may be the result of amplification of non-carbapenemase β-lactamase genes (eg, ESBL genes) with concurrent outer membrane porin disruption [215]. Carbapenemase-producing isolates account for 35%–83% of CRE cases in the United States, with higher percentages observed when restricting the definition of CRE to require resistance to meropenem or imipenem [216–218].

The most common carbapenemases in the United States are *K. pneumoniae* carbapenemases (KPCs), which are not limited to *K. pneumoniae* isolates. Other carbapenemases include New Delhi metallo-β-lactamases (NDMs), Verona integron-encoded metallo-β-lactamases (VIMs), imipenem-hydrolyzing metallo-β-lactamases (IMPs), and oxacillinases (eg, OXA-48-like) [218–220]. NDM, VIM, and IMP carbapenemases are collectively referred to as metallo-β-lactamases (MBLs) [221].

The CDC characterized over 42 000 CRE isolates collected between 2017 and 2019 and found that approximately 35% of CRE clinical or surveillance isolates in the United States carry 1 of the main 5 carbapenemase genes [216]. Of these carbapenemase-producing isolates, the specific prevalence by carbapenemase gene family was as follows: *bla*KPC (86%), *bla*NDM (9%), *bla*VIM (<1%), *bla*IMP (1%), or *bla*OXA- 48-like (4%) [216]. A more recent cohort of 261 consecutive clinical CRE isolates (defined as resistance to meropenem or imipenem) from 2019 to 2021 from across the United States found that 83% of isolates were carbapenemase producing (*bla*KPC [80%], *bla*NDM [15%], *bla*IMP [5%], *bla*OXA-48-like [7%]); between 2019 and 2021 the percentages of *bla*KPC decreased from 74% to 57%, whereas the percentages of isolates with MBL genes (eg, *bla*NDM, *bla*VIM, *bla*IMP) increased from 4% to 20% and those with *bla*OXA-48-like increased from 1% to 8% [218].

Knowledge of the carbapenemase produced when CRE is identified in clinical isolates is important in guiding treatment decisions as specific newer β-lactam antibiotics have activity against specific carbapenemases. Phenotypic tests such as the modified carbapenem inactivation method differentiate carbapenemase and non-carbapenemase-producing CRE but generally do not provide information on the specific carbapenemase present [16, 222]. This information is increasingly important given the evolving epidemiology of carbapenemases. Clinical microbiology laboratories are strongly encouraged to implement either nucleic acid or antigen testing to identify the presence of the specific carbapenemases produced by clinical CRE isolates. Treatment suggestions for CRE infections listed below assume that in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 3.1: What Are Preferred Antibiotics for the Treatment of Uncomplicated Cystitis Caused by CRE?

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

Rationale

Clinical trial data evaluating the efficacy of most preferred agents for uncomplicated CRE cystitis are not available. However, as nitrofurantoin, TMP-SMX, ciprofloxacin, or levofloxacin all achieve high concentrations in urine, they are expected to be effective for uncomplicated CRE cystitis, if the isolate is susceptible [5, 19–23].

A single dose of an aminoglycoside is an alternative option for uncomplicated CRE cystitis, for reasons described in Question 1.1. In general, higher percentages of CRE clinical isolates are susceptible to plazomicin compared to other aminoglycosides [46]. Oral fosfomycin is an alternative treatment option for uncomplicated cystitis caused by *E. coli*, including if carbapenem resistant, as discussed in Question 1.1 [19].

Colistin (the active form of the commercially available parenteral inactive prodrug colistimethate sodium) is an alternative agent for uncomplicated CRE cystitis. Colistin converts to its active form in the urinary tract [223]. Clinicians should

remain cognizant of the associated risk of nephrotoxicity. Polymyxin B should not be used as treatment for uncomplicated CRE cystitis, due to its predominantly nonrenal clearance and lower rates of success when compared to aminoglycosides [224, 225]. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are alternative options for uncomplicated CRE cystitis [131, 226–230].

Question 3.2: What Are Preferred Antibiotics for the Treatment of Pyelonephritis or cUTI Caused by CRE?

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

Rationale

Although the minority of CRE are expected to retain susceptibility to TMP-SMX, ciprofloxacin, or levofloxacin, they are preferred agents to treat CRE pyelonephritis or cUTI if susceptibility is demonstrated [40–42]. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis and cUTIs caused by CRE based on clinical trials showing noninferiority of these agents to common comparator agents for UTIs [131, 226–230]. Isolates included in these trials were overwhelmingly carbapenem susceptible.

Aminoglycosides are suggested as alternative agents for the treatment of CRE pyelonephritis or cUTI [45, 47, 48, 231], as described in Question 1.2.

Fosfomycin is not suggested for the treatment of pyelonephritis or cUTI given its limited renal parenchymal concentrations. More data are needed to evaluate the role of oral fosfomycin for patients with pyelonephritis or cUTI, particularly when administered as a multidose regimen and after several days of preferred therapy as further described in Question 1.2. Of note, in both clinical trials described in Question 1.2, no patients had CRE infections [33, 51].

Question 3.3: What Are the Preferred Antibiotics for the Treatment for Infections Caused by CRE Outside of the Urinary Tract that are Not Carbapenemase Producing?

Suggested approach: For infections caused by Enterobacterales isolates that are NOT carbapenemase producing that exhibit susceptibility to meropenem and imipenem (ie, MICs ≤1 μg/mL) but are not susceptible to ertapenem (ie, MICs ≥1 μg/mL), the use of extended-infusion meropenem (or imipenem-cilastatin) is suggested. For infections caused by Enterobacterales isolates that are NOT carbapenemase producing and that do not exhibit susceptibility to any carbapenem, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are preferred treatment options.

Rationale

For infections caused by Enterobacterales isolates that are not carbapenemase producing that exhibit susceptibility to meropenem and imipenem (ie, MICs ≤1 μg/mL) but are not susceptible to ertapenem (ie, MICs ≥1 μg/mL), extended-infusion meropenem (or imipenem-cilastatin) are suggested (Table 1). An evaluation of CRE isolates submitted to the CDC indicated that less than 3% of the 1249 isolates resistant to ertapenem but susceptible to meropenem and imipenem contained a carbapenemase gene [232]. Standard-infusion meropenem or imipenem-cilastatin may be reasonable for uncomplicated cystitis (Table 1).

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

It was previously considered standard practice to administer extended-infusion meropenem in combination with a second agent, frequently polymyxins or aminoglycosides, for the treatment of infections caused by CRE isolates with meropenem MICs as high as 8–16 μg/mL [233]. PK/PD data suggested that extended-infusion meropenem may lead to sufficient drug concentrations for the treatment of infections caused by organisms with carbapenem MICs in this range [234–236]. However, subsequent observational and trial data indicate increased mortality and excess nephrotoxicity associated with polymyxin or aminoglycoside-based regimens relative to newer β-lactam-β-lactamase inhibitor agents for the treatment of CRE infections [237–251]. Therefore, the panel advises against the use of extended-infusion carbapenems with or without the addition of a second agent for the treatment of CRE infections when susceptibility to meropenem or imipenem has not been demonstrated. It is plausible that the addition of vaborbactam or relebactam may decrease MICs of meropenem or imipenem even in isolates without a carbapenemase because of other β-lactamases (eg, ESBLs) that may be overproduced [252, 253].

Tigecycline or eravacycline are alternative options for the treatment of CRE infections not involving the bloodstream or urinary tract (Question 3.8). Their activity is independent of the presence or type of carbapenemase.

Question 3.4: What Are the Preferred Antibiotics for the Treatment of Infections Outside of the Urinary Tract Caused by CRE if KPC Production is Present?

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

Rationale

Preferred agents for KPC-producing infections include meropenem-vaborbactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam. All 3 agents appear to have greater than 95% activity against KPC-producing Enterobacterales in the United States [254]. Although all 3 are preferred agents for the treatment of KPC-producing infections, the panel slightly favors meropenem-vaborbactam, followed by ceftazidime-avibactam, and then imipenem-cilastatin-relebactam, based on available data regarding clinical outcomes (ie, fewest clinical data available for imipenem-cilastatin-relebactam) and the likelihood of emergence of resistance (ie, highest likelihood of emergence of resistance for ceftazidime-avibactam) [255]. These agents are associated with improved clinical outcomes and reduced toxicity compared to regimens previously used to treat KPC-producing infections, which were often polymyxin or aminoglycoside-based [237–246, 249–251, 256]. Clinical trials comparing these agents to each other (ie, meropenem-vaborbactam vs ceftazidime-avibactam) for the treatment of KPC-producing infections are not available.

An observational study compared the clinical outcomes of patients who received either meropenem-vaborbactam or ceftazidime-avibactam for at least 72 hours for the treatment of CRE infections [257]. Carbapenemase status was largely not reported. Clinical cure and 30-day mortality between the 26 patients who received meropenem-vaborbactam and 105 patients who received ceftazidime-avibactam were 85% and 61% (limited to patients with isolates exhibiting susceptibility to the agent administered) and 12% and 19%, respectively. Although these differences were not statistically significant, they numerically favor meropenem-vaborbactam. Of patients who experienced recurrent CRE infections, 0% (0 of 3) of patients receiving meropenem-vaborbactam and 20% (3 of 15) of patients receiving ceftazidime-avibactam had subsequent CRE isolates resistant to initial therapy. This study had a number of important limitations: likely selection bias due to its observational nature, relatively small numbers of patients, heterogenous sites of CRE infection, more than half of patients had polymicrobial infections, and more than half of patients received additional antibiotic therapy. These limitations notwithstanding, this study suggests that both meropenem-vaborbactam and ceftazidime-avibactam are reasonable treatment options for KPC-producing infections, although the emergence of resistance may be more common with ceftazidime-avibactam (Question 3.7). At least 2 groups have published their clinical experiences with the use of ceftazidime-avibactam and meropenem-vaborbactam for CRE infections, where KPCs were the predominant carbapenemase, and similarly found that patients who received meropenem-vaborbactam had a slightly higher likelihood of clinical cure and survival and a lower risk of emergence of resistance than patients treated with ceftazidime-avibactam [258–261].

Limited clinical data are available for imipenem-cilastatin-relebactam for the treatment of KPC-producing Enterobacterales. A clinical trial including patients with infections caused by gram-negative organisms not susceptible to imipenem assigned patients to receive either imipenem-cilastatin-relebactam vs imipenem-cilastatin and colistin [240]. Of patients with Enterobacterales infections, 40% (2 of 5 patients) and 100% (2 of 2 patients) experienced a favorable clinical response with imipenem-cilastatin-relebactam and imipenem-cilastatin in combination with colistin, respectively [240]. It is difficult to draw meaningful conclusions from these data given the small numbers. However, in vitro activity of imipenem-cilastatin-relebactam against KPC-producing Enterobacterales [262–266], clinical experience with imipenem-cilastatin, and the stability of relebactam as a β-lactamase inhibitor [267] suggest imipenem-cilastatin-relebactam is likely to be effective for KPC-producing Enterobacterales if an organism tests susceptible.

Cefiderocol is suggested as an alternative treatment option for CRE infections outside of the urine. Cefiderocol is a synthetic conjugate composed of a cephalosporin moiety and a siderophore, which binds to iron and facilitates bacterial cell entry using active iron transporters [268]. Once inside the periplasmic space, the cephalosporin moiety dissociates from iron and binds primarily to PBP3 to inhibit bacterial cell wall synthesis [269]. Over 95% of KPC-producing Enterobacterales test susceptible to cefiderocol [270]. Robust comparative effectiveness data specifically evaluating the role of cefiderocol for KPC-producing Enterobacterales infections are not available. Cefiderocol is suggested as an alternative agent for treating KPC-producing pathogens due to limited clinical outcomes data and to reserve it for the treatment of infections caused by MBL-producing Enterobacterales or glucose non-fermenting gram-negative organisms.

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

Question 3.5: What Are the Preferred Antibiotics for the Treatment of Infections Outside of the Urinary Tract Caused by CRE if NDM or Other MBL Production is Present?

Suggested approach: Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are preferred

treatment options for NDM and other MBL-producing Enterobacterales infections.

Rationale

There is no United States Food and Drug Administration (FDA)-approved beta-lactam/beta-lactamase inhibitor with activity against MBL-producing Enterobacterales, although several promising compounds are in late phases of development or have completed clinical trials. Preferred antibiotic options for NDM-producing Enterobacterales (or other MBLs), include ceftazidime-avibactam plus aztreonam, or cefiderocol monotherapy. NDMs hydrolyze penicillins, cephalosporins, and carbapenems, but not aztreonam. Although aztreonam is not hydrolyzed by NDMs, it can be hydrolyzed by other serine β-lactamases that are often co-produced by NDM-producing isolates (eg, ESBLs, AmpCs, KPCs, or OXA-48-like enzymes). Avibactam generally remains effective at inhibiting the activity of these other β-lactamases. Extrapolating estimates from aztreonam-avibactam, which is not currently clinically available in the United States, the combination of ceftazidime-avibactam and aztreonam is active against approximately 90% of MBL-producing Enterobacterales isolates [271–276]. The CLSI has endorsed the use of a broth disk elution method to evaluate the susceptibility of MBL-producing Enterobacterales to the combination of ceftazidime-avibactam/aztreonam [16, 277].

An observational study of 102 adults with bloodstream infections caused by MBL-producing Enterobacterales (82 were NDM-producing) from 2018–2019 compared the outcomes of 52 patients receiving ceftazidime-avibactam in combination with aztreonam vs 50 patients receiving a combination of other agents, primarily polymyxin or tigecycline-based therapy [278]. Thirty-day mortality was 19% for the ceftazidime-avibactam/aztreonam group and 44% for the alternate arm, with a significantly lower risk of mortality associated with the former in a propensity score-matched analysis. Another observational study of MBL-producing Enterobacterales infections (328 were NDM-producing, 58% bloodstream) from 2019–2022 included 215 patients receiving ceftazidime-avibactam/aztreonam, 33 patients receiving cefiderocol, and 26 patients receiving colistin-containing regimens [279]. Unadjusted 30-day mortality was 22%, 33%, and 50% for the ceftazidime-avibactam/aztreonam, cefiderocol, and colistin-containing regimens, respectively [279]. Ceftazidime-avibactam/aztreonam was associated with reduced 30-day mortality compared to colistin-based regimens.

Strategies for administering the combination of ceftazidime-avibactam and aztreonam are reviewed in Table 1 and Supplementary Material [280–282]. Patients should be monitored closely for elevations in liver enzymes, which was observed in approximately 40% of patients in a phase 1 study [283]. In rare situations where cefiderocol or combination therapy with ceftazidime-avibactam and aztreonam is not possible (eg, allergy or intolerance), combination therapy with aztreonam and meropenem-vaborbactam or imipenem-cilastatin-relebactam can be considered, provided OXA-type carbapenemases are not present [284, 285]. Clinical data investigating this approach are limited [286].

A second preferred option for the treatment of NDM and other MBL-producing Enterobacterales is cefiderocol. A cohort of 200 North American and European MBL-producing Enterobacterales from 2014 to 2019 indicated that approximately 92% of isolates were susceptible to cefiderocol [287]. However, resistance with NDM-producing Enterobacterales has been described with and without prior cefiderocol exposure and thus susceptibility should be confirmed [288–291]. A clinical trial including patients with MBL-producing Enterobacterales infections identified clinical cure in 80% (8 of 10) and 0% (0 of 4) of patients receiving cefiderocol vs alternate therapy (primarily polymyxin-based therapy), respectively [292]. Day 28 mortality occurred in 10% (1 of 10) and 75% (3 of 4) of patients, respectively [292]. Clinical trial data comparing ceftazidime-avibactam/aztreonam vs cefiderocol are not available and both agents are considered preferred treatment options for MBL-producing Enterobacterales infections.

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

Question 3.6: What Are the Preferred Antibiotics for the Treatment of Infections Outside of the Urinary Tract Caused by CRE if OXA-48-Like Production is Present?

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

Rationale

If OXA-48-like enzymes are produced by an Enterobacterales clinical isolate, ceftazidime-avibactam [293] is preferred and cefiderocol is an alternative option [294]. More than 95% of OXA-48-like-producing Enterobacterales isolates are susceptible to both ceftazidime-avibactam and cefiderocol [270, 295]. Meropenem-vaborbactam and imipenem-cilastatin-relebactam have limited against OXA-48-like producing isolates because vaborbactam and relebactam are unlikely to inhibit OXA-48-like enzymes and are not suggested, even if susceptible in vitro [262, 296–298].

Clinical trial data comparing ceftazidime-avibactam vs cefiderocol are not available. Moreover, limited clinical data investigating the clinical outcomes of patients with OXA-48-like infections treated with either agent are available. An observational study including 171 patients with OXA-48-like-producing Enterobacterales infections treated with ceftazidime-avibactam (without a comparator arm) identified 30-day mortality in 22%

of patients [299]. In an observational study of 76 patients with OXA-48-like-producing Enterobacterales bloodstream infections, 12% and 26% of patients died within 30 days among the ceftazidime-avibactam and alternative (eg, polymyxins) arms, respectively [293]. In a subgroup analysis of 10 patients with OXA-48-positive Enterobacterales who received cefiderocol therapy in 2 clinical trials, all were alive at day 28 and 7 achieved clinical cure [294]. Although both ceftazidime-avibactam and cefiderocol are expected to be effective against OXA-48-like-producing infections, cefiderocol is suggested as an alternative agent both because of less published clinical data and to reserve it for the treatment of infections caused by MBL-producing Enterobacterales or glucose non-fermenting gram-negative organisms.

Tigecycline or eravacycline are alternative options for the treatment of OXA-48-like-producing infections not involving the bloodstream or urinary tract (Question 3.8). Their activity is independent of the presence or type of carbapenemases.

Question 3.7: What Is the Likelihood of the Emergence of Resistance of CRE Isolates to the Newer β-Lactam Agents When Used to Treat CRE Infections?

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

Rationale

As with any β-lactam agent, treatment with a newer β-lactam for CRE infections (ie, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol) increases the likelihood that subsequent isolates causing infection will no longer be effectively treated with these agents. The most data on the emergence of resistance of CRE to novel agents focuses on KPC-producing isolates. The emergence of resistance of KPC-producing isolates to ceftazidime-avibactam most commonly occurs because of mutations in the *bla*KPC gene translating to amino acid changes in the KPC carbapenemase and increased hydrolysis of ceftazidime. These changes may result in a restoration of susceptibility to carbapenems, but the clinical significance of this finding is unknown [300–320]. Of note, amino acid substitutions in active sites of OXA carbapenemases also appear to contribute to OXA-48-like producers exhibiting ceftazidime-avibactam resistance [321]. Changes in outer membrane permeability and efflux systems are the primary drivers of the emergence of resistance of KPC-producing isolates to meropenem-vaborbactam [260, 309, 322–328] and imipenem-cilastatin-relebactam [329–331]. Increases in *bla*KPC copy numbers have been associated with resistance to all of these agents [332–334].

Diverse mechanisms of resistance of Enterobacterales to cefiderocol have been described [335, 336] including mutations in the TonB-dependent iron transport system [288, 290, 337–340], amino acid changes in AmpC β-lactamases [206, 207], and increased NDM expression [341]. Cefiderocol resistance appears notably higher in ceftazidime-avibactam resistant Enterobacterales isolates compared to ceftazidime-avibactam susceptible isolates (83% vs 7%) [342]. Increasing reports of amino acid insertions in PBP3, the active binding site of cefiderocol and aztreonam, are being described in NDM-producing *E. coli* isolates [316, 343–345] leaving no available β-lactam treatment options. Such reports remain rare in the United States [272, 291, 346].

Estimates of the emergence of resistance after clinical exposure to ceftazidime-avibactam and meropenem-vaborbactam are approximately 10%–20% [241, 245, 261, 304] and <5% [257, 260, 347], respectively. The most data are available for ceftazidime-avibactam, possibly in part because it was the first of the newer β-lactam agents active against CRE to receive FDA approval. Limited data exist on the frequency of emergence of resistance of CRE to imipenem-cilastatin-relebactam and cefiderocol.

It is recommended to repeat AST for the newer β-lactams when a patient previously infected with a CRE presents with a sepsis-like picture suggestive of a new or relapsed infection. Furthermore, if a patient was recently treated with ceftazidime-avibactam and presents with a sepsis-like condition, it is suggested to consider a different novel β-lactam agent at least until culture and AST data are available, particularly if AST results from the previous infection indicate that there are other active β-lactam agents. For example, if a patient with a KPC-producing bloodstream infection received a treatment course of ceftazidime-avibactam 1 month earlier and presents to medical care with symptoms suggestive of infection, consider administering an agent such as meropenem-vaborbactam until organism and AST results are available.

Question 3.8: What Is the Role of Tetracycline Derivatives for the Treatment of Infections Caused by CRE?

Suggested approach: Although β-lactam agents remain preferred treatment options for CRE infections, tigecycline and eravacycline are alternative options when β-lactam agents are either not active or unable to be tolerated. Tetracycline derivatives are not suggested for the treatment of CRE urinary tract infections or bloodstream infections.

Rationale

Tetracycline derivatives function independent of the presence or type of carbapenemase. More specifically, both carbapenemase-producing (eg, KPC, NDM, OXA-48-like carbapenemases) and non-carbapenemase-producing CRE may test susceptible to these agents [348–350]. The tetracycline-derivative agents achieve rapid tissue distribution following administration, resulting in limited urine and serum

concentrations [351]. Tetracycline derivatives are not suggested for urinary and bloodstream infections, and in at least 1 observational study have been associated with increased mortality compared to alternative agents for the treatment of CRE bloodstream infections [352]. Tigecycline or eravacycline can be considered as alternative options for intra-abdominal infections, skin and soft tissue infections, osteomyelitis, and respiratory infections when optimal dosing is used (Table 1). Nausea and emesis are reported in as many as 20%–40% of patients receiving tetracycline derivatives [353–355]. Of note, CLSI breakpoints are not available for tigecycline or eravacycline against Enterobacterales, but FDA breakpoints are available [356] (Table 2). A hollow fiber model [357] and clinical outcomes data [352] suggest that tigecycline MICs of ≥0.5 for CRE isolates are associated with poor outcomes.

Tigecycline has more published experience available for the treatment of CRE infections compared with eravacycline [358–361]. A meta-analysis of 15 clinical trials suggested that tigecycline monotherapy is associated with higher mortality than alternative regimens used for the treatment of pneumonia, not exclusively limited to pneumonia caused by the Enterobacterales [362]. Subsequent investigations have demonstrated that when high-dose tigecycline is prescribed (200 mg IV as a single dose followed 100 mg IV every 12 hours), mortality differences between tigecycline and comparator agents may no longer be evident [363–365]. Thus, if tigecycline is prescribed for the treatment of CRE infections, the panel recommends that high-dosages be administered [366] (Table 1).

The clinical relevance of differences in MIC distributions between tigecycline and eravacycline described in some studies is unclear because of differences in the PK/PD profile of these agents [367–369]. Fewer than 5 patients with CRE infections were included in clinical trials that investigated the efficacy of eravacycline [358, 370] and post-marketing clinical reports describing its efficacy for the treatment of CRE infections are limited [371].

Minimal clinical data are also available investigating the effectiveness of minocycline against CRE infections [372, 373], but data suggest a lower proportion of CRE isolates are susceptible to minocycline compared to tigecycline or eravacycline [350]. The panel suggests using minocycline with caution for the treatment of CRE infections. Data evaluating the activity of omadacycline, a tetracycline-derivative with both an IV and oral formulation, against CRE suggest reduced potency relative to other tetracycline derivatives and an unfavorable PK/PD profile (Question 1.3) [374–377]. Omadacycline is not suggested for the treatment of CRE infections.

Question 3.9: What Is the Role of Polymyxins for the Treatment of Infections Caused by CRE?

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

Rationale

Observational and clinical data indicate increased mortality and excess nephrotoxicity associated with polymyxin-based regimens relative to comparator agents [237–245, 251]. Concerns about the clinical effectiveness of polymyxins, PK/PD data, and accuracy of polymyxin susceptibility testing led the CLSI to eliminate a susceptible category for colistin and polymyxin B [378]. The panel suggests that these agents be avoided for the treatment of CRE infections, with the exception of colistin as an alternative agent against CRE cystitis. Polymyxin B should not be used as treatment for CRE cystitis, due to its predominantly nonrenal clearance [224].

Question 3.10: What Is the Role of Combination Antibiotic Therapy for the Treatment of Infections Caused by CRE?

Suggested approach: Combination antibiotic therapy (ie, the use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, tetracycline, or polymyxin) is not suggested for the treatment of infections caused by CRE.

Rationale

Although empiric combination antibiotic therapy increases the likelihood that at least 1 active therapeutic agent for patients at risk for CRE infections is being administered, data do not indicate that continued combination therapy—once the β-lactam agent has demonstrated in vitro activity—offers any additional benefit [379]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [379]. Additionally, clinical data indicating that combination therapy prevents the emergence of resistance are lacking.

Randomized trial data are not available comparing the novel β-lactam agents as monotherapy and as a component of combination therapy (eg, ceftazidime-avibactam vs ceftazidime-avibactam and tobramycin). The limited observational data available have not identified improved outcomes with combination therapy [250, 258, 299, 380]. An observational study compared the clinical outcomes of 165 patients receiving ceftazidime-avibactam and 412 patients receiving ceftazidime-avibactam plus a second agent for the treatment of KPC-producing infections [258]. Thirty-day mortality was essentially identical at approximately 25% in both study arms.

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

SECTION 4: PSEUDOMONAS AERUGINOSA WITH DIFFICULT-TO-TREAT RESISTANCE

MDR *P. aeruginosa* is defined as *P. aeruginosa* not susceptible to at least 1 antibiotic in at least 3 antibiotic classes for which *P. aeruginosa* susceptibility is generally expected: penicillins,

cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems [381]. In 2018, the concept of "difficult-to-treat" resistance was proposed [382]. In this guidance document, DTR is defined as *P. aeruginosa* exhibiting non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.

MDR *P. aeruginosa* or DTR *P. aeruginosa* generally evolve as a result of an interplay of multiple resistance mechanisms, including decreased expression of outer membrane porins (eg, OprD), increased production of or amino acid substitutions within *Pseudomonas*-derived cephalosporinase (PDC) enzymes (commonly referred to as pseudomonal AmpC enzymes), upregulation of efflux pumps (eg, MexAB-OprM), mutations in PBP targets, and the presence of expanded-spectrum β-lactamases (eg, *bla*OXA-10) [383, 384]. Carbapenemase production is a relatively uncommon cause of carbapenem resistance in *P. aeruginosa* isolates in the United States [385, 386] but is identified in significant portions of carbapenem-resistant *P. aeruginosa* in other regions of the world (eg, 69% in Latin America, 57% Asia), commonly due to the presence of *bla*KPC or *bla*VIM enzymes [385, 387–392]. These estimates suggest the prevalence of carbapenemase-producing *P. aeruginosa* will increase in the United States in coming years. There are other β-lactamase enzymes (eg, Guiana extended-spectrum beta-lactamase [GES], Vietnamese extended-spectrum beta-lactamase [VEB], *Pseudomonas* extended resistance [PER] enzymes, KPCs, and NDMs] rarely identified in *P. aeruginosa* isolates from patients in the United States that may confer elevated MICs to β-lactam agents, including some newer β-lactam agents [13, 385, 393].

Given that carbapenemases are uncommon in *P. aeruginosa* isolates in the United States, carbapenemase testing for DTR *P. aeruginosa* is not as critical as carbapenemase testing for CRE clinical isolates in United States hospitals. However, the panel encourages all clinical microbiology laboratories to perform AST for MDR and DTR *P. aeruginosa* isolates against newer β-lactam agents (ie, ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol). It is important to understand local DTR *P. aeruginosa* ASTs to guide empiric antibiotic decisions when AST results are pending. Treatment suggestions for DTR *P. aeruginosa* infections assume in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 4.1: What Are Preferred Antibiotics for the Treatment of Infections Caused by MDR *P. aeruginosa*?

Suggested approach: When *P. aeruginosa* isolates test susceptible to both traditional non-carbapenem β-lactam agents (ie, piperacillin-tazobactam, ceftazidime, cefepime, aztreonam) and carbapenems, the former are preferred over carbapenem therapy. For infections caused by *P. aeruginosa* isolates not susceptible to any carbapenem agent but susceptible to traditional β-lactams, the administration of a traditional non-carbapenem β-lactam as high-dose extended-infusion therapy is suggested. For critically ill patients or those with poor source control with *P. aeruginosa* isolates resistant to carbapenems but susceptible to traditional β-lactams, use of newer β-lactam agents to which *P. aeruginosa* test susceptible (eg, ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam) is also a reasonable treatment approach.

Rationale

In general, when a *P. aeruginosa* isolate tests susceptible to traditional β-lactam agents (ie, piperacillin-tazobactam, ceftazidime, cefepime, aztreonam), fluoroquinolones (ie, ciprofloxacin, levofloxacin), or carbapenems, the panel prefers an agent from the former 2 groups be prescribed over carbapenem therapy in an attempt to preserve the activity of carbapenems for future, increasingly drug-resistant infections.

P. aeruginosa not susceptible to a carbapenem agent (eg, meropenem or imipenem-cilastatin MICs ≥4 μg/mL) but susceptible to other traditional β-lactam agents constitute approximately 20% to 60% of carbapenem-resistant *P. aeruginosa* isolates [394–400]. This phenotype is generally due to lack of or limited production of OprD, which normally facilitates entry of carbapenem agents through the outer membrane of *P. aeruginosa* into the periplasmic space, but not the entry of other β-lactam agents [396–398]. Comparative effectiveness studies to guide treatment decisions for infections caused by *P. aeruginosa* resistant to carbapenems but susceptible to traditional non-carbapenem β-lactams are not available. If the isolate is susceptible to a traditional non-carbapenem β-lactam (eg, cefepime), the panel's preferred approach is to administer the non-carbapenem agent as high-dose extended-infusion therapy (eg, cefepime 2 g IV every 8 hours, infused over at least 3 hours) [401] (Table 1).

An alternative approach is to administer a newer β-lactam agent (eg, ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam). This approach is considered an alternative option to preserve the effectiveness of newer β-lactams for future, increasingly AMR infections. However, for critically ill patients or those with poor source control, use of newer β-lactams for *P. aeruginosa* infections resistant to carbapenems but susceptible to traditional non-carbapenem β-lactams is a reasonable consideration. Regardless of the antibiotic agent administered, patients infected with *P. aeruginosa* should be closely monitored to ensure clinical improvement as *P. aeruginosa* exhibits an impressive capacity to iteratively express additional resistance mechanisms while exposed to antibiotic therapy. As an example, an analysis of 767 episodes of *P. aeruginosa* bacteremia identified the emergence of resistance to traditional β-lactam agents within 30 days with the following likelihood: piperacillin-tazobactam (8%), ceftazidime (12%), meropenem (14%), and imipenem (27%) [402]. Clinicians are

advised to request repeat AST of subsequent clinical MDR *P. aeruginosa* isolates obtained from the same patient to monitor for the development of resistance.

Question 4.2: Are There Differences in Percent Activity Against DTR *P. aeruginosa* Across Available β-Lactam Agents?

Suggested approach: Differences in DTR *P. aeruginosa* isolates susceptibility percentages to newer β-lactams exist, in part due to regional differences in enzymatic mechanisms of resistance.

Rationale

Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are β-lactam antibiotics which may be active against DTR *P. aeruginosa* clinical isolates. Summarizing United States surveillance data, ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are active against approximately 90%, 85%, 86%, and 99% of carbapenem-non-susceptible *P. aeruginosa* isolates [270, 403], respectively; lower percent susceptibilities are exhibited by isolates from persons with cystic fibrosis [404, 405]. The panel suggests always obtaining AST results for the four newer β-lactam agents for DTR *P. aeruginosa* infections to guide treatment decisions.

Regional differences in susceptibility estimates across the newer agents exist, often because of varying prevalence of enzymatic-based resistance mechanisms. For example, as neither ceftolozane-tazobactam, ceftazidime-avibactam, nor imipenem-cilastatin-relebactam have activity against MBL-producing *P. aeruginosa* (eg, VIM, NDM enzymes), the percent activity of all of these agents will be reduced in settings where these enzymes are produced by *P. aeruginosa* (eg, Latin America, Middle East) [385]. As ceftolozane-tazobactam remains ineffective against KPC-producing *P. aeruginosa*, its percent activity will be reduced in regions of the world when KPC enzymes are more commonly produced by *P. aeruginosa* (eg, Latin America, China). Similarly, although ceftazidime-avibactam generally remains effective against GES-producing *P. aeruginosa*, imipenem-relebactam is less effective in the setting of GES enzymes; there will likely be higher percent susceptibility to ceftazidime-avibactam compared with other newer β-lactam-β-lactamase inhibitors in areas where GES enzymes are being produced (eg, Spain) [391, 392, 406].

The heavier side chain of ceftolozane compared to ceftazidime confers enhanced steric hindrance to limit PDC-mediated hydrolysis [407, 408]. Ceftolozane does not rely on an inhibitor to restore susceptibility to an otherwise inactive β-lactam agent (ie, ceftolozane has independent activity against DTR *P. aeruginosa* and does not need to rely on its β-lactamase inhibitor to maintain this activity). By definition, neither ceftazidime nor imipenem are active against DTR *P. aeruginosa*. Avibactam and relebactam expand activity of these agents mainly through inhibition of PDCs [127].

The panel does not suggest testing meropenem-vaborbactam activity against DTR *P. aeruginosa* isolates. Vaborbactam only marginally restores meropenem's activity against DTR *P. aeruginosa* [391]. There are no CLSI or FDA breakpoints for meropenem-vaborbactam against *P. aeruginosa*. Some *P. aeruginosa* isolates may appear susceptible to meropenem-vaborbactam but not meropenem, if applying the CLSI meropenem-vaborbactam Enterobacterales susceptible breakpoint of ≤4 μg/mL to *P. aeruginosa* isolates. This is likely an artifact of meropenem-vaborbactam being standardly administered as 2 grams IV every 8 hours, infused over 3 hours. Meropenem breakpoints (ie, ≤ 2 μg/mL) are based on a dosage regimen of 1 gram IV administered every 8 hours, as a 30-minute infusion [16]. If meropenem is infused as 2 grams IV every 8 hours over 3 hours it would likely achieve a similar likelihood of target attainment as meropenem-vaborbactam (ie, approximately 8 μg/mL) [409] .

As discussed in Question 3.4, cefiderocol is composed of a cephalosporin moiety and a siderophore, which facilitates bacterial cell entry using active iron transporters [268]. Combining data from 1500 carbapenem-non-susceptible *P. aeruginosa* isolates in surveillance studies, over 97% of isolates exhibited susceptibility to cefiderocol (ie, MICs ≤4 μg/mL) [129, 209, 410–415].

Question 4.3: What Are Preferred Antibiotics for the Treatment of Uncomplicated Cystitis Caused by DTR *P. aeruginosa*?

Suggested approach: Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are the preferred treatment options for uncomplicated cystitis caused by DTR *P. aeruginosa*. Tobramycin or amikacin (as a single dose) and colistin are alternative treatment options for uncomplicated cystitis caused by DTR *P. aeruginosa*.

Rationale

Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for uncomplicated DTR *P. aeruginosa* cystitis, based on clinical trials showing non-inferiority of these agents to common comparator agents for the treatment of UTIs [131, 228–230, 416]. Data are insufficient to favor 1 of these agents over others for the treatment of uncomplicated cystitis; available trials generally do not include patients infected by pathogens with DTR phenotypes. The suggested approach for the treatment of uncomplicated cystitis caused by DTR *P. aeruginosa* isolates confirmed to produce MBL enzymes (eg, *bla*VIM) is reviewed in Question 4.6.

A single dose of tobramycin or amikacin is an alternative option for uncomplicated cystitis caused by DTR *P. aeruginosa*. A single IV dose of tobramycin or amikacin are likely effective for uncomplicated cystitis as aminoglycosides are nearly exclusively eliminated by the renal route in their active form, with minimal toxicity, but robust clinical data are lacking [28].

As of 2023, there are no longer breakpoints for gentamicin for *P. aeruginosa* [16] (Table 2). Tobramycin breakpoints are available for *P. aeruginosa*, regardless of source (susceptible ≤1 μg/mL); however, amikacin breakpoints against *P. aeruginosa* are only available for infections originating from urinary sources (susceptible ≤16 μg/mL) [16]. Plazomicin has neither CLSI nor FDA breakpoints against *P. aeruginosa*. Surveillance studies indicate that plazomicin is unlikely to provide any incremental benefit against DTR *P. aeruginosa* if resistance to all other aminoglycosides is demonstrated [417].

Colistin, but not polymyxin B, is an alternate consideration for DTR *P. aeruginosa* cystitis as it converts to its active form in the urinary tract [223]. Clinicians should remain cognizant of the associated risk of nephrotoxicity.

The panel does not suggest the use of oral fosfomycin for DTR *P. aeruginosa* cystitis as it may be associated with a high likelihood of clinical failure. This is in part due to the presence of the *fosA* gene, which is found in the genome of almost all *P. aeruginosa* isolates [31].

Question 4.4: What Are Preferred Antibiotics for the Treatment of Pyelonephritis or cUTI Caused by DTR *P. aeruginosa*?

Suggested approach: Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis or cUTI caused by DTR *P. aeruginosa*. Once-daily tobramycin or amikacin are alternative agents for the treatment of DTR *P. aeruginosa* pyelonephritis or cUTI.

Rationale

Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for DTR *P. aeruginosa* pyelonephritis and cUTI, based on clinical trials showing non-inferiority of these agents to common comparator agents [131, 228–230, 416]. Data are insufficient to favor 1 of these agents over the others for the treatment of pyelonephritis or cUTI. Available trials generally do not include patients infected by *P. aeruginosa* with DTR phenotypes. The suggested approach for the treatment of pyelonephritis and cUTI caused by DTR *P. aeruginosa* isolates confirmed to produce MBL enzymes (eg, *bla*VIM) is reviewed in Question 4.6. Once-daily tobramycin or amikacin are alternative agents for the treatment of DTR *P. aeruginosa* pyelonephritis or cUTI [418], although there is a duration-dependent risk of nephrotoxicity [49, 50]. They may be helpful for completing treatment courses (eg, transitioning from another agent for terminal doses) given their prolonged duration of activity in the renal cortex and the convenience of once daily dosing [47, 48] (Table 1, Supplementary Material). Changes in the aminoglycoside breakpoints that were implemented in 2023 are reviewed in Question 4.3.

Question 4.5: What Are Preferred Antibiotics for the Treatment of Infections Outside of the Urinary Tract Caused by DTR *P. aeruginosa*?

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

Rationale

Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam are preferred options for the treatment of DTR *P. aeruginosa* infections outside of the urinary tract, based on in vitro activity [138, 139, 141, 264, 266, 329, 419–457], observational studies [458–463], and clinical trial data [131, 135, 145, 240, 464–468]. The vast majority of patients in clinical trials receiving newer β-lactam agents were not infected with DTR *P. aeruginosa*. Clinical trials comparing novel agents to each other (eg, ceftolozane-tazobactam vs ceftazidime-avibactam) are lacking. Rather, available studies focus on comparing newer β-lactam agents to older agents (eg, ceftolozane-tazobactam vs polymyxins), and generally focus on MDR *P. aeruginosa* and not DTR *P. aeruginosa*. The suggested approach for the treatment of infections outside of the urinary tract caused by DTR *P. aeruginosa* isolates confirmed to produce MBL enzymes (eg, *bla*VIM) is reviewed in Question 4.6.

An observational study including 200 patients with MDR *P. aeruginosa* infections compared the outcomes of patients receiving ceftolozane-tazobactam vs polymyxin- or aminoglycoside-based therapy [458]. Favorable clinical outcomes were observed in 81% of patients receiving ceftolozane-tazobactam vs 61% of patients receiving polymyxin- or aminoglycoside-based therapy; this difference achieved statistical significance. Pooled data from five clinical trials explored differences in clinical responses for 95 patients with MDR *P. aeruginosa* infections receiving ceftazidime-avibactam vs carbapenem-based comparators with a favorable clinical response observed in 57% (32 of 56 patients) vs 54% (21 of 39) of patients in the 2 treatment arms, respectively [469]. Only 66% of isolates were susceptible to ceftazidime-avibactam making interpretation of the results challenging [469]. An observational study compared 100 patients receiving ceftolozane-tazobactam and 100 patients receiving ceftazidime-avibactam with MDR *P. aeruginosa* and mortality was approximately 40% in both groups [470]. However, this study had several limitations (eg, AST not available for all included isolates, 40% received combination therapy, 50% polymicrobial infections, <50% bacteremia or pneumonia, suboptimal ceftolozane-tazobactam dosing).

A clinical trial including 24 patients infected with imipenem-non-susceptible *P. aeruginosa* identified a favorable clinical response in 81% (13 of 16) of patients receiving imipenem-

cilastatin-relebactam compared to 63% (5 of 8) receiving imipenem-cilastatin in combination with colistin [240]. Although not achieving statistical significance, potentially due to the small sample size, the numerical differences suggest improved outcomes with use of imipenem-cilastatin-relebactam over colistin-based regimens.

A clinical trial compared the outcomes of patients with infections due to carbapenem-resistant organisms treated with cefiderocol vs alternative therapy, which largely consisted of polymyxin-based therapy [230]. The trial included 22 unique patients with 29 carbapenem-resistant *P. aeruginosa* infections [230]. Mortality at the end of therapy was 18% in both the cefiderocol and alternative therapy arms for patients infected with *P. aeruginosa*. This trial suggests that cefiderocol performs as well as polymyxin-based regimens, but may not improve outcomes, as has been observed with some of the newer β-lactam-β-lactamase inhibitors [240, 458]. Observational data suggesting cefiderocol may be reasonable for the treatment of DTR *P. aeruginosa* infections are limited by small sample sizes and lack of non-cefiderocol treatment arms [471, 472]. The panel suggests cefiderocol as an alternative option when inactivity, intolerance, or unavailability preclude the use of the newer β-lactam-β-lactamase inhibitors.

Question 4.6: What Are Preferred Antibiotics for the Treatment of DTR *P. aeruginosa* that Produce Metallo-β-Lactamase Enzymes?

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

Rationale

P. aeruginosa producing MBLs remain uncommon in the United States [385, 386]. Such isolates are more common in other regions of the world [266, 385, 392, 473–475]. DTR *P. aeruginosa* isolates exhibiting resistance to all available β-lactam-β-lactamase inhibitors (ie, ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam) should raise suspicion for possible MBL production. MBL-producing *P. aeruginosa* isolates generally remain susceptible to cefiderocol [270].

Clinical data on the use of cefiderocol as a treatment for MBL-producing *P. aeruginosa* are limited. Seven patients with MBL-producing *P. aeruginosa* infections were included in 2 cefiderocol clinical trials [292]. Although limited in vitro data [476] and isolated case reports [477, 478] suggest potential clinical success with the combination of ceftazidime-avibactam and aztreonam for MBL-producing *P. aeruginosa* infections, this combination appears unlikely to present a meaningful incremental benefit over aztreonam alone for MBL-producing *P. aeruginosa* infections [273, 387]. Although avibactam may help reduce the effectiveness of PDC enzymes, the multiple other non-enzymatic mechanisms generally present in DTR *P. aeruginosa* are likely to impede aztreonam's ability to reach its PBP3 target. Extrapolating data from aztreonam-avibactam, it is anticipated that ceftazidime-avibactam and aztreonam have activity against <10% of MBL-producing *P. aeruginosa* [273].

Question 4.7: What Is the Likelihood of the Emergence of Resistance of DTR *P. aeruginosa* Isolates to the Newer β-Lactam Agents When Used to Treat DTR *P. aeruginosa* Infections?

Suggested approach: The emergence of resistance is a concern with all β-lactams used to treat DTR *P. aeruginosa* infections. Available data suggest the frequency may be the highest for ceftolozane-tazobactam and ceftazidime-avibactam, although fewer data are available investigating this issue for imipenem-cilstatin-relebactam and cefiderocol.

Rationale

As with most antibiotic agents, treatment of DTR *P. aeruginosa* with any of the newer β-lactam agents (ie, ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol) increases the likelihood that subsequent infections will no longer be effectively treated with these agents. The emergence of resistance to ceftolozane-tazobactam most commonly occurs because of amino acid substitutions, insertions, or deletions in PDCs [479–490]. These alterations occur most commonly in or adjacent to a particular region of the PDC known as the omega loop. Similarly, acquired resistance of *P. aeruginosa* to ceftazidime-avibactam is most frequently the result of alterations in PDCs [479, 481, 482, 484, 487, 489–492].

Mechanisms contributing to *P. aeruginosa* resistance to imipenem-cilastatin-relebactam are generally related to loss of OprD and overexpression of efflux pumps (eg, MexAB-OprM and/or MexEF-OprN) [329, 493, 494]. A number of diverse mechanisms of *P. aeruginosa* resistance to cefiderocol have been described [336, 495] including mutations in the TonB-dependent iron transport system [337–339, 496], amino acid changes in PDCs, as well as modifications in the PBP3 target [496–498].

Based on available data, the emergence of resistance of *P. aeruginosa* to newer β-lactams appears most evident for ceftolozane-tazobactam and ceftazidime-avibactam. This may be at least in part because these agents have been prescribed more frequently in clinical practice than imipenem-cilastatin-relebactam and cefiderocol [499]. Cross-resistance between ceftolozane-tazobactam and ceftazidime-avibactam is high because of structural similarities. In a cohort of 28 patients with DTR *P. aeruginosa* infections treated with ceftolozane-tazobactam and who had a subsequent DTR *P. aeruginosa* isolate after the start of therapy, the subsequent isolate was no longer susceptible to ceftolozane-tazobactam 50% of the time after a median duration of 15 days of therapy [490]. Over 80% of

patients with index isolates susceptible to ceftazidime-avibactam had subsequent isolates exhibiting resistance to ceftazidime-avibactam after ceftolozane-tazobactam exposure, and in the absence of ceftazidime-avibactam exposure. Another cohort study including 14 patients with index and subsequent *P. aeruginosa* isolates after ceftolozane-tazobactam described treatment-emergence resistance in 79% of paired isolates [489]. Both of these single-center experiences likely overestimate the likelihood of emergence of resistance to ceftolozane-tazobactam given that patients who did not have recurrent *P. aeruginosa* infections (hence, not included in the cohort) may have been less likely to develop ceftolozane-tazobactam resistant *P. aeruginosa* isolates. Nevertheless, estimates of emergence of resistance to ceftolozane-tazobactam and ceftazidime-avibactam remain concerning.

Limited data on the frequency of emergence of resistance to imipenem-cilastatin-relebactam exist. However, 1 report identified the emergence of non-susceptibility to this agent in 26% (5 of 19) of patients receiving imipenem-cilastatin-relebactam for the treatment of *P. aeruginosa* infections [493]. Of note, across 2 clinical trials, none of the 31 patients with *P. aeruginosa* infections treated with imipenem-cilastatin-relebactam developed treatment-emergent resistance [240, 467].

Similarly, estimates of the frequency of the emergence of resistance of *P. aeruginosa* to cefiderocol are incomplete but in a clinical trial, 6% (1/17) of *P. aeruginosa* isolates treated with cefiderocol developed resistance to this agent [230]. Another study indicated that cross-resistance to cefiderocol occurred in 3 of 14 (21%) isolates that developed treatment-emergent resistance to ceftolozane-tazobactam [495].

The panel suggests always repeating antibiotic susceptibility testing for the 4 newer β-lactams when a patient previously infected with a DTR *P. aeruginosa* presents with a sepsis-like picture suggestive of a new or relapsed infection. Furthermore, if a patient was recently treated with ceftolozane-tazobactam or ceftazidime-avibactam and presents to medical care with symptoms of recurrent infection, the panel suggests considering use of imipenem-cilastatin-relebactam or cefiderocol, particularly if 1 of these agents tested susceptible previously, at least until culture and AST data are available.

Question 4.8: What Is the Role of Combination Antibiotic Therapy for the Treatment of Infections Caused by DTR *P. aeruginosa*?

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

Rationale

Although empiric combination antibiotic therapy (eg, the addition of tobramycin to a β-lactam agent) to broaden the likelihood of at least 1 active agent for patients at risk for DTR *P. aeruginosa* infections is reasonable, data do not indicate that continued combination therapy—once the β-lactam agent has demonstrated in vitro activity—offers any additional benefit over monotherapy with the β-lactam antibiotic [379]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [379]. Additionally, clinical data indicating that combination therapy prevents the emergence of resistance are lacking.

Clinical trials comparing survival with ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol as monotherapy and as a component of combination therapy are not available (eg, ceftazidime-avibactam vs ceftazidime-avibactam and tobramycin). Observational studies have not identified a survival advantage with combination therapy [471, 500, 501]. Based on toxicities associated with aminoglycosides and polymyxins and clinical outcomes data not demonstrating a benefit with the use of combination therapy for *P. aeruginosa* infections [379], the panel does not suggest that combination therapy be routinely administered for DTR *P. aeruginosa* infections when susceptibility to a β-lactam agent has been demonstrated.

If no β-lactam agent demonstrates activity against DTR *P. aeruginosa*, tobramycin (if susceptibility is demonstrated) can be considered in combination with either ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol, preferentially selecting the β-lactam agent for which the MIC is closest to its susceptibility breakpoint. For example, if ceftolozane-tazobactam and ceftazidime-avibactam MICs against a DTR *P. aeruginosa* isolate are both >128/4 μg/mL (highly resistant) and the imipenem-cilastatin-relebactam MIC is 4/4 μg/mL (intermediate category), imipenem-cilastatin-relebactam in combination with tobramycin is favored. Data are lacking demonstrating a benefit to this approach and it should be considered as a last resort. This approach is suggested as it may increase the likelihood that at least 1 active agent is being included in the treatment regimen.

If tobramycin does not test susceptible, polymyxin B can be considered in combination with a newer β-lactam. Polymyxin B is preferred over colistin for infections outside the urinary tract because it is not administered as a prodrug and therefore can achieve more reliable plasma concentrations than colistin and it has a potentially reduced risk of nephrotoxicity, although limitations across studies preclude accurate determination of the differential risk of nephrotoxicity [502–507].

Question 4.9: What Is the Role of Nebulized Antibiotics for the Treatment of Respiratory Infections Caused by DTR *P. aeruginosa*?

Suggested approach: The panel does not suggest the use of nebulized antibiotics for the treatment of respiratory infections caused by DTR *P. aeruginosa*.

Rationale

There have been conflicting findings for the clinical effectiveness of nebulized antibiotics for the treatment of gram-negative pneumonia in observational studies [508–535]. At least 3 clinical trials investigated the outcomes of patients with gram-negative ventilator-associated pneumonia comparing nebulized antibiotics vs placebo. All 3 trials allowed for the use of systemic antibiotics. In brief, 1 trial compared the outcomes of 100 adults with pneumonia (34% caused by *P. aeruginosa*) treated with nebulized colistin vs placebo [536]; a second trial compared the outcomes of 142 adults with pneumonia (22% caused by *P. aeruginosa*) treated with nebulized amikacin/fosfomycin vs placebo [537]; and the third trial compared the outcomes of 508 adults with pneumonia (32% caused by *P. aeruginosa*) treated with nebulized amikacin vs placebo [538]. None of the 3 clinical trials demonstrated improved clinical outcomes or a survival benefit with nebulized antibiotics compared with placebo for the treatment of ventilator-associated pneumonia, including in a subgroup analyses of patients with drug-resistant pathogens [536–538]. A meta-analysis of 13 trials including 1733 adults with ventilator-associated pneumonia indicated that the addition of nebulized antibiotics was associated with at least partial resolution of clinical symptoms of infection compared to the control group; however, there was significant heterogeneity among the pathogens involved and the definition of clinical response across studies [539]. No survival benefit, reduction in intensive care unit length of stay, or reduction in ventilator days was observed in patients receiving nebulized antibiotics [539].

Reasons for the lack of clinical benefit with nebulized antibiotics in available trials are unclear. In a PK/PD modeling study, aerosolized delivery of the prodrug of colistin to critically ill patients achieved high active drug levels in epithelial lining fluid of the lungs [540]. However, it is likely that nebulized antibiotics do not achieve sufficient penetration and/or distribution throughout lung tissue to exert significant bactericidal activity [541], likely due in part to the use of parenteral formulations not specifically designed for inhalation in suboptimal delivery devices such as jet nebulizers [542, 543]. Professional societies have expressed conflicting views regarding the role of nebulized antibiotics as adjunctive therapy to IV antibiotics [544–546]. The panel suggests against the use of nebulized antibiotics as adjunctive therapy for DTR *P. aeruginosa* pneumonia due to the lack of benefit observed in clinical trials, concerns regarding unequal distribution in infected lungs, and concerns for respiratory complications such as bronchoconstriction with use of aerosolized antibiotics [547].

SECTION 5: CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections pose significant challenges in healthcare settings [548, 549]. In this guidance document, for simplicity, we will use the term "CRAB" as we recognize that most clinical microbiology laboratories may not be able to accurately separate carbapenem-resistant *A. baumannii* from other species within the *baumannii* and *calcoaceticus* complex [550].

The management of CRAB infections is difficult for several reasons. First, CRAB is most commonly recovered from respiratory specimens or wounds. It is not always clear if a CRAB isolate recovered in a respiratory or wound culture represents a colonizing organism in medically complex patients who are ill due to underlying host factors (eg, patients requiring mechanical ventilation, patients with extensive burns), or a true pathogen, leading to uncertainty about the need for antibiotic therapy. For the same reason, it is challenging to determine if poor clinical outcomes with CRAB infections are attributable to suboptimal antibiotic therapy or to underlying host factors.

Second, once *A. baumannii* exhibits carbapenem resistance, it generally has acquired resistance to most other antibiotics expected to be active against wild-type *A. baumannii* leaving few remaining therapeutic options. The production of OXA carbapenemases (eg, OXA-23, OXA-24/40) mediates resistance to β-lactams including carbapenems and sulbactam [550, 551]. CRAB isolates often produce additional serine β-lactamases (eg, *Acinetobacter baumannii*-derived cephalosporinases [ADCs]), further limiting the utility of common β-lactam agents. Sulbactam resistance is driven primarily by the presence of β-lactamases but also via mutations targeting PBPs (ie, PBP1a/1b, and PBP3) [552–554]. Aminoglycoside modifying enzymes or 16S rRNA methyltransferases generally preclude aminoglycosides as treatment options for CRAB [555–557]. Mutations in the chromosomally encoded quinolone resistance determining regions generally mediate resistance to fluoroquinolones [556].

Finally, despite the number of clinical trials conducted to investigate optimal treatment regimens for CRAB infections, data supporting a prioritization of specific agents with CRAB activity or the additive benefit of commonly used combination regimens for CRAB infections remain incomplete. This guidance document focuses on the treatment of moderate-severe CRAB infections.

Question 5.1: What Is the General Approach for the Treatment of Infections Caused by CRAB?

Suggested approach: The use of an antibiotic regimen which includes a sulbactam-containing agent is suggested for the treatment of CRAB infections. The preferred regimen is sulbactam-durlobactam in combination with a carbapenem (ie, imipenem-cilastatin or meropenem). An alternative regimen is high-dose ampicillin-sulbactam (total daily dose of 9 grams of the sulbactam component) in combination with at least 1 other agent (ie, polymyxin B, minocycline > tigecycline, or cefiderocol), if sulbactam-durlobactam is not available.

Rationale

The general approach for the treatment of CRAB infections is to administer combination therapy with at least 2 agents for the treatment of CRAB infections, at least until an appropriate clinical response is observed, given the limited data supporting the effectiveness of any single antibiotic agent. It is also generally suggested that at least 1 agent in the combination is sulbactam-based. The preferred sulbactam-based agent is sulbactam-durlobactam in combination with either imipenem-cilastatin or meropenem (Question 5.2).

An alternative approach, when sulbactam-durlobactam is not available, is the administration of high-dose ampicillin-sulbactam (total daily dose of 9 grams of the sulbactam component) as a component of combination therapy (Question 5.3). Sulbactam's unique activity against *A. baumannii* isolates has been observed through in vitro studies [558–560], animal models [561], and clinical outcomes data [562–567], as described in Question 5.2 and Question 5.3. When high-dose sulbactam is administered, combination therapy is suggested even though only 1 of 7 clinical trials found improved clinical outcomes with the use of combination antibiotic therapy for CRAB infections [562, 568–573] (Question 5.4).

Notably, the clinical trial that demonstrated a benefit with combination therapy was the only 1 that included high-dose ampicillin-sulbactam in the combination therapy arm [562]. Additional agents that can be considered in combination with high-dose ampicillin-sulbactam include polymyxin B (Question 5.5), minocycline (Question 5.6), tigecycline (Question 5.6), or cefiderocol (Question 5.7). Fosfomycin and rifampin are not suggested as components of combination therapy [570, 572, 573] (Question 5.3, Question 5.9).

As 2 large clinical trials have not demonstrated a benefit with the use of high-dose extended-infusion carbapenem therapy in combination with colistin for the treatment of CRAB infections [568, 569], meropenem or imipenem-cilastatin are not suggested as routine components of CRAB therapy, with the notable exception of when they are administered in combination with sulbactam-durlobactam (Question 5.8). Nebulized antibiotics are not suggested as adjunctive therapy for CRAB pneumonia, due to the lack of benefit observed in clinical trials [536–538], concerns regarding unequal distribution in infected lungs, and the potential for respiratory complications such as bronchoconstriction [541–543, 547] (Question 5.10).

Question 5.2: What Is the Role of Sulbactam-Durlobactam for the Treatment of Infections Caused by CRAB?

Suggested approach: Sulbactam-durlobactam is a preferred agent for the treatment of CRAB infections and is suggested to be administered in combination with imipenem-cilastatin or meropenem.

Rationale

Sulbactam-durlobactam became FDA-approved in May 2023. Durlobactam is a β-lactamase inhibitor with potent inhibition of class A (eg, TEM-1), class C (eg, ADC), and class D beta-lactamases (eg, OXA-24/40, OXA-23). It does not inhibit class B MBLs (eg, NDM), which are rarely produced by CRAB isolates in the United States but are increasingly problematic in other regions of the world (eg, at least 5% of CRAB isolates in Latin America from 2017–2019 contained a *bla*NDM and contemporary estimates are likely higher) [574, 575]. Durlobactam reduces the likelihood of sulbactam hydrolysis by binding to and inhibiting class A, C, and D β-lactamases enabling sulbactam to successfully reach its PBP targets [576]. Sulbactam-durlobactam is administered as 1 gram of sulbactam and 1 gram of durlobactam (2 grams total) every 6 hours as a 3-hour infusion [577] (Table 1). This dosing strategy achieves PK/PD target attainment goals for greater than 90% of *A. baumannii* isolates with sulbactam-durlobactam MICs of ≤4/4 μg/mL, the FDA and CLSI breakpoint [577].

Sulbactam-durlobactam was investigated in a clinical trial of patients with pneumonia or bloodstream infections caused by *A. baumannii* [567]. Patients were randomized to sulbactam-durlobactam or colistin; all patients also received imipenem-cilastatin, dosed as 1 gram of imipenem every 6 hours.

There were 125 patients with CRAB infections for whom the primary outcome of 28-day mortality was evaluated. Mortality occurred in 19% (12/63) of patients in the sulbactam-durlobactam group and 32% (20/62) in the colistin group, meeting the pre-specified non-inferiority criteria. Secondary outcomes also favored sulbactam-durlobactam, including clinical cure (62% vs 40%), microbiologic response (68% vs 42%) at the test of cure visit, and a lower risk of nephrotoxicity (13% vs 38%). It is important to note that the comparator arm in this trial (ie, colistin plus imipenem-cilastatin) is not a preferred treatment regimen for CRAB infections.

The additive clinical benefit of imipenem-cilastatin to sulbactam-durlobactam is unclear. Some studies suggest that the combination of sulbactam-durlobactam and imipenem-cilastatin lowers the MIC of sulbactam-durlobactam by 1- to 2-fold [578–580]. The potential benefit may be related to the additional PBPs that are targeted with multiple β-lactams (ie, sulbactam preferentially binds to PBP1 and PBP3 while imipenem preferentially binds to PBP2) [579, 581]. Both sulbactam and imipenem have an increased likelihood of successfully reaching their PBP targets under the protection of durlobactam. Moreover, its plausible that imipenem serves as a substrate for OXA-carbapenemase-mediated hydrolysis, potentially enabling more sulbactam to reach its PBP targets. In a hollow fiber infection model, the addition of a carbapenem to sulbactam-durlobactam led to enhanced reductions in bacterial growth [582]. Clinical data investigating the benefit of sulbactam-durlobactam for the treatment of CRAB

infections in the absence of imipenem-cilastatin are not available. Based on the available in vitro data, it is suggested that imipenem-cilastatin be administered as adjunctive therapy to sulbactam-durlobactam. Meropenem is likely a reasonable substitute for imipenem-cilastatin given their similar PBP targets [579, 580]. For patients requiring prolonged durations of therapy (eg, CRAB osteomyelitis) it may be reasonable to discontinue carbapenem therapy after clinical improvement has occurred.

Our understanding of mechanisms of resistance to sulbactam-durlobactam will evolve as this agent is increasingly used in clinical practice. Available data suggest high-level resistance of sulbactam-durlobactam is generally a result of MBL enzymes or PBP3 mutants [578, 583]. In settings of resistance to sulbactam-durlobactam (ie, MICs ≥16/4 μg/mL), the panel suggests considering optimally-dosed non-sulbactam based combinations (ie, cefiderocol, minocycline, tigecycline, polymyxin B) as sulbactam-based therapy is unlikely to be of substantial therapeutic value.

Question 5.3: What Is the Role of Ampicillin-Sulbactam for the Treatment of Infections Caused by CRAB?

Suggested approach: High-dose ampicillin-sulbactam, as a component of combination therapy, is suggested as an alternate agent for CRAB. This approach is suggested only when the unavailability of sulbactam-durlobactam precludes its use.

Rationale

As described in Question 5.2, sulbactam is a competitive, irreversible β-lactamase inhibitor that, in high doses, saturates PBP1a/1b and PBP3 of *A. baumannii* isolates [552, 584]. Sulbactam's unique activity against *A. baumannii* isolates has been demonstrated through PK/PD studies [558, 559, 585–590], animal models [561, 591], and clinical outcomes data [562–566]. The panel suggests high-dose ampicillin-sulbactam (total daily dose of 9 grams of the sulbactam component) as a component of combination therapy for CRAB infections (Table 1).

A review of available PK/PD data indicate that sulbactam total daily dosing of 9 grams is likely to achieve sufficient fT > MIC (regardless of a 40% or 60% fT > MIC threshold) for *A. baumannii* isolates with sulbactam MICs of up 16–32 μg/mL (ie, sulbactam-resistant isolates) [592]. Ampicillin-sulbactam uses a 2:1 formulation; for example, 3 grams of ampicillin-sulbactam is comprised of 2 grams of ampicillin and 1 gram of sulbactam. Ampicillin-sulbactam total daily dosages of 27 grams (equivalent to 9 grams of sulbactam) as extended or continuous infusions are suggested (eg, 9 grams [3 grams of sulbactam IV every 8 hours infused over 4 hours) 558, 559, 562, 563, 586, 593].

Durlobactam is a potent inhibitor of class A, C, and D enzymes commonly produced by CRAB [583, 594], enabling lower doses of sulbactam which can then successfully reach its PBP targets under the protection of durlobactam. Ampicillin-sulbactam does not have the added protection of a durlobactam-like beta-lactamase inhibitor.

Fewer than 50% of CRAB isolates test susceptible to ampicillin-sulbactam [595, 596]. Insufficient data exist to determine if standard-dose ampicillin-sulbactam and high-dose ampicillin-sulbactam have equivalent efficacy for CRAB infections caused by isolates susceptible to ampicillin-sulbactam. The panel favors high-dose ampicillin-sulbactam, given its theoretical benefit of saturating sulbactam's PBP targets, particularly as significant amounts of the agent will likely be hydrolyzed by β-lactamases prior to reaching their PBP targets and because of potential inaccuracies with commonly used approaches for ampicillin-sulbactam AST testing for CRAB (ie, "susceptible" may not actually be "susceptible" using AST methods other than reference broth microdilution) [597, 598].

Two meta-analyses have evaluated observational and clinical trial data for various treatment regimens against CRAB infections [565, 566]. A meta-analysis published in 2021 included 18 studies and 1835 patients and found that ampicillin-sulbactam (total daily dose of at least 6 grams of the sulbactam component) in combination with a second agent was the most effective regimen to reduce mortality in critically ill patients infected with CRAB [565]. An earlier meta-analysis published in 2017 included 23 observational studies or clinical trials and 2118 patients with CRAB infections [566]. This analysis identified sulbactam as having the greatest impact on reducing mortality when evaluating sulbactam-based, polymyxin-based, or tetracycline-based regimens.

At least 5 clinical trials evaluating mortality in patients with CRAB infections have included sulbactam in 1 of the treatment arms [599]. When comparing the mortality in the colistin-based arm vs the sulbactam-based arm in these trials the results were as follows: 42% vs 33% [600], 82% vs 42% [601], 63% vs 50% [562], 38% vs 17% [602], 32% vs 19% [567]. Although differences in mortality reached statistical significance in only 1 of these trials [601], all demonstrate a numerical reduction in mortality in the sulbactam-based arm, suggesting a potential benefit with the inclusion of sulbactam in the treatment regimen. Evaluating the totality of in vitro, animal, and clinical data, the panel considers high-dose ampicillin-sulbactam, in combination with a second agent, as an alternative option for the treatment of CRAB infections, when sulbactam-durlobactam is not available.

Question 5.4: What Is the Role of Combination Antibiotic Therapy for the Treatment of Infections Caused by CRAB?

Suggested approach: Combination therapy with at least 2 agents, whenever possible, is suggested for the treatment of CRAB infections, at least until clinical improvement is observed, because of the limited clinical data supporting any single antibiotic agent.

Rationale

Combination therapy is suggested for the treatment of CRAB infections, even if a single agent demonstrates activity. In situations when prolonged durations of therapy may be needed (eg, osteomyelitis), step-down therapy to a single active agent can be considered. In vitro and animal studies have had conflicting findings but several investigations indicate increased bacterial killing with various combination regimens [559, 603–611]. There are many observational studies evaluating the role of combination therapy vs monotherapy for the treatment of CRAB infections with differing results [612–632]. The heterogeneity in patient populations, infectious sources, inclusion of colonizing isolates, variation in antibiotics and dosages used, small numbers, and imbalances between treatment arms makes interpretation of a number of these studies challenging.

At least 7 trials have investigated the role of combination therapy for CRAB infections, and only 1 of the 7 trials indicated a potential benefit with combination therapy [562, 568–573]. Of note, because of inconsistent and unclear colistin dosing reported in studies, the panel elected not to report colistin dosing used in individual trials. None of the seven trials that included a polymyxin arm investigated the role of polymyxin B, which has a more favorable PK profile than colistin [224]. Only 1 of these trials included sulbactam in a treatment arm. Below is a summary of the 7 trials, a number of which are limited by small sample sizes.

A trial including 210 ICU patients with invasive CRAB infections compared the outcomes of patients receiving colistin alone vs 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 [571]. A second trial including 43 patients with CRAB pneumonia also compared colistin monotherapy and colistin in combination with rifampin [572]. 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 30-day mortality between the colistin and colistin plus rifampin arms (20% vs 33%, respectively) [573].

A fourth trial including patients with a variety of CRAB infections randomized 94 patients to receive colistin alone or colistin with fosfomycin [570]. Mortality within 28 days was 57% vs 47% in the colistin monotherapy and colistin-fosfomycin arms, respectively. IV fosfomycin is not currently available in the United States, making the results of this trial of limited relevance to this guidance document.

Two large trials evaluated the role of colistin monotherapy vs colistin in combination with meropenem [568, 569]. In the first study, 312 patients with CRAB bacteremia, pneumonia, or urinary tract infections were randomized to colistin alone vs colistin plus meropenem (2 grams IV every 8 hours as a 3-hour infusion) [569]. No difference in 28-day mortality (46% vs 52%) were observed between the groups [569]. The second trial included 329 patients with drug-resistant *A. baumannii* bloodstream infections or pneumonia randomized to colistin alone compared to colistin in combination with meropenem (1 gram IV every 8 hours as a 30-minute infusion) [568]. The 28-day mortality was 46% vs 42% in the colistin monotherapy and combination therapy arms, respectively [568]. For both trials, the addition of meropenem to colistin did not improve survival in patients with severe CRAB infections.

The seventh trial included 39 CRAB pneumonia patients, with clinical isolates demonstrating susceptibility to both colistin and sulbactam [562]. Patients were randomized to colistin monotherapy vs colistin in combination with high-dose sulbactam (total daily dose of 8 grams of the sulbactam component) [562]. Clinical improvement by day five was observed in 16% and 70% of patients in the colistin vs colistin-sulbactam arms, respectively, achieving statistical significance. 28-day mortality occurred in 63% and 50% of patients, respectively. Investigators were unblinded to treatment assignment. Moreover, patients were allowed to transition to other antibiotics after day five, precluding an accurate comparison of clinical failure or mortality between the groups.

Although only 1 of 7 clinical trials demonstrated any statistically significant benefit with combination therapy for CRAB infections, the panel favors the use of combination therapy for CRAB infections for the following reasons: (1) the vast majority of clinical trials included combinations not generally administered in clinical practice (eg, colistin and rifampin) making the applicability of trial results limited; (2) there is a lack of robust clinical data supporting the treatment of CRAB infections with any single agent demonstrating in vitro activity against CRAB; the use of 2 agents may increase the likelihood that at least 1 active agent is being administered; and (3) 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. When considering the high mortality associated with CRAB infections, the benefit of using 2 agents may outweigh the risks. Potential options for consideration as components of combination therapy in addition to high-dose ampicillin-sulbactam include: tetracycline derivatives (with the most experience available for minocycline), polymyxin B, or cefiderocol (Questions 5.3 to 5.6).The decision to preferentially select 1 agent over another should be based on patient and infection specific factors (eg, polymyxin B may be less appealing for patients with chronic kidney diseases [Question 5.5], minocycline may be less appealing for bloodstream infections [Question 5.6]). As previous stated, when sulbactam-durlobactam is administered, it is suggested to be used in combination with a carbapenem [Question 5.2].

Question 5.5: What Is the Role of the Polymyxins for the Treatment of Infections Caused by CRAB?

Suggested approach: Polymyxin B can be considered in combination with at least 1 other agent for the treatment of CRAB infections.

Rationale

The polymyxins, including both colistin and polymyxin B, have reliable in vitro activity against CRAB isolates, with most of the published literature focusing on colistin. The panel preferentially suggests polymyxin B when considering polymyxin-based regimens, based on its more favorable PK profile than colistin [224, 545, 633]. Colistin is favored for CRAB UTIs, as it converts to its active form in the urinary tract. In comparison, there is minimal excretion of polymyxin B in the urine. There is no CLSI susceptible category for the polymyxins against *A. baumannii*; the benefit of polymyxins is likely diminished when polymyxin MICs are >2 μg/mL [634]. Due to certain chemical properties of the polymyxins (eg, poor diffusion through agar, adherence to microtiter plates) obtaining accurate polymyxin MICs is challenging [635].

The panel advises against polymyxin monotherapy for the following reasons: First, concentrations of polymyxins in serum achieved with conventional dosing strategies are highly variable and may be inadequate for effective bactericidal activity [224]. Similarly, the activity of IV polymyxins in pulmonary epithelial lining fluid is suboptimal and generally does not result in adequate bacterial killing in the lungs [636–638]. Second, dosages required to treat systemic infections approach the threshold for nephrotoxicity, making the therapeutic window extremely narrow (ie, ∼2 μg/mL may be required to achieve 1-log10 reduction in bacterial growth, but this is also the threshold associated with nephrotoxicity) [639]. Finally, in the largest clinical trials (over 300 patients in each trial) evaluating the role of colistin monotherapy, mortality was relatively high at 46% in both trials [568, 569].

Question 5.6: What Is the Role of Tetracycline Derivatives for the Treatment of Infections Caused by CRAB?

Suggested approach: High-dose minocycline or high-dose tigecycline can be considered in combination with at least 1 other agent for the treatment of CRAB infections. The panel prefers minocycline over tigecycline because of the long-standing clinical experience with this agent and the availability of CLSI breakpoints.

Rationale

Several tetracycline derivatives have in vitro activity against CRAB including minocycline, tigecycline, and eravacycline [640, 641]. A general concern with tetracycline derivatives is that they achieve rapid tissue distribution following administration, resulting in limited concentrations in the urine and serum [39]. Tetracycline derivatives are not suggested as monotherapy for bloodstream infections. 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 [642, 643].

There has been considerable clinical experience with the use of minocycline since its introduction in the 1960s [644]. It is commercially available in both oral and IV formulations. Data from critically ill patients who received a single 200 mg dose of minocycline was used to develop a population PK model; a dose of 200 mg of IV minocycline administered every 12 hours was predicted to result in a suboptimal PK/PD profile for organisms with MICs >1 μg/mL [645]. This is important to recognize as the CLSI breakpoints for minocycline against *A. baumannii* is ≤4 μg/mL [16]. Caution is advised with the use of minocycline for CRAB isolates with MICs of 2–4 μg/mL where susceptibility might be reported but suboptimal antibiotic concentrations may be present at sites of infection. International surveillance data suggest minocycline is active against approximately 60%–80% of CRAB isolates, but this is likely an overestimation given a susceptibility breakpoint of ≤4 μg/mL was applied [646, 647]. Minocycline has not been subjected to rigorous trials for the treatment of CRAB infections, although case series describing its use are available [373, 648–651]. Drawing conclusions on the effectiveness of minocycline from these observational reports is challenging as they have important limitations (eg, small sample sizes, selection bias, inadequate distinctions between colonization and infection, heterogeneous sites of infection). Despite the limitations of available data, the panel considers minocycline a treatment option for CRAB infections (dosed at 200 mg twice daily either IV or orally) when used as a component of a combination regimen (Table 1).

Tigecycline is a tetracycline derivative only available as an IV formulation. Neither CLSI nor FDA breakpoints are available for tigecycline against *A. baumannii* isolates; minocycline MICs cannot be used to predict tigecycline MICs as differences in the likelihood of susceptibility across the tetracycline derivatives exist [652]. Several observational studies and a meta-analysis of 15 trials suggest that tigecycline monotherapy is associated with higher mortality compared to alternative regimens used for the treatment of pneumonia, not exclusively limited to CRAB pneumonia [362, 618, 653, 654]. Subsequent investigations have suggested that when high-dose tigecycline is prescribed (200 mg IV as a single dose followed 100 mg IV q12h), mortality differences between tigecycline and comparator agents are no longer evident [363–365].

Similar to minocycline, efficacy of tigecycline may be limited when MICs are >1 μg/mL based on PK data derived from critically ill patients [655]. If tigecycline is prescribed for the treatment of CRAB infections, the panel suggests that high doses are used (Table 1). As with minocycline, tigecycline is suggested to

be prescribed in combination with at least 1 additional agent for CRAB infections. Both agents are associated with nausea in 20%–50% of patients, and this is likely more common with higher dosages [353–355].

Although eravacycline MICs are generally 2- to 8-fold lower than tigecycline MICs against CRAB [652, 656, 657], the clinical relevance of the differences in MIC distributions between these agents is unclear due to differences in the PK profile of tigecycline and eravacycline. As with tigecycline, no CLSI breakpoints exist for eravacycline. Small numbers of patients with CRAB infections were included in clinical trials investigating the efficacy of eravacycline [358, 370]. Limited post-marketing clinical reports describing its efficacy for the treatment of CRAB infections are available [658, 659]. In an observational study of 93 patients with CRAB pneumonia, eravacycline was associated with longer durations of mechanical ventilation (11 vs 7 days) and higher 30-day mortality (33% vs 15%) compared to alternative regimens [659]. All 4 patients with CRAB bloodstream infections receiving eravacycline died. In light of the limited clinical data supporting the use of eravacycline, the panel suggests limiting its use to situations when other agents are either not active, unable to be tolerated or unavailable.

Preclinical data evaluating the activity of omadacycline, a tetracycline derivative with both an IV and oral formulation, suggest reduced efficacy against CRAB isolates relative to other tetracycline derivatives. A PK/PD profile suggests omadacycline has very limited activity against CRAB isolates [374–377]. Clinical data are limited to a small, uncontrolled case series [660]. The panel does not suggest the use of omadacycline to treat CRAB infections.

Question 5.7: 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 or resistance to other agents precludes their use. When cefiderocol is used to treat CRAB infections, the panel suggests prescribing it as part of a combination regimen.

Rationale

Cefiderocol is a cephalosporin conjugated to a siderophore with preclinical and clinical data investigating its role against CRAB isolates. International surveillance studies indicate that approximately 95% of CRAB isolates are susceptible to cefiderocol using the CLSI breakpoint of ≤4 μg/mL [270, 661] (Table 2). Determining CRAB susceptibility to cefiderocol, however, is challenging, in part due to variable iron concentrations in media. Moreover, MIC results are not always reproducible across methods, heteroresistance may be observed, and broth microdilution results can be challenging to interpret as trailing endpoints, haziness, or a paradoxical effect may obscure interpretation [662–664]. Furthermore, preclinical data suggest higher cefiderocol PK/PD targets needed for *A. baumannii* are higher than for other gram-negative organisms and bactericidal activity of cefiderocol in animal models of *A. baumannii* infections has been variable [665–668].

A clinical trial including 54 patients with CRAB infections identified mortality at the end of the study to be 49% (19 of 39 patients) vs 18% (3 of 17 patients) in the cefiderocol vs alternative therapy arms (largely composed of polymyxin–based regimens), respectively [230]. Poor outcomes with cefiderocol were observed in patients with pneumonia and bloodstream infections. A second trial that included a subgroup of 47 patients with CRAB pneumonia identified 14-day mortality in 22% (5 of 23 patients) vs 17% (4 of 24) of patients in the cefiderocol and meropenem arm, respectively – suggesting outcomes were similar between cefiderocol and a relatively inactive agent [669]. Because of the heterogeneity of regimens used in the alternative arms in the first trial and the relatively small numbers of patients with CRAB when combining both trials, contextualizing the results is challenging.

In an observational study, 30-day mortality was 34% vs 56% for 124 patients with CRAB infections receiving cefiderocol vs colistin-based regimens, respectively [670]. Recurrent CRAB infections, however, were more likely in the cefiderocol arm (17% vs 7%). Among the 8 patients in the cefiderocol group who experienced a recurrent CRAB infection, 50% had subsequent isolates exhibiting resistance to cefiderocol. Additional observational data suggest cefiderocol may be reasonable for the treatment of CRAB infections but these studies are generally limited by small sample sizes, lack of a comparator group or heterogenous comparator groups, and high percentages of concomitant coronavirus disease 2019 (COVID-19) infections [671–673].

Combining available data, the panel suggests that if cefiderocol is prescribed for the treatment of CRAB infections, it should be used with caution and as a component of combination therapy, to increase the likelihood that at least 1 effective agent is included as part of the treatment regimen. The panel also suggests limiting consideration of cefiderocol for CRAB infections after other regimens have been exhausted.

Question 5.8: What Is the Role of Extended-Infusion Meropenem or Imipenem-Cilastatin for the Treatment of Infections Caused by CRAB?

Suggested approach: Meropenem or imipenem-cilastatin are not suggested for the treatment of CRAB infections, with the exception of co-administration with sulbactam-durlobactam.

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 microbiological efficacy against CRAB [558–560]. Although at least 2 observational studies suggest favorable outcomes with the inclusion of carbapenems in 3-drug combinations (ie, ampicillin-sulbactam, carbapenem, colistin), these

studies did not compare outcomes of 3-drug combinations vs 2-drug combinations of ampicillin-sulbactam and colistin [634, 674]. As described in Question 5.4, 2 randomized trials evaluated the role of colistin monotherapy vs colistin plus meropenem and neither trial demonstrated a benefit with the combination of colistin plus meropenem for the treatment of CRAB infections [568, 569]. A secondary analysis of 1 of the trials found that improved clinical outcomes were not observed with the combination of colistin and meropenem even when in vitro synergy was present [675].

Imipenem-cilastatin may retain activity against some meropenem-resistant isolates [676–678]; however, MICs of both agents against CRAB isolates are almost always significantly higher than 8 μg/mL [568, 569]. With highly elevated MICs, it appears unlikely that either meropenem or imipenem-cilastatin would offer any incremental benefit when used as a component of combination therapy, with the notable exception of sulbactam-durlobactam (Question 5.2).

Question 5.9: What Is the Role of the Rifamycins for the Treatment of Infections Caused by CRAB?

Suggested approach: Rifampin or other rifamycins are not suggested for the treatment of CRAB infections.

Rationale

The rifamycin class of antibiotics includes agents such as rifampin, rifabutin, and rifapentine that inhibit bacterial RNA polymerase [679]. 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 [680–682].

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 [681].

Three clinical trials compared the clinical outcomes of CRAB-infected patients receiving colistin alone vs colistin in combination with rifampin (Question 5.4) [571–573]. None of these trials demonstrated a survival benefit with the addition of rifampin. Admittedly, there are limitations to all these trials including suboptimal dosing of colistin and small sample sizes. It is unknown if a clinical benefit would have been observed if rifabutin had been used in place of rifampin [683]. In light of the known toxicities and drug interactions associated with the rifamycins [684] and the absence of a benefit observed in clinical trials, the panel does not favor the use of rifamycins as components of CRAB therapy.

Question 5.10: What Is the Role of Nebulized Antibiotics for the Treatment of Respiratory Infections Caused by CRAB?

Suggested approach: Nebulized antibiotics are not suggested 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 [508–535]. At least 3 randomized trials evaluated the outcomes of patients with gram-negative ventilator-associated pneumonia comparing nebulized antibiotics vs placebo. All 3 trials allowed for the use of systemic antibiotics, at the discretion of the treating clinician. In brief, 1 trial compared the outcomes of 100 adults with pneumonia (65% caused by *A. baumannii*) treated with nebulized colistin vs placebo [536]; a second trial compared the outcomes of 142 adults with pneumonia (20% caused by *A. baumannii*) treated with nebulized amikacin/fosfomycin vs placebo [537]; and the third trial compared the outcomes of 508 adults with pneumonia (29% caused by *A. baumannii*) treated with nebulized amikacin vs placebo [538]. None of the 3 clinical trials demonstrated improved clinical outcomes or a survival benefit with the use of nebulized antibiotics compared with placebo for the treatment of ventilator-associated pneumonia, including in subgroup analyses of drug-resistant pathogens [536–538].

A meta-analysis of 13 trials including 1733 adults with ventilator-associated pneumonia indicated that no survival benefit, reduction in intensive care unit lengths of stay, or reduction in ventilator days was observed in patients receiving nebulized antibiotics [539].

Reasons for the lack of clinical benefit in these trials are unclear. In a PK/PD modeling study, aerosolized delivery of the prodrug of colistin to critically ill patients achieved high active drug levels in the epithelial lining fluid of the lungs [540]. However, it is likely that nebulized antibiotics do not achieve sufficient penetration and/or distribution throughout lung tissue to exert significant bactericidal activity [541], likely due in part to the use of parenteral formulations not specifically designed for inhalation in suboptimal delivery devices such as jet nebulizers [542, 543]. Professional societies have expressed conflicting views regarding the role of nebulized antibiotics as adjunctive therapy to IV antibiotics [544–546]. 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 patients receiving aerosolized antibiotics [547].

SECTION 6: STENOTROPHOMONAS MALTOPHILIA

Stenotrophomonas maltophilia is an aerobic, glucose nonfermenting, gram-negative bacillus that is ubiquitous in water environments [685]. The organism has a long history of changing nomenclatures and a complicated phylogeny [686–688]. Although generally believed to be less pathogenic than many

other nosocomial organisms, *S. maltophilia* produces biofilm and virulence factors that enable colonization or infection in vulnerable hosts, such as those with underlying lung disease, persons who inject drugs, and people with hematological malignancies [689].

S. maltophilia infections pose management challenges similar to those of CRAB infections. First, although *S. maltophilia* has the potential to cause serious disease, it is often unclear if *S. maltophilia* represents a colonizing organism or a true pathogen, particularly in patients with underlying pulmonary conditions such as cystic fibrosis or ventilator dependency [690–694]. *S. maltophilia* is often recovered as a component of a polymicrobial infection—further complicating decisions on the necessity of targeted *S. maltophilia* therapy [686, 695]. Importantly, *S. maltophilia* can be a true pathogen that causes considerable morbidity and mortality, particularly in patients with hematologic malignancies where it can cause hemorrhagic pneumonia or bacteremia [696–702].

Second, treatment selection is hampered by antimicrobial resistance genes and gene mutations carried by *S. maltophilia* isolates [686, 688, 703]. 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 hydrolyzes extended-spectrum cephalosporins and aztreonam [686].

S. maltophilia exhibits intrinsic resistance to aminoglycosides via chromosomal aminoglycoside acetyl transferase enzymes [704]. Furthermore, *S. maltophilia* can accumulate multidrug efflux pumps that reduce the activity of TMP-SMX, tetracyclines, and fluoroquinolones, and chromosomal Sm*qnr* genes that further reduce the effectiveness of fluoroquinolones [705–708].

Third, a "standard of care" antibiotic regimen for *S. maltophilia* infections against which to compare the effectiveness of various treatment regimens is not evident [709]. Clinical trials comparing the effectiveness of commonly used agents for *S. maltophilia* are lacking. Data to prioritize among agents with in vitro activity against *S. maltophilia* and to determine the additive benefit of commonly used combination therapy regimens remain incomplete.

Finally, *S. maltophilia* AST determination is problematic. The CLSI has established breakpoints for 6 agents against *S. maltophilia*: cefiderocol, chloramphenicol, levofloxacin, minocycline, ticarcillin-clavulanate, and TMP-SMX. As of 2023, CLSI breakpoints are no longer available for ceftazidime and it is no longer considered an effective treatment option for *S. maltophilia* [16]. Ticarcillin-clavulanate manufacturing has been discontinued and chloramphenicol is rarely used in the United States due to significant toxicities [710], leaving 4 agents for which interpretable antibiotic MIC data can be provided to clinicians. Confidence in MIC interpretive criteria for several of the remaining agents is challenged by concerns about the reproducibility of MICs using testing methods commonly employed in clinical laboratories [711, 712], limited PK/PD data used to inform breakpoints for most agents, and insufficient data to identify correlations between MICs and clinical outcomes. This guidance document focuses on the treatment of moderate-severe *S. maltophilia* infections.

Question 6.1: What Is a General Approach for the Treatment of Infections Caused by *S. maltophilia*?

Suggested approach: Any of 2 approaches are preferred options for the treatment of *S. maltophilia* infections: (1) the use of 2 of the following agents: cefiderocol, minocycline, TMP-SMX, or levofloxacin or (2) the combination of ceftazidime-avibactam and aztreonam.

Rationale

Given that the isolation of *S. maltophilia* in culture often represents colonization and not infection, it is prudent to carefully distinguish colonization with *S. maltophilia* from infection to avoid unnecessary antibiotic use. In situations of *S. maltophilia* infection, either of 2 approaches are suggested. One option is combination therapy with at least 2 active agents (ie, cefiderocol, minocycline, TMP-SMX, or levofloxacin)—listed in order of preference—at least until clinical improvement is observed, primarily because of the limited supportive data for any individual agent (Questions 6.2, 6.4 to 6.6). Alternatively, the combination of ceftazidime-avibactam and aztreonam can be administered, with the acknowledgement that limited clinical data are available supporting this combination (Question 6.3).

Several investigations suggest increased killing of *S. maltophilia* with combination agents presumed to have in vitro activity against *S. maltophilia* including cefiderocol, minocycline, TMP-SMX, and fluoroquinolones, compared to monotherapy [713–716]. Clinical outcomes data comparing monotherapy and combination therapy are 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 [709, 717–719]. A multicenter, observational study of 307 patients with *S. maltophilia* pneumonia found that combination therapy (largely TMP/SMX with either moxifloxacin or levofloxacin) was not associated with reduced overall 30-day mortality overall compared to monotherapy (largely TMP/SMX or moxifloxacin or levofloxacin) but was associated with reduced mortality in immunocompromised patients and in severely ill patients [720]. As described in Question 6.2, 6.4 to 6.6, there are either concerning PK/PD data or limited clinical data with cefiderocol, minocycline, TMP-SMX, and levofloxacin individually. The panel favors combination therapy for the treatment of *S. maltophilia* infections, at least until clinical improvement has occurred.

Question 6.2: What Is the Role of Cefiderocol for the Treatment of Infections Caused by *S. maltophilia*?

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

Rationale

Surveillance studies indicate susceptibility of *S. maltophilia* isolates to cefiderocol approaches 100%, even against isolates resistant to other commonly prescribed agents [410, 412, 661, 715, 721, 722]. The CLSI has a susceptible only breakpoint for cefiderocol against *S. maltophilia*, because of a paucity of *S. maltophilia* isolates that are not susceptible to cefiderocol [16]. Of note, although the emergence of resistance of *S. maltophilia* to cefiderocol has not been described in patient isolates, cefiderocol-resistant *S. maltophilia* mutants have been identified in in vitro models—the clinical significance of which remains unclear [723, 724].

Neutropenic thigh and lung animal infection models demonstrate potent activity of cefiderocol against *S. maltophilia* and indicate that in vivo efficacy against *S. maltophilia* appears to correlate with in vitro efficacy, using simulated human dosing [668, 725–727]. A neutropenic rabbit *S. maltophilia* pneumonia model using human simulated dosages of cefiderocol demonstrated that cefiderocol was able to eradicate *S. maltophilia* in lung tissue, in contrast to TMP-SMX where residual bacteria were present [727]. Moreover, 87% of cefiderocol treated rabbits survived compared to 25% of TMP-SMX treated rabbits. No untreated rabbits survived.

A clinical trial evaluating the role of cefiderocol for carbapenem-resistant infections included five patients with *S. maltophilia* infections [230, 728]. All 5 patients were assigned to the cefiderocol arm, precluding comparisons between treatment regimens. Four out of 5 patients died. If limiting the analysis to the 3 patients with *S. maltophilia* infections without *A. baumannii* coinfection, 2 of 3 patients died. Additional clinical data evaluating the role of cefiderocol for the treatment of *S. maltophilia* infections are limited to case reports but several indicate favorable outcomes after failing traditional regimens [729–733]. Despite the limited availability of clinical data, PK/PD data [734] and animal models [668, 725–727] are encouraging for the use of cefiderocol in treating *S. maltophilia* infections. Data are not available to guide the decision to use cefiderocol as a component of combination therapy or as monotherapy. Given the limited clinical experiences with cefiderocol for the treatment of *S. maltophilia* infections, the panel suggests cefiderocol be considered as a component of combination therapy at least until clinical improvement is observed.

Question 6.3: What Is the Role of Ceftazidime-Avibactam and Aztreonam for the Treatment of Infections Caused by *S. maltophilia*?

Suggested approach: Ceftazidime-avibactam and aztreonam is a preferred treatment combination for *S. maltophilia* infections.

Rationale

The combination of ceftazidime-avibactam and aztreonam (which mimics aztreonam-avibactam) can be used to overcome the activity of both the L1 and L2 β-lactamases intrinsic to *S. maltophilia* [688, 735–740]. The L1 metallo-β-lactamase hydrolyzes ceftazidime but not aztreonam. The L2 serine β-lactamase hydrolyzes ceftazidime and aztreonam but is inactivated by avibactam. Therefore, the combination of ceftazidime-avibactam and aztreonam enables aztreonam to bypass inactivation and successfully reach its target PBPs of *S. maltophilia.* Surveillance data indicate aztreonam-avibactam is active against approximately 92% of *S. maltophilia* isolates [735, 736, 738, 739]. Despite limited available clinical data with this regimen for the treatment of *S. maltophilia* infections [737, 741–743], the combination of ceftazidime-avibactam and aztreonam is a preferred treatment option for *S. maltophilia* infections. Strategies for administering the combination of ceftazidime-avibactam and aztreonam are reviewed in Table 1 and Supplementary Material [280–282]. Patients should be monitored closely for elevations in liver enzymes, which was observed in approximately 40% of patients in a phase 1 study [283]. The CLSI has endorsed the use of a broth disk elution method to evaluate the susceptibility of *S. maltophilia* isolates to the combination of ceftazidime-avibactam and aztreonam [16, 277].

Question 6.4: What Is the Role of Tetracycline Derivatives for the Treatment of Infections Caused by *S. maltophilia*?

Suggested approach: High-dose minocycline, as a component of combination therapy, is an option for the treatment of *S. maltophilia* infections.

Rationale

Surveillance studies report that minocycline has activity against approximately 70%–90% of *S. maltophilia* isolates [716, 744–746]. These data were generated using minocycline susceptibility breakpoints of ≤4 μg/mL. In 2023, the CLSI lowered the minocycline breakpoints from ≤4 μg/mL to ≤1 μg/mL for *S. maltophilia* [16] (Table 2), and the proportion of *S. maltophilia* isolates susceptible to minocycline will be reduced. Among the tetracycline derivatives, CLSI breakpoints are only available for minocycline [16].

Minocycline dosages of 200 mg IV every 12 hours have a >90% probability of achieving PK/PD targets associated with bacterial stasis in a neutropenic mouse thigh model for organisms with MICs of 1 μg/mL but only a 50% probability of achieving targets associated with 1-log kill [747].

Clinical outcomes data investigating the role of tetracycline derivatives for the treatment of *S. maltophilia* infections are challenging to interpret. Several observational studies have been conducted but are limited by small sample sizes, use of standard-dose and not high-dose minocycline or tigecycline, lack of a comparator arm, heterogeneity in sites of infection,

or use of additional antibiotic agents [748–752]. Studies that included a comparator arm did not indicate any clear failure signals with tetracycline derivatives compared to TMP-SMX or fluoroquinolones.

Despite limitations with interpreting available clinical data, the panel considers high-dose minocycline as a treatment option for *S. maltophilia* infections, when administered as a component of combination therapy. Because of the slightly more favorable in vitro data with minocycline, more favorable PK/PD data, oral formulation, and potentially improved tolerability of minocycline relative to tigecycline, the panel favors minocycline.

In vitro and in vivo data on the role of eravacycline against *S. maltophilia* are scarce.

Omadacycline, a tetracycline derivative with oral and IV formulations, has limited in vitro activity against *S. maltophilia* relative to other tetracycline derivatives [744]. The panel does not suggest the use of eravacycline or omadacycline for the treatment of *S. maltophilia* infections.

A general concern with tetracycline derivatives is that they achieve rapid tissue distribution following administration, resulting in limited concentrations in the urine and serum [39]. Therefore, they are not suggested for *S. maltophilia* UTIs and should be used with caution and as a component of combination therapy for the treatment of bloodstream infections. Nausea and emesis are reported in as many as 20%–40% of patients receiving minocycline or tigecycline [353–355].

Question 6.5: What Is the Role of Trimethoprim-sulfamethoxazole for the Treatment of Infections Caused by *S. maltophilia*?

Suggested approach: TMP-SMX, as a component of combination therapy, is an option for the treatment of *S. maltophilia* infections.

Rationale

Surveillance studies have consistently shown that TMP-SMX has more than a 90% likelihood of in vitro activity against *S. maltophilia* [753, 754], although there is an increasing recognition of *S. maltophilia* isolates resistant to TMP-SMX [715, 753, 755, 756]. Despite the longstanding clinical experience with use of TMP-SMX for *S. maltophilia* infections, several PK/PD studies have emerged indicating that TMP-SMX is not bactericidal against *S. maltophilia*, even those with low TMP MICs, regardless of the TMP-SMX dosage [713, 715, 716, 757, 758]. At best, TMP-SMX may have the potential to achieve stasis against *S. maltophilia*.

This is in contrast to organisms like *E. coli* where at least a 1-log kill can be observed in the presence of TMP-SMX at similar exposures [757]. Some in vitro studies suggest stasis—and possibly even a 1-log kill-can be more reliably achieved when TMP-SMX is administered as a component of combination therapy [713, 716].

In a neutropenic rabbit lung *S. maltophilia* model, 5 mg/kg dose twice daily reduced the burden of *S. maltophilia* in lung tissue, but did not eradicate the bacteria. In contrast, cefiderocol achieved complete bacterial clearance [727]. Moreover, only 25% of rabbits receiving TMP-SMX survived, compared to 87% receiving cefiderocol.

Rigorous clinical data investigating the effectiveness of TMP-SMX for *S. maltophilia* infections are lacking. An observational study of 1581 patients with *S. maltophilia* identified in respiratory or blood cultures and treated with TMP-SMX or levofloxacin monotherapy was undertaken using an administrative database [759]. This work suggested that TMP-SMX therapy may be associated with increased mortality compared to levofloxacin in patients with *S. maltophilia* recovered from respiratory cultures and that TMP-SMX therapy was associated with prolonged hospitalizations. However, there are significant limitations to this study making its findings challenging to interpret (eg, wide study interval [2005–2017] during which many changes in clinical practice likely occurred, inability to distinguish colonization and infection, inability to adjust for source control, incomplete AST data, inclusion of polymicrobial infections, residual confounding by indication). Given these limitations, the applicability to guide clinical practice is unclear.

Prior to the publication of this work, the largest study evaluating TMP-SMX treatment was a case series of 91 patients with *S. maltophilia* bloodstream infections, in whom mortality was 25% within 14 days [719]. The small number of patients in the study who received an agent other than TMP-SMX precluded a comparative effectiveness evaluation. Several relatively small observational studies comparing TMP-SMX and other agents (namely tetracycline derivatives or fluoroquinolones) have been undertaken and generally demonstrated similar outcomes between treatment agents [748, 750, 760–765].

Given the toxicity of TMP-SMX (eg, hypersensitivity, hyperkalemia, myelosuppression, nephrotoxicity), no established dose-response relationship [757], the absence of clinical evidence supporting any particular dose, and evidence that TMP dosing of >15 mg/kg/day may lead to an increased risk of adverse events without any incremental clinical benefit [766], a dose range of 10–15 mg/kg (trimethoprim component) of TMP/SMX is suggested for patients with *S. maltophilia* infections (Table 1). Doses between 10 and 15 mg/kg/day should provide bacteriostasis for the majority of susceptible isolates. TMP-SMX is a treatment option for *S. maltophilia* infections, when used in combination with a second agent.

Question 6.6: What Is the Role of Fluoroquinolones for the Treatment of Infections Caused by *S. maltophilia*?

Suggested approach: Levofloxacin, as a component of combination therapy, is an option for the treatment of *S. maltophilia* infections.

Rationale

S. maltophilia isolates frequently harbor Sm*qnr* resistance determinants that interfere with fluoroquinolone binding to gyrase and topoisomerase, leading to increased fluoroquinolone MICs [688, 705]. Fluoroquinolone MICs may increase further as a result of overexpression of multidrug-resistant efflux pumps [753, 767–769]. Baseline susceptibility percentages of *S. maltophilia* to levofloxacin vary from approximately 30% to 80% in surveillance studies [715, 716, 770, 771]. Several studies have shown that *S. maltophilia* isolates that test susceptible to levofloxacin can develop elevated levofloxacin MICs during therapy [761, 762, 764, 772]. CLSI breakpoints exist for levofloxacin against *S. maltophilia*, but not for ciprofloxacin or moxifloxacin [16]. In 2023, the CLSI added a comment to the levofloxacin breakpoint stating "levofloxacin should not be used alone for antimicrobial therapy" for *S. maltophilia* infections [16].

Time-kill curves evaluating ciprofloxacin, levofloxacin, and moxifloxacin monotherapy generally indicate that these agents are inadequate at sustained inhibition of *S. maltophilia* growth [745, 773–776] but suggest that levofloxacin and moxifloxacin may have sufficient activity as components of combination therapy [715, 716]. PK/PD modeling data suggest that fluoroquinolone monotherapy may be insufficient to achieve appropriate target attainment for *S. maltophilia* infections, even when administered at high dosages [745]. Neutropenic mouse models suggest that even 750 mg of IV levofloxacin daily may not reliably achieve PK/PD targets associated with bacterial stasis or 1-log killing against a substantial proportion *S. maltophilia* isolates that have MIC values within the wild-type distribution [777]. Levofloxacin and moxifloxacin were both associated with improved survival (50%) compared to placebo (0%) in a mouse model of hemorrhagic *S. maltophilia* pneumonia [778]. Taken together, these data suggest that fluoroquinolones may not provide sufficient benefit as monotherapy but may provide some additive value when administered as a component of combination therapy.

Clinical data evaluating fluoroquinolones for the treatment of *S. maltophilia* clinical infections mostly focus on levofloxacin. A meta-analysis including 663 patients from 14 observational studies compared mortality between fluoroquinolones and TMP-SMX, with approximately 50% of patients receiving fluoroquinolones (including, ciprofloxacin [34%] and levofloxacin [57%]) and 50% receiving TMP-SMX [760]. 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 distinguishing colonization and infection is less problematic, a benefit with fluoroquinolone use was not evident.

As discussed in Question 6.4, an observational study of 1581 patients with *S. maltophilia* identified in respiratory or blood cultures and treated with TMP-SMX or levofloxacin was undertaken using an administrative database [759]. Although this work suggested that levofloxacin may be protective against mortality in patients with *S. maltophilia* recovered from respiratory cultures and marginally protective against mortality regardless of the culture site, there are limitations to this study making its findings challenging to interpret.

Several observational studies comparing fluoroquinolones to other agents (ie, TMP-SMX, tigecycline) did not identify increased clinical failure signals in the fluoroquinolone arm [745, 755, 759]. There are several limitations to these studies including selection bias, small sample sizes, heterogeneity in host and microbial data, and the use of additional active agents.

Due to suboptimal results with fluoroquinolone monotherapy in in vitro studies, known mechanisms of resistance of *S. maltophilia* to fluoroquinolones, relatively low probability of achieving systemic exposures that correlate with stasis or 1-log kill in animal models, the emergence of resistance during therapy, and inherent biases in observational data, the panel suggests levofloxacin be used as a component of combination therapy, when prescribed for the treatment of *S. maltophilia* infections.

Because of the absence of breakpoints 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 [779].

Question 6.7: What Is the Role of Ceftazidime for the Treatment of Infections Caused by *S. maltophilia*?

Suggested approach: Ceftazidime is not a suggested treatment option for *S. maltophilia* infections due to the presence of β-lactamase genes intrinsic to *S. maltophilia* that are expected to render ceftazidime inactive. As of 2024, CLSI breakpoints for *S. maltophilia* to ceftazidime are no longer available.

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. In vitro models suggest ceftazidime is unable to substantially prevent *S. maltophilia* growth [716]. Comparative effectiveness studies evaluating the role of ceftazidime against *S. maltophilia* infections are virtually non-existent [780]. As of 2024, the CLSI no longer has susceptibility breakpoints for ceftazidime against *S. maltophilia*.

CONCLUSIONS

The field of AMR is dynamic and rapidly evolving, and the treatment of AMR infections will continue to challenge

clinicians. As newer antibiotics against resistant pathogens are incorporated into clinical practice, we are learning more about their effectiveness and propensity to resistance. This treatment guidance will be updated approximately annually and is available at: https://www.idsociety.org/practice-guideline/amr-guidance/.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The following list includes what has been reported to IDSA. To provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guidance topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the Board of Directors liaison to the Standards and Practice Guidelines Committee and, if necessary, the Conflicts of Interest and Ethics Committee. The assessment of disclosed relationships for possible conflicts of interests is based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). IDSA requests panel members to disclose activities and financial relationships/investments related to consultant/advisory roles, promotional speakers' bureau, stocks/bonds, honoraria, expert testimony, ownership interest, research grants, organizational benefits, intellectual property, other numeration, activities with other organizations, and relevant financial interest of family members. Readers of this guidance should be mindful of this when the list of disclosures is reviewed. J. J. serves as scientific advisor for Shionogi and Gilead Sciences; received honoraria from Clinical Care Options; owned stock in Vaxart. A. J. M. serves as a scientific advisor for Cepheid, DayZero Diagnostics, and OpGen; provided expert testimony sponsored by BioMerieux Inc. M. J. S. receives research funding from Merck, bioMéreiux, SNIPRBiome, Selux Diagnostics; receives renumeration from AbbVie; serves on a Data and Safety Monitoring Board for AbbVie; received consulting fees from Shionogi and has served on a Data and Safety Monitoring Board for Spero Therapeutics. R. A. B. receives research funding from Venatorx Pharmaceuticals; received research funding from Shionogi, Merck, Entasis Therapeutics, Wockhardt, Allecra Therapeutics, AstraZeneca, Harrington Family Foundation, Tetraphase Pharmaceuticals, Steris, and Melinta Therapeutics; received an honorarium from Unilab. All other authors report no potential conflicts.

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References

1. Antimicrobial Resistance C. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet **2022**; 399:629–55.
2. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC, **2019**.
3. Li Cecilia L, Claeys KC, Justo JA, Heil EL. No crystal ball? Using risk factors and scoring systems to predict Extended-Spectrum Beta-Lactamase Producing Enterobacterales (ESBL-E) and Carbapenem-Resistant Enterobacterales (CRE) infections. Curr Infect Dis Rep **2022**; 24:147–58.
4. Soto CL, Hsu AJ, Lee JH, et al. Identifying effective durations of antibiotic therapy for the treatment of carbapenem-resistant enterobacterales bloodstream infections: a multicenter observational study. Clin Infect Dis **2023**; 78:27–30.
5. 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: e103–20.
6. Heil EL, Bork JT, Abbo LM, et al. Optimizing the management of uncomplicated gram-negative bloodstream infections: consensus guidance using a modified delphi process. Open Forum Infect Dis **2021**; 8:ofab434.
7. Tamma PD, Sharara SL, Pana ZD, et al. Molecular epidemiology of ceftriaxone non-susceptible enterobacterales isolates in an academic medical center in the United States. Open Forum Infect Dis **2019**; 6:ofz353.
8. Tamma PD, Smith TT, Adebayo A, et al. Prevalence of bla CTX-M genes in Gram-negative bloodstream isolates across 66 hospitals in the United States. J Clin Microbiol **2021**; 59:e00127-21.
9. Castanheira M, Kimbrough JH, DeVries S, Mendes RE, Sader HS. Trends of beta-lactamase occurrence among *Escherichia coli* and *Klebsiella pneumoniae* in United States hospitals during a 5-year period and activity of antimicrobial agents against isolates stratified by beta-lactamase type. Open Forum Infect Dis **2023**; 10:ofad038.
10. Bush K, Bradford PA. Epidemiology of beta-lactamase-producing pathogens. Clin Microbiol Rev **2020**; 33:e00047-19.
11. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother **2010**; 54:969–76.
12. Castanheira M, Farrell SE, Krause KM, Jones RN, Sader HS. Contemporary diversity of beta-lactamases among Enterobacteriaceae in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent beta-lactamase groups. Antimicrob Agents Chemother **2014**; 58:833–8.
13. Castanheira M, Simner PJ, Bradford PA. Extended-spectrum beta-lactamases: an update on their characteristics, epidemiology and detection. JAC Antimicrob Resist **2021**; 3:dlab092.
14. Hareza D, Cosgrove SE, Simner PJ, et al. Is carbapenem therapy necessary for the treatment of non-CTX-M ESBL-producing enterobacterales bloodstream infections? Clin Infect Dis. **2024**; 78:1103–10.
15. Robberts FJ, Kohner PC, Patel R. Unreliable extended-spectrum beta-lactamase detection in the presence of plasmid-mediated AmpC in Escherichia coli clinical isolates. J Clin Microbiol **2009**; 47:358–61.
16. Clinical and Laboratory Standards Institute. M100: performance standards for antimicrobial susceptibility testing. 34 ed. **2024**.
17. Tamma PD, Humphries RM. PRO: testing for ESBL production is necessary for ceftriaxone-non-susceptible Enterobacterales: perfect should not be the enemy of progress. JAC Antimicrob Resist **2021**; 3:dlab019.
18. Mathers AJ, Lewis JS 2nd. CON: testing for ESBL production is unnecessary for ceftriaxone-resistant enterobacterales. JAC Antimicrob Resist **2021**; 3:dlab020.
19. Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. JAMA **2018**; 319:1781–9.
20. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med **2007**; 167:2207–12.
21. Gossius G, Vorland L. A randomised comparison of single-dose vs. three-day and ten-day therapy with trimethoprim-sulfamethoxazole for acute cystitis in women. Scand J Infect Dis **1984**; 16:373–9.
22. Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA **2005**; 293:949–55.
23. Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA **2012**; 307:583–9.
24. Tanne JH. FDA adds "black box" warning label to fluoroquinolone antibiotics. BMJ **2008**; 337:a816.
25. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. Antimicrob Agents Chemother **2013**; 57:2326–32.
26. Kazakova SV, Baggs J, McDonald LC, et al. Association between antibiotic use and hospital-onset *Clostridioides difficile* infection in US acute care hospitals, 2006–2012: an ecologic analysis. Clin Infect Dis **2020**; 70:11–8.
27. Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis **2005**; 41:1254–60.

28. 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:e02165-18.
29. Zilberberg MD, Nathanson BH, Sulham K, Shorr AF. Antimicrobial susceptibility and cross-resistance patterns among common complicated urinary tract infections in U.S. hospitals, 2013 to 2018. Antimicrob Agents Chemother **2020**; 64: e00346-20.
30. Sastry S, Clarke LG, Alrowais H, Querry AM, Shutt KA, Doi Y. Clinical appraisal of fosfomycin in the era of antimicrobial resistance. Antimicrob Agents Chemother **2015**; 59:7355–61.
31. Ito R, Mustapha MM, Tomich AD, et al. Widespread fosfomycin resistance in Gram-negative bacteria attributable to the chromosomal fosA gene. mBio **2017**; 8:e00749-17.
32. 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:e00634-19.
33. Rouphael N, Winokur P, Keefer MC, et al. Daily fosfomycin versus levofloxacin for complicated urinary tract infections. mBio **2023**; 14:e0167723.
34. Campbell JD, Lewis JS 2nd, McElmeel ML, Fulcher LC, Jorgensen JH. Detection of favorable oral cephalosporin-clavulanate interactions by in vitro disk approximation susceptibility testing of extended-spectrum-Beta-lactamase-producing members of the enterobacteriaceae. J Clin Microbiol **2012**; 50:1023–6.
35. Thomson GK, Ayaz M, Lutes K, Thomson KS. An improved extended-spectrum-beta-lactamase detection test utilizing aztreonam plus clavulanate. J Clin Microbiol **2018**; 56:e01309-17.
36. Estebanez A, Pascual R, Gil V, Ortiz F, Santibanez M, Perez Barba C. Fosfomycin in a single dose versus a 7-day course of amoxicillin-clavulanate for the treatment of asymptomatic bacteriuria during pregnancy. Eur J Clin Microbiol Infect Dis **2009**; 28:1457–64.
37. Mukerji AC, Sharma MM, Taneja OP, Saxena SN, Bhatnagar RK, Ghosh-Ray B. A clinical trial of alpha-6-deoxyoxytetracycline (doxycycline) in the treatment of urinary tract infections. Chemotherapy **1969**; 14:77–85.
38. Musher DM, Minuth JN, Thorsteinsson SB, Holmes T. Effectiveness of achievable urinary concentrations of tetracyclines against "tetracycline-resistant" pathogenic bacteria. J Infect Dis **1975**; 131(Suppl):S40–4.
39. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother **2006**; 58:256–65.
40. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet **2012**; 380:484–90.
41. Ren H, Li X, Ni ZH, et al. Treatment of complicated urinary tract infection and acute pyelonephritis by short-course intravenous levofloxacin (750 mg/day) or conventional intravenous/oral levofloxacin (500 mg/day): prospective, open-label, randomized, controlled, multicenter, non-inferiority clinical trial. Int Urol Nephrol **2017**; 49:499–507.
42. 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**; 283:1583–90.
43. Marchaim D, Chopra T, Bhargava A, et al. Recent exposure to antimicrobials and carbapenem-resistant enterobacteriaceae: the role of antimicrobial stewardship. Infect Control Hosp Epidemiol **2012**; 33:817–30.
44. Bergeron MG, Trottier S. Influence of single or multiple doses of gentamicin and netilmicin on their cortical, medullary, and papillary distribution. Antimicrob Agents Chemother **1979**; 15:635–41.
45. Wagenlehner FME, Cloutier DJ, Komirenko AS, et al. Once-daily plazomicin for complicated urinary tract infections. N Engl J Med **2019**; 380:729–40.
46. Sader HS, Mendes RE, Kimbrough JH, Kantro V, Castanheira M. Impact of the recent clinical and laboratory standards institute breakpoint changes on the antimicrobial spectrum of aminoglycosides and the activity of plazomicin against multidrug-resistant and carbapenem-resistant enterobacterales from United States medical centers. Open Forum Infect Dis **2023**; 10:ofad058.
47. Elbaz M, Zadka H, Weiss-Meilik A, Ben-Ami R. Effectiveness and safety of an institutional aminoglycoside-based regimen as empirical treatment of patients with pyelonephritis. J Antimicrob Chemother **2020**; 75:2307–13.
48. Chou A, Welch E, Hunter A, Trautner BW. Antimicrobial treatment options for difficult-to-treat resistant Gram-negative bacteria causing cystitis, pyelonephritis, and prostatitis: a narrative review. Drugs **2022**; 82:407–38.
49. Bertino JS Jr, Booker LA, Franck PA, Jenkins PL, Franck KR, Nafziger AN. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. J Infect Dis **1993**; 167:173–9.
50. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis **2007**; 45:753–60.
51. Ten Doesschate T, Kuiper S, van Nieuwkoop C, et al. Fosfomycin vs ciprofloxacin as oral step-down treatment for *Escherichia coli* febrile urinary tract infections in women: a randomized, placebo-controlled, double-blind, multicenter trial. Clin Infect Dis **2022**; 75:221–9.
52. Kaye KS, Rice LB, Dane AL, et al. Fosfomycin for injection (ZTI-01) versus piperacillin-tazobactam for the treatment of complicated urinary tract infection including acute pyelonephritis: ZEUS, a phase 2/3 randomized trial. Clin Infect Dis **2019**; 69:2045–56.
53. Karaiskos I, Galani L, Sakka V, et al. Oral fosfomycin for the treatment of chronic bacterial prostatitis. J Antimicrob Chemother **2019**; 74:1430–7.
54. Grayson ML, Macesic N, Trevillyan J, et al. Fosfomycin for treatment of prostatitis: new tricks for old dogs. Clin Infect Dis **2015**; 61:1141–3.
55. Gardiner BJ, Mahony AA, Ellis AG, et al. Is fosfomycin a potential treatment alternative for multidrug-resistant Gram-negative prostatitis? Clin Infect Dis **2014**; 58:e101–5.
56. Kwan ACF, Beahm NP. Fosfomycin for bacterial prostatitis: a review. Int J Antimicrob Agents **2020**; 56:106106.
57. Di Stefano AFD, Radicioni MM, Morano F, et al. Fosfomycin pharmacokinetic profile in plasma and urine and quantitative estimation in prostate and seminal vesicles after one and two consecutive doses of oral fosfomycin trometamol in healthy male volunteers. Antibiotics (Basel) **2022**; 11:1458.
58. Cai T, Tamanini I, Mattevi D, et al. Fosfomycin trometamol and N-acetyl-L-cysteine as combined oral therapy of difficult-to-treat chronic bacterial prostatitis: results of a pilot study. Int J Antimicrob Agents **2020**; 56:105935.
59. Burgos J, Hoyos-Mallecot Y, Ferre-Losa C, et al. Oral fosfomycin for treatment of acute bacterial prostatitis caused by multidrug-resistant Enterobacterales. Microbiol Spectr **2023**; 11:e0213623.
60. Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or klebsiella pneumoniae bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA **2018**; 320:984–94.
61. Zhanel GG, Wiebe R, Dilay L, et al. Comparative review of the carbapenems. Drugs **2007**; 67:1027–52.
62. Liebchen U, Kratzer A, Wicha SG, Kees F, Kloft C, Kees MG. Unbound fraction of ertapenem in intensive care unit patients. J Antimicrob Chemother **2014**; 69: 3108–11.
63. Burkhardt O, Kumar V, Katterwe D, et al. Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. J Antimicrob Chemother **2007**; 59: 277–84.
64. Brink AJ, Richards GA, Schillack V, Kiem S, Schentag J. Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. Int J Antimicrob Agents **2009**; 33:432–6.
65. Zusman O, Farbman L, Tredler Z, et al. Association between hypoalbuminemia and mortality among subjects treated with ertapenem versus other carbapenems: prospective cohort study. Clin Microbiol Infect **2015**; 21:54–8.
66. Lee NY, Huang WH, Tsui KC, Hsueh PR, Ko WC. Carbapenem therapy for bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*. Diagn Microbiol Infect Dis **2011**; 70:150–3.
67. Chen M, Nafziger AN, Drusano GL, Ma L, Bertino JS Jr. Comparative pharmacokinetics and pharmacodynamic target attainment of ertapenem in normal-weight, obese, and extremely obese adults. Antimicrob Agents Chemother **2006**; 50:1222–7.
68. Kiffer CR, Kuti JL, Eagye KJ, Mendes C, Nicolau DP. Pharmacodynamic profiling of imipenem, meropenem and ertapenem against clinical isolates of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* spp. from Brazil. Int J Antimicrob Agents **2006**; 28:340–4.
69. Lass J, Tamme K, Kipper K, Starkopf J. Dosing of ertapenem in an extreme obesity: a case report of 250 kg patient. Case Rep Crit Care **2017**; 2017:5310768.
70. Goutelle S, Valour F, Gagnieu MC, et al. Population pharmacokinetics and probability of target attainment of ertapenem administered by subcutaneous or intravenous route in patients with bone and joint infection. J Antimicrob Chemother **2018**; 73:987–94.
71. Ferry T, Goutelle S, Gagnieu M-C, et al. High doses of ertapenem (1g/12h) administered subcutaneously optimize the ertapemem exposure in patients with Bone in Joint Infections (BJI): a Monte Carlo simulation study. Open Forum Infect Dis **2016**; 3. doi:10.1093/ofid/ofw172.1536
72. Henderson A, Paterson DL, Chatfield MD, et al. Association between minimum inhibitory concentration, beta-lactamase genes and mortality for patients treated with piperacillin/tazobactam or meropenem from the MERINO study. Clin Infect Dis **2020**; 73:e3842–50.
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**; 179:316–23.

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:ofz364.
75. Bush K, Macalintal C, Rasmussen BA, Lee VJ, Yang Y. Kinetic interactions of tazobactam with beta-lactamases from all major structural classes. Antimicrob Agents Chemother **1993**; 37:851–8.
76. Livermore DM, Andrews JM, Hawkey PM, et al. Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly? J Antimicrob Chemother **2012**; 67:1569–77.
77. Zhou M, Wang Y, Liu C, et al. Comparison of five commonly used automated susceptibility testing methods for accuracy in the China Antimicrobial Resistance Surveillance System (CARSS) hospitals. Infect Drug Resist **2018**; 11:1347–58.
78. Walkty A, Karlowsky JA, Lagacé-Wiens PRS, et al. Presence of the narrow-spectrum OXA-1 β-lactamase enzyme is associated with elevated piperacillin/tazobactam MIC values among ESBL-producing *Escherichia coli* clinical isolates (CANWARD, 2007-18). JAC Antimicrob Resist **2022**; 4:dlac027. doi:10.1093/jacamr/dlac027
79. Livermore DM, Day M, Cleary P, et al. OXA-1 beta-lactamase and non-susceptibility to penicillin/beta-lactamase inhibitor combinations among ESBL-producing Escherichia coli. J Antimicrob Chemother **2019**; 74:326–33.
80. Burgess DS, Hall RG 2nd. In vitro killing of parenteral beta-lactams against standard and high inocula of extended-spectrum beta-lactamase and non-ESBL producing Klebsiella pneumoniae. Diagn Microbiol Infect Dis **2004**; 49:41–6.
81. Harada Y, Morinaga Y, Kaku N, et al. In vitro and in vivo activities of piperacillin-tazobactam and meropenem at different inoculum sizes of ESBL-producing Klebsiella pneumoniae. Clin Microbiol Infect **2014**; 20: O831–9.
82. Thomson KS, Moland ES. Cefepime, piperacillin-tazobactam, and the inoculum effect in tests with extended-spectrum beta-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother **2001**; 45:3548–54.
83. 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:e00105-19.
84. Monogue ML, Heil EL, Aitken SL, Pogue JM. The role of tazobactam-based combinations for the management of infections due to extended-spectrum beta-lactamase-producing Enterobacterales: insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy **2021**; 41:864–80.
85. Crass RL, Pai MP. Pharmacokinetics and pharmacodynamics of beta-lactamase inhibitors. Pharmacotherapy **2019**; 39:182–95.
86. Sharara SL, Amoah J, Pana ZD, Simner PJ, Cosgrove SE, Tamma PD. Is piperacillin-tazobactam effective for the treatment of pyelonephritis caused by ESBL-producing organisms? Clin Infect Dis **2019**; 71:e331–7.
87. Dizbay M, Ozger HS, Karasahin O, Karasahin EF. Treatment efficacy and superinfection rates in complicated urinary tract infections treated with ertapenem or piperacillin tazobactam. Turk J Med Sci **2016**; 46:1760–4.
88. Yoon YK, Kim JH, Sohn JW, Yang KS, Kim MJ. Role of piperacillin/tazobactam as a carbapenem-sparing antibiotic for treatment of acute pyelonephritis due to extended-spectrum beta-lactamase-producing Escherichia coli. Int J Antimicrob Agents **2017**; 49:410–5.
89. Branton AC, Vu CH, Venugopalan V, et al. Re-evaluation of cefepime or piperacillin/tazobactam to decrease use of carbapenems in ESBL-producing Enterobacterales urinary tract infections (REDUCE-UTI). JAC Antimicrob Resist **2023**; 5:dlad021.
90. Stefanos SS, Sakaan S, Samarin M, et al. Assessing clinical cure of empirical piperacillin/tazobactam for ESBL urinary tract infections (ACCEPT-UTI). JAC Antimicrob Resist **2023**; 5:dlad055.
91. Seo YB, Lee J, Kim YK, et al. Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. BMC Infect Dis **2017**; 17:404.
92. Gutierrez-Gutierrez B, Perez-Galera S, Salamanca E, et al. A multinational, preregistered cohort study of beta-lactam/beta-lactamase inhibitor combinations for treatment of bloodstream infections due to extended-spectrum-beta-lactamase-producing enterobacteriaceae. Antimicrob Agents Chemother **2016**; 60:4159–69.
93. Harris PN, Yin M, Jureen R, et al. Comparable outcomes for beta-lactam/beta-lactamase inhibitor combinations and carbapenems in definitive treatment of bloodstream infections caused by cefotaxime-resistant Escherichia coli or Klebsiella pneumoniae. Antimicrob Resist Infect Control **2015**; 4:14.
94. Ng TM, Khong WX, Harris PN, et al. Empiric piperacillin-tazobactam versus carbapenems in the treatment of bacteraemia due to extended-spectrum beta-lactamase-producing enterobacteriaceae. PLoS One **2016**; 11:e0153696.
95. Tamma PD, Han JH, Rock C, et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum beta-lactamase bacteremia. Clin Infect Dis **2015**; 60: 1319–25.
96. Tsai HY, Chen YH, Tang HJ, et al. Carbapenems and piperacillin/tazobactam for the treatment of bacteremia caused by extended-spectrum beta-lactamase-producing *Proteus mirabilis*. Diagn Microbiol Infect Dis **2014**; 80:222–6.
97. Rodríguez-Baño J, Navarro MD, Retamar P, Picon E, Pascual A. Extended-spectrum beta-lactamases-red espanola de investigacion en patologia infecciosa/grupo de estudio de infeccion hospitalaria G. beta-lactam/beta-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli*: a post hoc analysis of prospective cohorts. Clin Infect Dis **2012**; 54:167–74.
98. Nasir N, Ahmed S, Razi S, Awan S, Mahmood SF. Risk factors for mortality of patients with ceftriaxone resistant *E. coli* bacteremia receiving carbapenem versus beta lactam/beta lactamase inhibitor therapy. BMC Res Notes **2019**; 12:611.
99. Xiao T, Yang K, Zhou Y, et al. Risk factors and outcomes in non-transplant patients with extended-spectrum beta-lactamase-producing Escherichia coli bacteremia: a retrospective study from 2013 to 2016. Antimicrob Resist Infect Control **2019**; 8:144.
100. Ko JH, Lee NR, Joo EJ, et al. Appropriate non-carbapenems are not inferior to carbapenems as initial empirical therapy for bacteremia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae: a propensity score weighted multicenter cohort study. Eur J Clin Microbiol Infect Dis **2018**; 37: 305–11.
101. Meini S, Laureano R, Tascini C, et al. Clinical outcomes of elderly patients with bloodstream infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae in an Italian Internal Medicine ward. Eur J Intern Med **2018**; 48:50–6.
102. Ofer-Friedman H, Shefler C, Sharma S, et al. Carbapenems versus piperacillin-tazobactam for bloodstream infections of nonurinary source caused by extended-spectrum beta-lactamase-producing enterobacteriaceae. Infect Control Hosp Epidemiol **2015**; 36:981–5.
103. Tamma PD, Rodríguez-Baño J. The use of noncarbapenem beta-lactams for the treatment of extended-spectrum beta-lactamase infections. Clin Infect Dis **2017**; 64:972–80.
104. Bitterman R, Paul M, Leibovici L, Mussini C. PipEracillin Tazobactam Versus mERoPENem for Treatment of Bloodstream Infections Caused by Cephalosporin-resistant Enterobacteriaceae (PETERPEN). Available at: https://clinicaltrials.gov/ct2/show/NCT03671967. Accessed 31 December 2022.
105. Tamma PD, Harris PNA, Mathers AJ, Wenzler E, Humphries RM. Breaking down the breakpoints: rationale for the 2022 clinical and laboratory standards institute revised piperacillin-tazobactam breakpoints against enterobacterales. Clin Infect Dis **2022**; 77:1585–90.
106. Yu WL, Pfaller MA, Winokur PL, Jones RN. Cefepime MIC as a predictor of the extended-spectrum beta-lactamase type in *Klebsiella pneumoniae*, Taiwan. Emerg Infect Dis **2002**; 8:522–4.
107. Smith KP, Brennan-Krohn T, Weir S, Kirby JE. Improved accuracy of cefepime susceptibility testing for extended-spectrum-beta-lactamase-producing enterobacteriaceae with an on-demand digital dispensing method. J Clin Microbiol **2017**; 55:470–8.
108. Kim SA, Altshuler J, Paris D, Fedorenko M. Cefepime versus carbapenems for the treatment of urinary tract infections caused by extended-spectrum beta-lactamase-producing enterobacteriaceae. Int J Antimicrob Agents **2018**; 51:155–8.
109. Zanetti G, Bally F, Greub G, et al. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. Antimicrob Agents Chemother **2003**; 47:3442–7.
110. Wang R, Cosgrove SE, Tschudin-Sutter S, et al. Cefepime therapy for cefepime-susceptible extended-spectrum beta-lactamase-producing enterobacteriaceae bacteremia. Open Forum Infect Dis **2016**; 3:ofw132.
111. 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: 7558–63.
112. Chopra T, Marchaim D, Veltman J, et al. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*. Antimicrob Agents Chemother **2012**; 56:3936–42.
113. Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. Clin Infect Dis **2013**; 56:488–95.

114. Kusumoto M, Kanao Y, Narita H, et al. *In vitro* efficacy of cephamycins against multiple extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae* isolates from dogs and cats. J Vet Med Sci **2023**; 85:653–6.
115. Stewart AG, Cottrell K, Henderson A, et al. In vitro activity of cefotetan against ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* bloodstream isolates from the MERINO trial. Microbiol Spectr **2021**; 9:e0022621.
116. Lee CH, Su LH, Tang YF, Liu JW. Treatment of ESBL-producing *Klebsiella pneumoniae* bacteraemia with carbapenems or flomoxef: a retrospective study and laboratory analysis of the isolates. J Antimicrob Chemother **2006**; 58:1074–7.
117. Yang CC, Li SH, Chuang FR, et al. Discrepancy between effects of carbapenems and flomoxef in treating nosocomial hemodialysis access-related bacteremia secondary to extended spectrum beta-lactamase producing Klebsiella pneumoniae in patients on maintenance hemodialysis. BMC Infect Dis **2012**; 12:206.
118. Doi A, Shimada T, Harada S, Iwata K, Kamiya T. The efficacy of cefmetazole against pyelonephritis caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. Int J Infect Dis **2013**; 17:e159–63.
119. Pilmis B, Parize P, Zahar JR, Lortholary O. Alternatives to carbapenems for infections caused by ESBL-producing enterobacteriaceae. Eur J Clin Microbiol Infect Dis **2014**; 33:1263–5.
120. Matsumura Y, Yamamoto M, Nagao M, et al. Multicenter retrospective study of cefmetazole and flomoxef for treatment of extended-spectrum-beta-lactamase-producing Escherichia coli bacteremia. Antimicrob Agents Chemother **2015**; 59:5107–13.
121. Lee CH, Su LH, Chen FJ, et al. Comparative effectiveness of flomoxef versus carbapenems in the treatment of bacteraemia due to extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae* with emphasis on minimum inhibitory concentration of flomoxef: a retrospective study. Int J Antimicrob Agents **2015**; 46:610–5.
122. Fukuchi T, Iwata K, Kobayashi S, Nakamura T, Ohji G. Cefmetazole for bacteremia caused by ESBL-producing enterobacteriaceae comparing with carbapenems. BMC Infect Dis **2016**; 16:427.
123. Senard O, Lafaurie M, Lesprit P, et al. Efficacy of cefoxitin versus carbapenem in febrile male urinary tract infections caused by extended spectrum beta-lactamase-producing *Escherichia coli*: a multicenter retrospective cohort study with propensity score analysis. Eur J Clin Microbiol Infect Dis **2020**; 39:121–9.
124. Dequidt T, Bastian S, Nacher M, et al. Cefoxitin versus carbapenems as definitive treatment for extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* bacteremia in intensive care unit: a propensity-matched retrospective analysis. Crit Care **2023**; 27:418.
125. Hayakawa K, Matsumura Y, Uemura K, et al. Effectiveness of cefmetazole versus meropenem for invasive urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. Antimicrob Agents Chemother **2023**; 67:e0051023.
126. Chabert P, Provoost J, Cohen S, et al. Pharmacokinetics, efficacy and tolerance of cefoxitin in the treatment of cefoxitin-susceptible extended-spectrum beta-lactamase producing Enterobacterales infections in critically ill patients: a retrospective single-center study. Ann Intensive Care **2022**; 12:90.
127. Bush K, Bradford PA. Interplay between beta-lactamases and new beta-lactamase inhibitors. Nat Rev Microbiol **2019**; 17:295–306.
128. Jacobs MR, Abdelhamed AM, Good CE, et al. ARGONAUT-I: activity of cefiderocol (S- 649266), a siderophore cephalosporin, against Gram-negative bacteria, including carbapenem-resistant nonfermenters and enterobacteriaceae with defined extended-spectrum beta-lactamases and carbapenemases. Antimicrob Agents Chemother **2019**; 63:e01801-18.
129. 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**; 53:456–66.
130. 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**; 60:2849–57.
131. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis **2016**; 16:661–73.
132. Mendes RE, Castanheira M, Woosley LN, Stone GG, Bradford PA, Flamm RK. Molecular beta-lactamase characterization of aerobic gram-negative pathogens recovered from patients enrolled in the ceftazidime-avibactam phase 3 trials for complicated intra-abdominal infections, with efficacies analyzed against susceptible and resistant subsets. Antimicrob Agents Chemother **2017**; 61: e02447-16.
133. Mendes RE, Castanheira M, Woosley LN, Stone GG, Bradford PA, Flamm RK. Characterization of beta-lactamase content of ceftazidime-resistant pathogens recovered during the pathogen-directed phase 3 REPRISE trial for ceftazidime-avibactam: correlation of efficacy against beta-lactamase producers. Antimicrob Agents Chemother **2019**; 63:e02655-18.
134. 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 Enterobacterales?: a systematic review and meta-analysis. Antimicrob Agents Chemother **2020**; 65:e01052-20.
135. Torres A, Zhong N, Pachl J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis **2018**; 18:285–95.
136. Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and *Pseudomonas aeruginosa* with various resistance patterns isolated in U.S. hospitals (2011–2012). Antimicrob Agents Chemother **2013**; 57:6305–10.
137. Sutherland CA, Nicolau DP. Susceptibility profile of ceftolozane/tazobactam and other parenteral antimicrobials against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* from US hospitals. Clin Ther **2015**; 37:1564–71.
138. Shortridge D, Pfaller MA, Castanheira M, Flamm RK. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and *Pseudomonas aeruginosa* collected from patients with bloodstream infections isolated in United States hospitals (2013–2015) as part of the Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) surveillance program. Diagn Microbiol Infect Dis **2018**; 92:158–63.
139. Shortridge D, Pfaller MA, Castanheira M, Flamm RK. Antimicrobial activity of ceftolozane-tazobactam tested against enterobacteriaceae and pseudomonas aeruginosa with various resistance patterns isolated in U.S. hospitals (2013–2016) as part of the surveillance program: program to assess ceftolozane-tazobactam susceptibility. Microb Drug Resist **2018**; 24:563–77.
140. Sader HS, Castanheira M, Streit JM, Flamm RK. Frequency of occurrence and antimicrobial susceptibility of bacteria isolated from patients hospitalized with bloodstream infections in United States medical centers (2015–2017). Diagn Microbiol Infect Dis **2019**; 95:114850.
141. Sader HS, Flamm RK, Carvalhaes CG, Castanheira M. Comparison of ceftazidime-avibactam and ceftolozane-tazobactam in vitro activities when tested against gram-negative bacteria isolated from patients hospitalized with pneumonia in United States medical centers (2017–2018). Diagn Microbiol Infect Dis **2020**; 96:114833.
142. Nicasio AM, VanScoy BD, Mendes RE, et al. Pharmacokinetics-pharmacodynamics of tazobactam in combination with piperacillin in an in vitro infection model. Antimicrob Agents Chemother **2016**; 60:2075–80.
143. VanScoy B, Mendes RE, Nicasio AM, et al. Pharmacokinetics-pharmacodynamics of tazobactam in combination with ceftolozane in an in vitro infection model. Antimicrob Agents Chemother **2013**; 57:2809–14.
144. Popejoy MW, Paterson DL, Cloutier D, et al. Efficacy of ceftolozane/tazobactam against urinary tract and intra-abdominal infections caused by ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*: a pooled analysis of phase 3 clinical trials. J Antimicrob Chemother **2017**; 72:268–72.
145. Kollef MH, Novacek M, Kivistik U, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis **2019**; 19:1299–311.
146. Martin-Loeches I, Timsit JF, Kollef MH, et al. Clinical and microbiological outcomes, by causative pathogen, in the ASPECT-NP randomized, controlled, phase 3 trial comparing ceftolozane/tazobactam and meropenem for treatment of hospital-acquired/ventilator-associated bacterial pneumonia. J Antimicrob Chemother **2022**; 77:1166–77.
147. 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**; 69:1446–55.
148. Jacoby GA. Ampc beta-lactamases. Clin Microbiol Rev **2009**; 22:161–82.
149. Philippon A, Arlet G, Labia R, Iorga BI. Class C beta-lactamases: molecular characteristics. Clin Microbiol Rev **2022**; 35:e0015021.
150. 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**; 21:1107–13.
151. 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**; 5:3709–14.

152. Philippon A, Arlet G, Jacoby GA. Plasmid-determined AmpC-type beta-lactamases. Antimicrob Agents Chemother **2002**; 46:1–11.
153. Eliopoulos GM. Induction of beta-lactamases. J Antimicrob Chemother **1988**; 22(Suppl A):37–44.
154. Bennett PM, Chopra I. Molecular basis of beta-lactamase induction in bacteria. Antimicrob Agents Chemother **1993**; 37:153–8.
155. Lindberg F, Westman L, Normark S. Regulatory components in *Citrobacter freundii* ampC beta-lactamase induction. Proc Natl Acad Sci U S A **1985**; 82: 4620–4.
156. 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**; 53:1076–80.
157. 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**; 45:2287–98.
158. Matsen JM, Blazevic DJ, Ryan JA, Ewing WH. Characterization of indole-positive *Proteus mirabilis*. Appl Microbiol **1972**; 23:592–4.
159. 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: 995–1000.
160. Chow JW, Fine MJ, Shlaes DM, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med **1991**; 115:585–90.
161. 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**; 45:2628–30.
162. 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**; 41:236–49.
163. Tamma PD, Girdwood SC, Gopaul R, et al. The use of cefepime for treating AmpC beta-lactamase-producing Enterobacteriaceae. Clin Infect Dis **2013**; 57: 781–8.
164. Kohlmann R, Bahr T, Gatermann SG. Species-specific mutation rates for ampC derepression in Enterobacterales with chromosomally encoded inducible AmpC beta-lactamase. J Antimicrob Chemother **2018**; 73:1530–6.
165. Lazarus JE, Wang Y, Waldor MK, Hooper DC. Divergent genetic landscapes drive lower levels of AmpC induction and stable de-repression in Serratia marcescens compared to Enterobacter cloacae. Antimicrob Agents Chemother **2023**; 68:e0119323.
166. Hardy ME, Kenney RM, Tibbetts RJ, Shallal AB, Veve MP. Leveraging stewardship to promote ceftriaxone use in severe infections with low- and no-risk AmpC Enterobacterales. Antimicrob Agents Chemother **2023**; 67:e0082623.
167. 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.
168. Seoane A, Francia MV, Garcia Lobo JM. Nucleotide sequence of the ampC-ampR region from the chromosome of *Yersinia enterocolitica*. Antimicrob Agents Chemother **1992**; 36:1049–52.
169. 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**; 44:3220–3.
170. Sanders CC, Bradford PA, Ehrhardt AF, et al. Penicillin-binding proteins and induction of AmpC beta-lactamase. Antimicrob Agents Chemother **1997**; 41: 2013–5.
171. Weber DA, Sanders CC. Diverse potential of beta-lactamase inhibitors to induce class I enzymes. Antimicrob Agents Chemother **1990**; 34:156–8.
172. Livermore DM, Oakton KJ, Carter MW, Warner M. Activity of ertapenem (MK-0826) versus Enterobacteriaceae with potent beta-lactamases. Antimicrob Agents Chemother **2001**; 45:2831–7.
173. Kurpiel PM, Hanson ND. Point mutations in the inc antisense RNA gene are associated with increased plasmid copy number, expression of blaCMY-2 and resistance to piperacillin/tazobactam in *Escherichia coli*. J Antimicrob Chemother **2012**; 67:339–45.
174. Akata K, Muratani T, Yatera K, et al. Induction of plasmid-mediated AmpC beta-lactamase DHA-1 by piperacillin/tazobactam and other beta-lactams in Enterobacteriaceae. PLoS One **2019**; 14:e0218589.
175. 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: 1014–23.
176. Dahyot S, Mammeri H. Hydrolysis spectrum extension of CMY-2-like beta-lactamases resulting from structural alteration in the Y-X-N loop. Antimicrob Agents Chemother **2012**; 56:1151–6.
177. Custodio MM, Sanchez D, Anderson B, Ryan KL, Walraven C, Mercier RC. Emergence of resistance in *Klebsiella aerogenes* to piperacillin-tazobactam and ceftriaxone. Antimicrob Agents Chemother **2021**; 65:e01038-20.
178. Hancock RE, Bellido F. Antibacterial in vitro activity of fourth generation cephalosporins. J Chemother **1996**; 8(Suppl 2):31–6.
179. 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):S25–8.
180. 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**; 71:296–306.
181. 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.
182. Fung-Tomc JC, Gradelski 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**; 40:1289–93.
183. 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**; 58:1554–63.
184. 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**; 55:105860.
185. Hoellinger B, Kaeuffer C, Boyer P, et al. Cefepime vs carbapenems for treating third-generation cephalosporin-resistant AmpC beta-lactamase-hyperproducing Enterobacterales bloodstream infections: a multicenter retrospective study. Int J Infect Dis **2023**; 134:273–9.
186. Kunz Coyne AJ, El Ghali A, Lucas K, et al. High-dose cefepime vs carbapenems for bacteremia caused by enterobacterales with moderate to high risk of clinically significant AmpC beta-lactamase production. Open Forum Infect Dis **2023**; 10: ofad034.
187. Szabo D, Bonomo RA, Silveira F, et al. SHV-type extended-spectrum beta-lactamase production is associated with reduced cefepime susceptibility in Enterobacter cloacae. J Clin Microbiol **2005**; 43:5058–64.
188. Hareza D, Simner PJ, Bergman Y, Jacobs E, Cosgrove SE, Tamma PD. The frequency of extended-spectrum beta-lactamase genes harbored by enterobacterales isolates at high risk for clinically significant chromosomal ampC expression. Open Forum Infect Dis **2023**; 10:ofad175.
189. 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:ofz248.
190. Peters DM Jr, Winter JB, Droege CA, Ernst NE, Liao S. Comparison of ceftriaxone and antipseudomonal beta-lactam antibiotics utilized for potential AmpC beta-lactamase-producing organisms. Hosp Pharm **2021**; 56:560–68.
191. Drozdinsky G, Neuberger A, Rakedzon S, et al. Treatment of bacteremia caused by *Enterobacter* spp.: should the potential for AmpC induction dictate therapy? A retrospective study. Microb Drug Resist **2021**; 27:410–14.
192. da Cunha Ferreira T, Martins IS. Risk factors of death in bloodstream infections caused by AmpC beta-lactamase-producing enterobacterales in patients with neoplasia. Infect Drug Resist **2021**; 14:3083–97.
193. 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**; 9:254.
194. 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.
195. Mounier R, Le Guen R, Woerther PL, et al. Clinical outcome of wild-type AmpC-producing Enterobacterales infection in critically ill patients treated with beta-lactams: a prospective multicenter study. Ann Intensive Care **2022**; 12:107.
196. Carrie C, Bardonneau G, Petit L, et al. Piperacillin-tazobactam should be preferred to third-generation cephalosporins to treat wild-type inducible AmpC-producing Enterobacterales in critically ill patients with hospital or ventilator-acquired pneumonia. J Crit Care **2020**; 56:6–11.
197. Maillard A, Delory T, Bernier J, et al. Effectiveness of third-generation cephalosporins or piperacillin compared with cefepime or carbapenems for severe infections caused by wild-type AmpC beta-lactamase-producing Enterobacterales: a

multi-centre retrospective propensity-weighted study. Int J Antimicrob Agents **2023**; 62:106809.
198. Nukaga M, Papp-Wallace KM, Hoshino T, et al. Probing the mechanism of inactivation of the FOX-4 cephamycinase by avibactam. Antimicrob Agents Chemother **2018**; 62:e02371-17.
199. 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:e00276-17.
200. Lu B, Wong M, Ha D, et al. Piperacillin/tazobactam versus cefepime or carbapenems for cefoxitin-non-susceptible *Enterobacter cloacae*, *Klebsiella aerogenes*, *Citrobacter freundii*, *Serratia marcescens* and *Morganella morganii* bacteraemia in immunocompromised patients. J Antimicrob Chemother **2023**; 78:1009–14.
201. 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: ofab387.
202. Zhanel GG, Lawrence CK, Adam H, et al. Imipenem-relebactam and meropenem-vaborbactam: two novel carbapenem-beta-lactamase inhibitor combinations. Drugs **2018**; 78:65–98.
203. 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**; 56:105925.
204. Sader HS, Mendes RE, Doyle TB, Davis AP, Castanheira M. Characterization of *Enterobacter cloacae* and *Citrobacter freundii* species complex isolates with decreased susceptibility to cephalosporins from United States hospitals and activity of ceftazidime/avibactam and comparator agents. JAC Antimicrob Resist **2021**; 3:dlab136.
205. Torres A, Wible M, Tawadrous M, et al. Efficacy and safety of ceftazidime/avibactam in patients with infections caused by beta-lactamase-producing Gram-negative pathogens: a pooled analysis from the phase 3 clinical trial programme. J Antimicrob Chemother **2023**; 78:2672–82.
206. 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**; 71:2713–16.
207. 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.
208. Shropshire WC, Endres BT, Borjan J, et al. High-level ceftazidime/avibactam resistance in *Escherichia coli* conferred by the novel plasmid-mediated beta-lactamase CMY-185 variant. J Antimicrob Chemother **2023**; 78:2442–50.
209. 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.
210. 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. Int J Antimicrob Agents **2015**; 46:502–10.
211. 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:e00675-18.
212. 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**; 22:301.
213. 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**; 130:842–45.
214. Centers for Disease Control and Prevention. About carbapenem resistant Enterobacterales. Available at: https://www.cdc.gov/cre/about/?CDC_AAref_Val=https://www.cdc.gov/hai/organisms/cre/index.html. Accessed 24 August 2024.
215. Shropshire WC, Aitken SL, Pifer R, et al. IS26-mediated amplification of blaOXA-1 and blaCTX-M-15 with concurrent outer membrane porin disruption associated with de novo carbapenem resistance in a recurrent bacteraemia cohort. J Antimicrob Chemother **2021**; 76:385–95.
216. Sabour S, Huang Y, Bhatnagar A, et al. Detection and characterization of targeted carbapenem-resistant healthcare-associated threats: findings from the antibiotic resistance laboratory network, 2017 to 2019. Antimicrob Agents Chemother **2021**; 65:e0110521.
217. van Duin D, Arias CA, Komarow L, et al. Molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in the USA (CRACKLE-2): a prospective cohort study. Lancet Infect Dis **2020**; 20:731–41.
218. Sader HS, Mendes RE, Carvalhaes CG, Kimbrough JH, Castanheira M. Changing epidemiology of carbapenemases among carbapenem-resistant Enterobacterales from United States hospitals and the activity of aztreonam-avibactam against contemporary enterobacterales (2019–2021). Open Forum Infect Dis **2023**; 10: ofad046.
219. Aitken SL, Tarrand JJ, Deshpande LM, et al. High rates of nonsusceptibility to ceftazidime-avibactam and identification of New Delhi metallo-beta-lactamase production in enterobacteriaceae bloodstream infections at a major cancer center. Clin Infect Dis **2016**; 63:954–58.
220. Senchyna F, Gaur RL, Sandlund J, et al. Diversity of resistance mechanisms in carbapenem-resistant Enterobacteriaceae at a health care system in Northern California, from 2013 to 2016. Diagn Microbiol Infect Dis **2019**; 93:250–7.
221. Mojica MF, Rossi MA, Vila AJ, Bonomo RA. The urgent need for metallo-beta-lactamase inhibitors: an unattended global threat. Lancet Infect Dis **2022**; 22:e28–34.
222. Tamma PD, Simner PJ. Phenotypic detection of carbapenemase-producing organisms from clinical isolates. J Clin Microbiol **2018**; 56:e01140-18.
223. Sorli L, Luque S, Li J, et al. Colistin for the treatment of urinary tract infections caused by extremely drug-resistant *Pseudomonas aeruginosa*: dose is critical. J Infect **2019**; 79:253–61.
224. 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**; 57:524–31.
225. Satlin MJ, Kubin CJ, Blumenthal JS, et al. Comparative effectiveness of aminoglycosides, polymyxin B, and tigecycline for clearance of carbapenem-resistant *Klebsiella pneumoniae* from urine. Antimicrob Agents Chemother **2011**; 55: 5893–9.
226. Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. Clin Infect Dis **2016**; 63:754–62.
227. Kaye KS, Bhowmick T, Metallidis S, et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. JAMA **2018**; 319:788–99.
228. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis **2018**; 18:1319–28.
229. Sims M, Mariyanovski V, McLeroth P, et al. Prospective, randomized, double-blind, phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections. J Antimicrob Chemother **2017**; 72:2616–26.
230. 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**; 21:226–40.
231. USCAST, The National Antimicrobial Susceptibility Testing Committee for the United States. Aminoglycoside In Vitro Susceptibility Test Interpretive Criteria Evaluations. Version 1.3, **2019**. Available at: http://www.uscast.org
232. Adelman MW, Bower CW, Grass JE, et al. Distinctive features of ertapenem-mono-resistant carbapenem-resistant Enterobacterales in the United States: a cohort study. Open Forum Infect Dis **2022**; 9:ofab643.
233. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother **2014**; 58:2322–8.
234. Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother **2009**; 64:142–50.
235. Kuti JL, Dandekar PK, Nightingale CH, Nicolau DP. Use of Monte Carlo simulation to design an optimized pharmacodynamic dosing strategy for meropenem. J Clin Pharmacol **2003**; 43:1116–23.
236. Li C, Kuti JL, Nightingale CH, Nicolau DP. Population pharmacokinetic analysis and dosing regimen optimization of meropenem in adult patients. J Clin Pharmacol **2006**; 46:1171–8.

237. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. Antimicrob Agents Chemother **2017**; 61:e00883-17.
238. van Duin D, Lok JJ, Earley M, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant enterobacteriaceae. Clin Infect Dis **2018**; 66:163–71.
239. 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**; 7:439–55.
240. 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**; 70:1799–808.
241. Karaiskos I, Daikos GL, Gkoufa A, et al. Ceftazidime/avibactam in the era of carbapenemase-producing *Klebsiella pneumoniae*: experience from a national registry study. J Antimicrob Chemother **2021**; 76:775–83.
242. Hakeam HA, Alsahli H, Albabtain L, Alassaf S, Al Duhailib Z, Althawadi S. Effectiveness of ceftazidime-avibactam versus colistin in treating carbapenem-resistant Enterobacteriaceae bacteremia. Int J Infect Dis **2021**; 109:1–7.
243. Caston JJ, Lacort-Peralta I, Martin-Davila P, et al. Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing Enterobacteriaceae in hematologic patients. Int J Infect Dis **2017**; 59:118–23.
244. Alraddadi BM, Saeedi M, Qutub M, Alshukairi A, Hassanien A, Wali G. Efficacy of ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant enterobacteriaceae. BMC Infect Dis **2019**; 19:772.
245. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by *Klebsiella pneumoniae* carbapenemase-producing K. pneumoniae. Clin Infect Dis **2019**; 68:355–64.
246. Zheng G, Cai J, Zhang L, et al. Ceftazidime/avibactam-based versus polymyxin B-based therapeutic regimens for the treatment of carbapenem-resistant klebsiella pneumoniae infection in critically ill patients: a retrospective cohort study. Infect Dis Ther **2022**; 11:1917–34.
247. Chen Y, Huang HB, Peng JM, Weng L, Du B. Efficacy and safety of ceftazidime-avibactam for the treatment of carbapenem-resistant enterobacterales bloodstream infection: a systematic review and meta-analysis. Microbiol Spectr **2022**; 10:e0260321.
248. Wilson GM, Fitzpatrick MA, Suda KJ, et al. Comparative effectiveness of antibiotic therapy for carbapenem-resistant Enterobacterales (CRE) bloodstream infections in hospitalized US veterans. JAC Antimicrob Resist **2022**; 4:dlac106.
249. Qu J, Xu J, Liu Y, Hu C, Zhong C, Lv X. Real-world effectiveness of ceftazidime/avibactam versus polymyxin B in treating patients with carbapenem-resistant Gram-negative bacterial infections. Int J Antimicrob Agents **2023**; 62:106872.
250. Perez-Nadales E, Fernandez-Ruiz M, Natera AM, et al. Efficacy of ceftazidime-avibactam in solid organ transplant recipients with bloodstream infections caused by carbapenemase-producing *Klebsiella pneumoniae*. Am J Transplant **2023**; 23:1022–34.
251. Satlin MJ, Chen L, Gomez-Simmonds A, et al. Impact of a rapid molecular test for *Klebsiella pneumoniae* carbapenemase and ceftazidime-avibactam use on outcomes after bacteremia caused by carbapenem-resistant enterobacterales. Clin Infect Dis **2022**; 75:2066–75.
252. Shortridge D, Deshpande LM, Streit JM, Castanheira M. Activity of meropenem/vaborbactam and comparators against non-carbapenemase-producing carbapenem-resistant Enterobacterales isolates from Europe. JAC Antimicrob Resist **2022**; 4:dlac097.
253. Bonnin RA, Bernabeu S, Emeraud C, et al. In vitro activity of imipenem-relebactam, meropenem-vaborbactam, ceftazidime-avibactam and comparators on carbapenem-resistant non-carbapenemase-producing enterobacterales. Antibiotics (Basel) **2023**; 12:102.
254. Sader HS, Mendes RE, Duncan L, Kimbrough JH, Carvalhaes CG, Castanheira M. Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam activities against multidrug-resistant Enterobacterales from United States medical centers (2018–2022). Diagn Microbiol Infect Dis **2023**; 106:115945.
255. Di Bella S, Giacobbe DR, Maraolo AE, et al. Resistance to ceftazidime/avibactam in infections and colonisations by KPC-producing Enterobacterales: a systematic review of observational clinical studies. J Glob Antimicrob Resist **2021**; 25:268–81.
256. Alosaimy S, Jorgensen SCJ, Lagnf AM, et al. Real-world multicenter analysis of clinical outcomes and safety of meropenem-vaborbactam in patients treated for serious gram-negative bacterial infections. Open Forum Infect Dis **2020**; 7:ofaa051.
257. Ackley R, Roshdy D, Meredith J, et al. Meropenem-vaborbactam versus ceftazidime-avibactam for treatment of carbapenem-resistant enterobacteriaceae infections. Antimicrob Agents Chemother **2020**; 64:e02313-19.
258. Tumbarello M, Raffaelli F, Giannella M, et al. Ceftazidime-avibactam use for KPC-Kp infections: a retrospective observational multicenter study. Clin Infect Dis **2021**; 73:1664–76.
259. Tumbarello M, Raffaelli F, Cascio A, et al. Compassionate use of meropenem/vaborbactam for infections caused by KPC-producing *Klebsiella pneumoniae*: a multicentre study. JAC Antimicrob Resist **2022**; 4:dlac022.
260. Shields RK, McCreary EK, Marini RV, et al. Early experience with meropenem-vaborbactam for treatment of carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis **2019**; 71:667–71.
261. Shields RK, Nguyen MH, Chen L, Press EG, Kreiswirth BN, Clancy CJ. Pneumonia and renal replacement therapy are risk factors for ceftazidime-avibactam treatment failures and resistance among patients with carbapenem-resistant Enterobacteriaceae infections. Antimicrob Agents Chemother **2018**; 62:e02497-17.
262. Canver MC, Satlin MJ, Westblade LF, et al. Activity of imipenem-relebactam and comparator agents against genetically characterized isolates of carbapenem-resistant Enterobacteriaceae. Antimicrob Agents Chemother **2019**; 63:e00672-19.
263. Kulengowski B, Burgess DS. Imipenem/relebactam activity compared to other antimicrobials against non-MBL-producing carbapenem-resistant Enterobacteriaceae from an academic medical center. Pathog Dis **2019**; 77:ftz040.
264. Walkty A, Karlowsky JA, Baxter MR, et al. In vitro activity of imipenem-relebactam against various resistance phenotypes/genotypes of Enterobacterales and *Pseudomonas aeruginosa* isolated from patients across Canada as part of the CANWARD study, 2016–2019. Diagn Microbiol Infect Dis **2021**; 101:115418.
265. Yang TY, Hsieh YJ, Kao LT, et al. Activities of imipenem-relebactam combination against carbapenem-nonsusceptible Enterobacteriaceae in Taiwan. J Microbiol Immunol Infect **2021**; 55:86–94.
266. Lob SH, Karlowsky JA, Young K, et al. In vitro activity of imipenem-relebactam against resistant phenotypes of Enterobacteriaceae and *Pseudomonas aeruginosa* isolated from intraabdominal and urinary tract infection samples—SMART Surveillance Europe 2015–2017. J Med Microbiol **2020**; 69:207–17.
267. Papp-Wallace KM, Barnes MD, Alsop J, et al. Relebactam is a potent inhibitor of the KPC-2 beta-lactamase and restores imipenem susceptibility in KPC-producing Enterobacteriaceae. Antimicrob Agents Chemother **2018**; 62:e00174-18.
268. McCreary EK, Heil EL, Tamma PD. New perspectives on antimicrobial agents: cefiderocol. Antimicrob Agents Chemother **2021**; 65:e0217120.
269. 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:e01454-17.
270. Wise MG, Karlowsky JA, Hackel MA, et al. In vitro activity of cefiderocol against meropenem-nonsusceptible gram-negative bacilli with defined beta-lactamase carriage: SIDERO-WT surveillance studies, 2014–2019. Microb Drug Resist **2023**; 29:360–70.
271. Bhatnagar A, Boyd S, Sabour S, et al. Aztreonam-avibactam susceptibility testing program for metallo-beta-lactamase-producing enterobacterales in the antibiotic resistance laboratory network, March 2019 to December 2020. Antimicrob Agents Chemother **2021**; 65:e0048621.
272. Sader HS, Mendes RE, Pfaller MA, Shortridge D, Flamm RK, Castanheira M. Antimicrobial activities of aztreonam-avibactam and comparator agents against contemporary (2016) clinical enterobacteriaceae isolates. Antimicrob Agents Chemother **2018**; 62:e01856-17.
273. Mauri C, Maraolo AE, Di Bella S, Luzzaro F, Principe L. The revival of aztreonam in combination with avibactam against metallo-beta-lactamase-producing gram-negatives: a systematic review of in vitro studies and clinical cases. Antibiotics (Basel) **2021**; 10:1012.
274. Rossolini GM, Stone G, Kantecki M, Arhin FF. In vitro activity of aztreonam/avibactam against isolates of Enterobacterales collected globally from ATLAS in 2019. J Glob Antimicrob Resist **2022**; 30:214–21.
275. Sader HS, Mendes RE, Arends SJR, Carvalhaes CG, Castanheira M. Antimicrobial activities of aztreonam-avibactam and comparator agents tested against Enterobacterales from European hospitals analysed by geographic region and infection type (2019–2020). Eur J Clin Microbiol Infect Dis **2022**; 41:477–87.
276. Sader HS, Carvalhaes CG, Arends SJR, Castanheira M, Mendes RE. Aztreonam/avibactam activity against clinical isolates of Enterobacterales collected in Europe, Asia and Latin America in 2019. J Antimicrob Chemother **2021**; 76:659–66.

277. Harris H, Tao L, Jacobs EB, et al. Multicenter evaluation of an MIC-based aztreonam and ceftazidime-avibactam broth disk elution test. J Clin Microbiol **2023**; 61:e0164722.
278. Falcone M, Daikos GL, Tiseo G, et al. Efficacy of ceftazidime-avibactam plus aztreonam in patients with bloodstream infections caused by metallo-beta-lactamase-producing Enterobacterales. Clin Infect Dis **2021**; 72:1871–8.
279. Falcone M, Giordano C, Leonildi A, et al. Clinical features and outcomes of infections caused by metallo-beta-lactamases producing Enterobacterales: a 3-year prospective study from an endemic area. Clin Infect Dis **2023**; 78:1111–9.
280. 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**; 75:2622–32.
281. Falcone M, Menichetti F, Cattaneo D, et al. Pragmatic options for dose optimization of ceftazidime/avibactam with aztreonam in complex patients. J Antimicrob Chemother **2021**; 76:1025–31.
282. Lodise TP, O'Donnell JN, Balevic S, et al. Pharmacokinetics of ceftazidime-avibactam in combination with aztreonam (COMBINE) in a phase 1, open-label study of healthy adults. Antimicrob Agents Chemother **2022**; 66:e0093622.
283. Lodise TP, O'Donnell JN, Raja S, et al. Safety of ceftazidime-avibactam in combination with aztreonam (COMBINE) in a phase I, open-label study in healthy adult volunteers. Antimicrob Agents Chemother **2022**; 66:e0093522.
284. Biagi M, Wu T, Lee M, Patel S, Butler D, Wenzler E. Searching for the optimal treatment for metallo- and serine-beta-lactamase producing enterobacteriaceae: aztreonam in combination with ceftazidime-avibactam or meropenem-vaborbactam. Antimicrob Agents Chemother **2019**; 63:e01426-19.
285. Biagi M, Lee M, Wu T, et al. Aztreonam in combination with imipenem-relebactam against clinical and isogenic strains of serine and metallo-beta-lactamase-producing enterobacterales. Diagn Microbiol Infect Dis **2022**; 103:115674.
286. Belati A, Bavaro DF, Diella L, De Gennaro N, Di Gennaro F, Saracino A. Meropenem/vaborbactam plus aztreonam as a possible treatment strategy for bloodstream infections caused by ceftazidime/avibactam-resistant klebsiella pneumoniae: a retrospective case series and literature review. Antibiotics (Basel) **2022**; 11:373.
287. Takemura M, Wise MG, Hackel MA, Sahm DF, Yamano Y. In vitro activity of cefiderocol against MBL-producing gram-negative bacteria collected in North America and Europe in five consecutive annual multinational SIDERO-WT surveillance studies (2014–2019). J Antimicrob Chemother **2023**; 78:2019–27.
288. McElheny CL, Fowler EL, Iovleva A, Shields RK, Doi Y. In vitro evolution of cefiderocol resistance in an NDM-producing *Klebsiella pneumoniae* due to functional loss of CirA. Microbiol Spectr **2021**; 9:e0177921.
289. Coppi M, Antonelli A, Niccolai C, et al. Nosocomial outbreak by NDM-1-producing *Klebsiella pneumoniae* highly resistant to cefiderocol, Florence, Italy, August 2021 to June 2022. Euro Surveill **2022**; 27:2200795.
290. Lan P, Lu Y, Chen Z, et al. Emergence of high-level cefiderocol resistance in carbapenem-resistant *Klebsiella pneumoniae* from bloodstream infections in patients with hematologic malignancies in China. Microbiol Spectr **2022**; 10: e0008422.
291. Senchyna F, Murugesan K, Rotunno W, Nadimpalli SS, Deresinski S, Banaei N. Sequential treatment failure with aztreonam-ceftazidime-avibactam followed by cefiderocol due to preexisting and acquired mechanisms in a New Delhi Metallo-beta-lactamase-producing *Escherichia coli* causing fatal bloodstream infection. Clin Infect Dis **2024**; 78:1425–8.
292. Timsit JF, Paul M, Shields RK, et al. Cefiderocol for the treatment of infections due to metallo-B-lactamase-producing pathogens in the CREDIBLE-CR and APEKS-NP phase 3 randomized studies. Clin Infect Dis **2022**; 75:1081–4.
293. Lima O, Sousa A, Longueira-Suarez R, et al. Ceftazidime-avibactam treatment in bacteremia caused by OXA-48 carbapenemase-producing *Klebsiella pneumoniae*. Eur J Clin Microbiol Infect Dis **2022**; 41:1173–82.
294. Longshaw C, Roger E, Santerre Henriksen A, Baba T, Nguyen S, Yamano Y. Evidence for efficacy of cefiderocol against OXA-48-containing isolates from the APEKS-NP and CREDIBLE-CR trials. Antimicrob Agents Chemother **2022**; 66:e0110022.
295. Castanheira M, Doyle TB, Collingsworth TD, Sader HS, Mendes RE. Increasing frequency of OXA-48-producing Enterobacterales worldwide and activity of ceftazidime/avibactam, meropenem/vaborbactam and comparators against these isolates. J Antimicrob Chemother **2021**; 76:3125–34.
296. Asempa TE, Kois AK, Gill CM, Nicolau DP. Phenotypes, genotypes and breakpoints: an assessment of beta-lactam/beta-lactamase inhibitor combinations against OXA-48. J Antimicrob Chemother **2023**; 78:636–45.
297. Horwich-Scholefield S, Lloyd T, Varghese V, Yette E, Huang S, Pandori M. Imipenem-relebactam susceptibility and genotypic characteristics of carbapenem-resistant enterobacterales (CRE) identified during population-based surveillance. Antimicrob Agents Chemother **2021**; 65:e0228820.
298. Bonnin RA, Bernabeu S, Emeraud C, et al. Susceptibility of OXA-48-producing Enterobacterales to imipenem/relebactam, meropenem/vaborbactam and ceftazidime/avibactam. Int J Antimicrob Agents **2022**; 60:106660.
299. Alqahtani H, Alghamdi A, Alobaidallah N, et al. Evaluation of ceftazidime/avibactam for treatment of carbapenemase-producing carbapenem-resistant Enterobacterales with OXA-48 and/or NDM genes with or without combination therapy. JAC Antimicrob Resist **2022**; 4:dlac104.
300. Humphries RM, Yang S, Hemarajata P, et al. First report of ceftazidime-avibactam resistance in a KPC-3-expressing *Klebsiella pneumoniae* isolate. Antimicrob Agents Chemother **2015**; 59:6605–7.
301. Winkler ML, Papp-Wallace KM, Bonomo RA. Activity of ceftazidime/avibactam against isogenic strains *of Escherichia coli* containing KPC and SHV beta-lactamases with single amino acid substitutions in the Omega-loop. J Antimicrob Chemother **2015**; 70:2279–86.
302. Livermore DM, Warner M, Jamrozy D, et al. In vitro selection of ceftazidime-avibactam resistance in Enterobacteriaceae with KPC-3 carbapenemase. Antimicrob Agents Chemother **2015**; 59:5324–30.
303. Shields RK, Chen L, Cheng S, et al. Emergence of ceftazidime-avibactam resistance due to plasmid-borne blaKPC-3 mutations during treatment of carbapenem-resistant *Klebsiella pneumoniae* infections. Antimicrob Agents Chemother **2017**; 61:e02097-16.
304. Shields RK, Potoski BA, Haidar G, et al. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis **2016**; 63: 1615–8.
305. Compain F, Arthur M. Impaired inhibition by avibactam and resistance to the ceftazidime-avibactam combination due to the D(179)Y substitution in the KPC-2 beta-lactamase. Antimicrob Agents Chemother **2017**; 61:e00451-17.
306. Giddins MJ, Macesic N, Annavajhala MK, et al. Successive emergence of ceftazidime-avibactam resistance through distinct genomic adaptations in blaKPC-2-harboring *Klebsiella pneumoniae* sequence type 307 isolates. Antimicrob Agents Chemother **2018**; 62:e02101-17.
307. Gottig S, Frank D, Mungo E, et al. Emergence of ceftazidime/avibactam resistance in KPC-3-producing *Klebsiella pneumoniae* in vivo. J Antimicrob Chemother **2019**; 74:3211–6.
308. Castanheira M, Arends SJR, Davis AP, Woosley LN, Bhalodi AA, MacVane SH. Analyses of a ceftazidime-avibactam-resistant *Citrobacter freundii* isolate carrying bla KPC-2 reveals a heterogenous population and reversible genotype. mSphere **2018**; 3:e00408-18.
309. Wilson WR, Kline EG, Jones CE, et al. Effects of KPC variant and porin genotype on the in vitro activity of meropenem-vaborbactam against carbapenem-resistant Enterobacteriaceae. Antimicrob Agents Chemother **2019**; 63: e02048-18.
310. Zhang P, Shi Q, Hu H, et al. Emergence of ceftazidime/avibactam resistance in carbapenem-resistant *Klebsiella pneumoniae* in China. Clin Microbiol Infect **2020**; 26:124e1–4.
311. Venditti C, Nisii C, D'Arezzo S, et al. Molecular and phenotypical characterization of two cases of antibiotic-driven ceftazidime-avibactam resistance in bla KPC-3-harboring *Klebsiella pneumoniae*. Infect Drug Resist **2019**; 12:1935–40.
312. Cano A, Guzman-Puche J, Garcia-Gutierrez M, et al. Use of carbapenems in the combined treatment of emerging ceftazidime/avibactam-resistant and carbapenem-susceptible KPC-producing *Klebsiella pneumoniae* infections: report of a case and review of the literature. J Glob Antimicrob Resist **2020**; 22: 9–12.
313. Gaibani P, Re MC, Campoli C, Viale PL, Ambretti S. Bloodstream infection caused by KPC-producing *Klebsiella pneumoniae* resistant to ceftazidime/avibactam: epidemiology and genomic characterization. Clin Microbiol Infect **2020**; 26:516.e1–4.
314. Hemarajata P, Humphries RM. Ceftazidime/avibactam resistance associated with L169P mutation in the omega loop of KPC-2. J Antimicrob Chemother **2019**; 74:1241–3.
315. Raisanen K, Koivula I, Ilmavirta H, et al. Emergence of ceftazidime-avibactam-resistant *Klebsiella pneumoniae* during treatment, Finland, December 2018. Euro Surveill **2019**; 24:1900256.
316. Zhang Y, Kashikar A, Brown CA, Denys G, Bush K. Unusual *Escherichia coli* PBP 3 insertion sequence identified from a collection of carbapenem-resistant enterobacteriaceae tested in vitro with a combination of ceftazidime-, ceftaroline-, or aztreonam-avibactam. Antimicrob Agents Chemother **2017**; 61:e00389-17.
317. Alsenani TA, Viviani SL, Kumar V, et al. Structural characterization of the D179N and D179Y variants of KPC-2 beta-lactamase: omega-loop destabilization as a mechanism of resistance to ceftazidime-avibactam. Antimicrob Agents Chemother **2022**; 66:e0241421.

318. Gaibani P, Amadesi S, Lazzarotto T, Ambretti S. Genome characterization of a *Klebsiella pneumoniae* co-producing OXA-181 and KPC-121 resistant to ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam and cefiderocol isolated from a critically ill patient. J Glob Antimicrob Resist **2022**; 30:262–4.
319. Machuca I, Guzman-Puche J, Perez-Nadales E, et al. Community-acquired bacteraemia by *Klebsiella pneumoniae* producing KPC-3 and resistant to ceftazidime/avibactam. J Glob Antimicrob Resist **2022**; 30:399–402.
320. Li X, Zhang J, Yang C, et al. Increased expression and amplification of blaKPC-2 contributes to resistance to ceftazidime/avibactam in a sequence type 11 carbapenem-resistant *Klebsiella pneumoniae* strain. Microbiol Spectr **2022**; 10: e0095522.
321. Frohlich C, Sorum V, Thomassen AM, Johnsen PJ, Leiros HS, Samuelsen O. OXA-48-mediated ceftazidime-avibactam resistance is associated with evolutionary trade-offs. mSphere **2019**; 4:e00024-19.
322. Lomovskaya O, Sun D, Rubio-Aparicio D, et al. Vaborbactam: spectrum of beta-lactamase inhibition and impact of resistance mechanisms on activity in Enterobacteriaceae. Antimicrob Agents Chemother **2017**; 61:e01443-17.
323. Sun D, Rubio-Aparicio D, Nelson K, Dudley MN, Lomovskaya O. Meropenem-vaborbactam resistance selection, resistance prevention, and molecular mechanisms in mutants of KPC-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother **2017**; 61:e01694-17.
324. Pfaller MA, Huband MD, Mendes RE, Flamm RK, Castanheira M. In vitro activity of meropenem/vaborbactam and characterisation of carbapenem resistance mechanisms among carbapenem-resistant Enterobacteriaceae from the 2015 meropenem/vaborbactam surveillance programme. Int J Antimicrob Agents **2018**; 52:144–50.
325. Lapuebla A, Abdallah M, Olafisoye O, et al. Activity of meropenem combined with RPX7009, a novel beta-lactamase inhibitor, against Gram-negative clinical isolates in New York City. Antimicrob Agents Chemother **2015**; 59:4856–60.
326. Zhou M, Yang Q, Lomovskaya O, et al. In vitro activity of meropenem combined with vaborbactam against KPC-producing Enterobacteriaceae in China. J Antimicrob Chemother **2018**; 73:2789–96.
327. Castanheira M, Rhomberg PR, Flamm RK, Jones RN. Effect of the beta-lactamase inhibitor vaborbactam combined with meropenem against serine carbapenemase-producing Enterobacteriaceae. Antimicrob Agents Chemother **2016**; 60:5454–8.
328. Griffith DC, Sabet M, Tarazi Z, Lomovskaya O, Dudley MN. Pharmacokinetics/pharmacodynamics of vaborbactam, a novel beta-lactamase inhibitor, in combination with meropenem. Antimicrob Agents Chemother **2019**; 63:e01659-18.
329. Lapuebla A, Abdallah M, Olafisoye O, et al. Activity of imipenem with relebactam against gram-negative pathogens from New York City. Antimicrob Agents Chemother **2015**; 59:5029–31.
330. Balabanian G, Rose M, Manning N, Landman D, Quale J. Effect of porins and blaKPC expression on activity of imipenem with relebactam in Klebsiella pneumoniae: can antibiotic combinations overcome resistance? Microb Drug Resist **2018**; 24:877–81.
331. Gaibani P, Bovo F, Bussini L, et al. Dynamic evolution of imipenem/relebactam resistance in a KPC-producing *Klebsiella pneumoniae* from a single patient during ceftazidime/avibactam-based treatments. J Antimicrob Chemother **2022**; 77: 1570–7.
332. 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**; 34:773–819.
333. Gaibani P, Giani T, Bovo F, et al. Resistance to ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam in gram-negative MDR bacilli: molecular mechanisms and susceptibility testing. Antibiotics (Basel) **2022**; 11: 628.
334. Gaibani P, Bianco G, Amadesi S, Boattini M, Ambretti S, Costa C. Increased blaKPC copy number and OmpK35 and OmpK36 porins disruption mediated resistance to imipenem/relebactam and meropenem/vaborbactam in a KPC-producing Klebsiella pneumoniae clinical isolate. Antimicrob Agents Chemother **2022**; 66:e0019122.
335. Frohlich C, Sorum V, Tokuriki N, Johnsen PJ, Samuelsen O. Evolution of beta-lactamase-mediated cefiderocol resistance. J Antimicrob Chemother **2022**; 77:2429–36.
336. Karakonstantis S, Rousaki M, Kritsotakis EI. Cefiderocol: systematic review of mechanisms of resistance, heteroresistance and in vivo emergence of resistance. Antibiotics (Basel) **2022**; 11:723.
337. Ito A, Nishikawa T, Ishii R, et al. 696. Mechanism of cefiderocol high MIC mutants obtained in non-clinical FoR studies. Open Forum Infect Dis **2018**; 5(Suppl 1):S251. Poster presented at: IDWeek 2018, San Francisco, CA, 3–7 October 2018. Poster 696.
338. Kohira N, Nakamura R, Ito A, Nishikawa T, Ota M, Sato T. Resistance acquisition studies of cefiderocol by serial passage and in vitro pharmacodynamic model under human simulated exposure. In 2018: Poster presented at: American Society of Microbiology Annual Meeting. Atlanta, GA, 6–11 June 2018. Poster Saturday-619.
339. Kohira N, Ito A, Ota M, et al. Frequency of Resistance Acquisition and Resistance Mechanisms to Cefiderocol. 2018: Poster presented at: American Society of Microbiology Annual Meeting. Atlanta, GA. 6–11 June 2018. Poster 619.
340. Simner PJ, Beisken S, Bergman Y, Ante M, Posch AE, Tamma PD. Defining baseline mechanisms of cefiderocol resistance in the Enterobacterales. Microb Drug Resist **2021**; 28:161–70.
341. Simner PJ, Mostafa HH, Bergman Y, et al. Progressive development of cefiderocol resistance in *Escherichia coli* during therapy is associated with an increase in blaNDM-5 copy number and gene expression. Clin Infect Dis **2022**; 75:47–54.
342. Bianco G, Boattini M, Comini S, et al. In vitro activity of cefiderocol against ceftazidime-avibactam susceptible and resistant KPC-producing Enterobacterales: cross-resistance and synergistic effects. Eur J Clin Microbiol Infect Dis **2022**; 41:63–70.
343. Periasamy H, Joshi P, Palwe S, Shrivastava R, Bhagwat S, Patel M. High prevalence of *Escherichia coli* clinical isolates in India harbouring four amino acid inserts in PBP3 adversely impacting activity of aztreonam/avibactam. J Antimicrob Chemother **2020**; 75:1650–1.
344. Poirel L, Ortiz de la Rosa JM, Sakaoglu Z, Kusaksizoglu A, Sadek M, Nordmann P. NDM-35-producing ST167 *Escherichia coli* highly resistant to beta-lactams including cefiderocol. Antimicrob Agents Chemother **2022**; 66:e0031122.
345. Wang Q, Jin L, Sun S, et al. Occurrence of high levels of cefiderocol resistance in carbapenem-resistant *Escherichia coli* before its approval in China: a report from China CRE-network. Microbiol Spectr **2022**; 10:e0267021.
346. Simner PJ, Bergman Y, Conzemius R, et al. An NDM-producing Escherichia coli clinical isolate exhibiting resistance to cefiderocol and the combination of ceftazidime-avibactam and aztreonam: another step toward pan-beta-lactam resistance. Open Forum Infect Dis **2023**; 10:ofad276.
347. Alosaimy S, Lagnf AM, Morrisette T, et al. Real-world, multicenter experience with meropenem-vaborbactam for gram-negative bacterial infections including carbapenem-resistant enterobacterales and *Pseudomonas aeruginosa*. Open Forum Infect Dis **2021**; 8:ofab371.
348. Castanheira M, Doyle TB, Kantro V, Mendes RE, Shortridge D. Meropenem-vaborbactam activity against carbapenem-resistant enterobacterales isolates collected in U.S. hospitals during 2016 to 2018. Antimicrob Agents Chemother **2020**; 64:e01951-19.
349. Johnston BD, Thuras P, Porter SB, et al. Activity of cefiderocol, ceftazidime-avibactam, and eravacycline against carbapenem-resistant Escherichia coli isolates from the United States and international sites in relation to clonal background, resistance genes, coresistance, and region. Antimicrob Agents Chemother **2020**; 64:e00797-20.
350. Tamma PD, Bergman Y, Jacobs EB, et al. Comparing the activity of novel antibiotic agents against carbapenem-resistant Enterobacterales clinical isolates. Infect Control Hosp Epidemiol **2023**; 44:762–7.
351. Falagas ME, Karageorgopoulos DE, Dimopoulos G. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of tigecycline. Curr Drug Metab **2009**; 10:13–21.
352. Zhou C, Jin L, Wang Q, et al. Bloodstream infections caused by carbapenem-resistant enterobacterales: risk factors for mortality, antimicrobial therapy and treatment outcomes from a prospective multicenter study. Infect Drug Resist **2021**; 14:731–42.
353. 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**; 13:102–9.
354. 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**; 16:1274–81.
355. Fanning WL, Gump DW. Distressing side-effects of minocycline hydrochloride. Arch Intern Med **1976**; 136:761–2.
356. United States Food and Drug Administration. FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria. Available at: https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria. Accessed 24 December 2023.
357. Amann LF, Broeker A, Riedner M, et al. Pharmacokinetic/pharmacodynamic evaluation of tigecycline dosing in a hollow fiber infection model against clinical bla-KPC producing Klebsiella Pneumoniae isolates. Diagn Microbiol Infect Dis **2023**; 108:116153.

358. 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**; 152:224–232.
359. Eckmann C, Montravers P, Bassetti M, et al. Efficacy of tigecycline for the treatment of complicated intra-abdominal infections in real-life clinical practice from five European observational studies. J Antimicrob Chemother **2013**; 68(Suppl 2): ii25–35.
360. Babinchak T, Ellis-Grosse E, Dartois N, et al. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. Clin Infect Dis **2005**; 41(Suppl 5):S354–67.
361. Zhao C, Wang X, Zhang Y, et al. In vitro activities of Eravacycline against 336 isolates collected from 2012 to 2016 from 11 teaching hospitals in China. BMC Infect Dis **2019**; 19:508.
362. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother **2011**; 66:1963–71.
363. 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**; 37:1049–64.
364. 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:e12467.
365. 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:R90.
366. Ni W, Han Y, Liu J, et al. Tigecycline treatment for carbapenem-resistant enterobacteriaceae infections: a systematic review and meta-analysis. Medicine (Baltimore) **2016**; 95:e3126.
367. Morrissey I, Olesky M, Hawser S, et al. In vitro activity of eravacycline against gram-negative bacilli isolated in clinical laboratories worldwide from 2013 to 2017. Antimicrob Agents Chemother **2020**; 64:e01699-19.
368. Teo JQ, Chang HY, Tan SH, et al. Comparative activities of novel therapeutic agents against molecularly characterized clinical carbapenem-resistant enterobacterales isolates. Microbiol Spectr **2023**; 11:e0100223.
369. Lee YL, Ko WC, Lee WS, et al. In-vitro activity of cefiderocol, cefepime/zidebactam, cefepime/enmetazobactam, omadacycline, eravacycline and other comparative agents against carbapenem-nonsusceptible Enterobacterales: results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) in 2017–2020. Int J Antimicrob Agents **2021**; 58:106377.
370. 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: 921–9.
371. Alosaimy S, Molina KC, Claeys KC, et al. Early experience with eravacycline for complicated infections. Open Forum Infect Dis **2020**; 7:ofaa071.
372. Khatri A, Lobo S, Nog R, Lee L, Wang G, Dhand A. Minocycline in the treatment of carbapenem-resistant *Klebsiella pneumoniae*. Open Forum Infect Dis **2017**; 4(Suppl 1):S143. Poster presented at: IDWeek 2017, San Diego, CA, 4–8 October 2018. Poster 364.
373. 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.
374. 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:e02327-17.
375. 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:e02488-19.
376. Noel AR, Attwood M, Bowker KE, MacGowan AP. In vitro pharmacodynamics of omadacycline against Escherichia coli and Acinetobacter baumannii. J Antimicrob Chemother **2021**; 76:667–70.
377. 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**; 39:1559–72.
378. 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:e523–29.
379. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clin Microbiol Rev **2012**; 25:450–70.
380. Aslan AT, Ezure Y, Horcajada JP, Harris PNA, Paterson DL. In vitro, in vivo and clinical studies comparing the efficacy of ceftazidime-avibactam monotherapy with ceftazidime-avibactam-containing combination regimens against carbapenem-resistant Enterobacterales and multidrug-resistant *Pseudomonas aeruginosa* isolates or infections: a scoping review. Front Med (Lausanne) **2023**; 10:1249030.
381. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect **2012**; 18:268–81.
382. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. Clin Infect Dis **2018**; 67: 1803–14.
383. Pang Z, Raudonis R, Glick BR, Lin TJ, Cheng Z. Antibiotic resistance in *Pseudomonas aeruginosa*: mechanisms and alternative therapeutic strategies. Biotechnol Adv **2019**; 37:177–92.
384. Glen KA, Lamont IL. Beta-lactam resistance in Pseudomonas aeruginosa: current status, future prospects. Pathogens **2021**; 10:1638.
385. Reyes J, Komarow L, Chen L, et al. Global epidemiology and clinical outcomes of carbapenem-resistant *Pseudomonas aeruginosa* and associated carbapenemases (POP): a prospective cohort study. Lancet Microbe **2023**; 4:e159–70.
386. Karlowsky JA, Lob SH, DeRyke CA, et al. In vitro activity of ceftolozane-tazobactam, imipenem-relebactam, ceftazidime-avibactam, and comparators against *Pseudomonas aeruginosa* isolates collected in United States hospitals according to results from the SMART surveillance program, 2018 to 2020. Antimicrob Agents Chemother **2022**; 66:e0018922.
387. Karlowsky JA, Kazmierczak KM, de Jonge BLM, Hackel MA, Sahm DF, Bradford PA. In vitro activity of aztreonam-avibactam against Enterobacteriaceae and *Pseudomonas aeruginosa* isolated by clinical laboratories in 40 countries from 2012 to 2015. Antimicrob Agents Chemother **2017**; 61:e00472-17.
388. Karlowsky JA, Kazmierczak KM, Bouchillon SK, de Jonge BLM, Stone GG, Sahm DF. In vitro activity of ceftazidime-avibactam against clinical isolates of Enterobacteriaceae and *Pseudomonas aeruginosa* collected in Asia-Pacific countries: results from the INFORM global surveillance program, 2012 to 2015. Antimicrob Agents Chemother **2018**; 62:e02569-17.
389. Escandon-Vargas K, Reyes S, Gutierrez S, Villegas MV. The epidemiology of carbapenemases in Latin America and the Caribbean. Expert Rev Anti Infect Ther **2017**; 15:277–97.
390. Gill CM, Aktathorn E, Alfouzan W, et al. The ERACE-PA global surveillance program: ceftolozane/tazobactam and ceftazidime/avibactam in vitro activity against a global collection of carbapenem-resistant Pseudomonas aeruginosa. Eur J Clin Microbiol Infect Dis **2021**; 40:2533–41.
391. Lee SY, Gill CM, Nicolau DP, Group E-PGS. Activity of novel beta-lactam/beta-lactamase inhibitor combinations against serine carbapenemase-producing carbapenem-resistant *Pseudomonas aeruginosa*. J Antimicrob Chemother **2023**:78:2795–800;
392. Torrens G, van der Schalk TE, Cortes-Lara S, et al. Susceptibility profiles and resistance genomics of *Pseudomonas aeruginosa* isolates from European ICUs participating in the ASPIRE-ICU trial. J Antimicrob Chemother **2022**; 77:1862–72.
393. Gray HK, Beaird OE, Smith EA, Schaenman JM, Yang S. Domestically acquired NDM-1-producing *Pseudomonas aeruginosa*, Southern California, USA, 2023. Emerg Infect Dis **2023**; 29:2382–5.
394. Gajdacs M. Carbapenem-resistant but cephalosporin-susceptible *Pseudomonas aeruginosa* in urinary tract infections: opportunity for colistin sparing. Antibiotics (Basel) **2020**; 9:153.
395. Gill CM, Aktathorn E, Alfouzan W, et al. Elevated MICs of susceptible anti-pseudomonal cephalosporins in non-carbapenemase-producing, carbapenem-resistant *Pseudomonas aeruginosa*: implications for dose optimization. Antimicrob Agents Chemother **2021**; 65:AAC0120421.
396. Khalili Y, Yekani M, Goli HR, Memar MY. Characterization of carbapenem-resistant but cephalosporin-susceptible *Pseudomonas aeruginosa*. Acta Microbiol Immunol Hung **2019**; 66:529–40.
397. Campana EH, Xavier DE, Petrolini FV, Cordeiro-Moura JR, Araujo MR, Gales AC. Carbapenem-resistant and cephalosporin-susceptible: a worrisome phenotype among *Pseudomonas aeruginosa* clinical isolates in Brazil. Braz J Infect Dis **2017**; 21:57–62.
398. Zeng ZR, Wang WP, Huang M, Shi LN, Wang Y, Shao HF. Mechanisms of carbapenem resistance in cephalosporin-susceptible *Pseudomonas aeruginosa* in China. Diagn Microbiol Infect Dis **2014**; 78:268–70.
399. Zaidenstein R, Miller A, Tal-Jasper R, et al. Therapeutic management of *Pseudomonas aeruginosa* bloodstream infection non-susceptible to carbapenems but susceptible to "old" cephalosporins and/or to penicillins. Microorganisms **2018**; 6:6.

400. Li S, Jia X, Li C, et al. Carbapenem-resistant and cephalosporin-susceptible *Pseudomonas aeruginosa*: a notable phenotype in patients with bacteremia. Infect Drug Resist **2018**; 11:1225–35.
401. Bauer KA, West JE, O'Brien JM, Goff DA. Extended-infusion cefepime reduces mortality in patients with *Pseudomonas aeruginosa* infections. Antimicrob Agents Chemother **2013**; 57:2907–12.
402. Babich T, Naucler P, Valik JK, et al. Ceftazidime, carbapenems, or piperacillin-tazobactam as single definitive therapy for *Pseudomonas aeruginosa* bloodstream infection: a multisite retrospective study. Clin Infect Dis **2020**; 70:2270–80.
403. Sader HS, Mendes RE, Arends SJR, Carvalhaes CG, Shortridge D, Castanheira M. Comparative activity of newer beta-lactam/beta-lactamase inhibitor combinations against *Pseudomonas aeruginosa* isolates from US medical centres (2020–2021). Int J Antimicrob Agents **2023**; 61:106744.
404. Sader HS, Duncan LR, Doyle TB, Castanheira M. Antimicrobial activity of ceftazidime/avibactam, ceftolozane/tazobactam and comparator agents against *Pseudomonas aeruginosa* from cystic fibrosis patients. JAC Antimicrob Resist **2021**; 3:dlab126.
405. Atkin SD, Abid S, Foster M, et al. Multidrug-resistant Pseudomonas aeruginosa from sputum of patients with cystic fibrosis demonstrates a high rate of susceptibility to ceftazidime-avibactam. Infect Drug Resist **2018**; 11:1499–510.
406. Gill CM, Nicolau DP, Group E-PGS. Phenotypic and genotypic profile of ceftolozane/tazobactam-non-susceptible, carbapenem-resistant Pseudomonas aeruginosa. J Antimicrob Chemother **2022**; 78:252–6.
407. Murano K, Yamanaka T, Toda A, et al. Structural requirements for the stability of novel cephalosporins to AmpC beta-lactamase based on 3D-structure. Bioorg Med Chem **2008**; 16:2261–75.
408. Castanheira M, Mills JC, Farrell DJ, Jones RN. Mutation-driven beta-lactam resistance mechanisms among contemporary ceftazidime-nonsusceptible *Pseudomonas aeruginosa* isolates from U.S. hospitals. Antimicrob Agents Chemother **2014**; 58:6844–50.
409. Jaruratanasirikul S, Sriwiriyajan S, Punyo J. Comparison of the pharmacodynamics of meropenem in patients with ventilator-associated pneumonia following administration by 3-hour infusion or bolus injection. Antimicrob Agents Chemother **2005**; 49:1337–9.
410. 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:e01955–19.
411. Falagas ME, Skalidis T, Vardakas KZ, Legakis NJ; Hellenic Cefiderocol Study G. Activity of cefiderocol (S-649266) against carbapenem-resistant gram-negative bacteria collected from inpatients in Greek hospitals. J Antimicrob Chemother **2017**; 72:1704–8.
412. 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:e01968-17.
413. Kazmierczak KM, Tsuji M, Wise MG, et al. In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-non-susceptible gram-negative bacilli, including serine carbapenemase- and metallo-beta-lactamase-producing isolates (SIDERO-WT-2014 study). Int J Antimicrob Agents **2019**; 53:177–84.
414. 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:e00093-17.
415. Karlowsky JA, Walkty AJ, Baxter MR, et al. In vitro activity of cefiderocol against extensively drug-resistant *Pseudomonas aeruginosa*: CANWARD, 2007 to 2019. Microbiol Spectr **2022**; 10:e0172422.
416. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet **2015**; 385:1949–56.
417. Walkty A, Adam H, Baxter M, et al. In vitro activity of plazomicin against 5,015 gram-negative and gram-positive clinical isolates obtained from patients in Canadian hospitals as part of the CANWARD study, 2011–2012. Antimicrob Agents Chemother **2014**; 58:2554–63.
418. Lopez Montesinos I, Gomez-Zorrilla S, Palacios-Baena ZR, et al. Aminoglycoside or polymyxin monotherapy for treating complicated urinary tract infections caused by extensively drug-resistant *Pseudomonas aeruginosa*: a propensity score-adjusted and matched cohort study. Infect Dis Ther **2022**; 11:335–50.
419. Castanheira M, Duncan LR, Mendes RE, Sader HS, Shortridge D. Activity of ceftolozane-tazobactam against *Pseudomonas aeruginosa* and Enterobacteriaceae isolates collected from respiratory tract specimens of hospitalized patients in the United States during 2013 to 2015. Antimicrob Agents Chemother **2018**; 62:e02125-17.
420. Sader HS, Castanheira M, Shortridge D, Mendes RE, Flamm RK. Antimicrobial activity of ceftazidime-avibactam tested against multidrug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* isolates from U.S. medical centers, 2013 to 2016. Antimicrob Agents Chemother **2017**; 61:e01045-17.
421. Carvalhaes CG, Castanheira M, Sader HS, Flamm RK, Shortridge D. Antimicrobial activity of ceftolozane-tazobactam tested against gram-negative contemporary (2015–2017) isolates from hospitalized patients with pneumonia in US medical centers. Diagn Microbiol Infect Dis **2019**; 94:93–102.
422. Fraile-Ribot PA, Zamorano L, Orellana R, et al. Activity of imipenem-relebactam against a large collection of Pseudomonas aeruginosa clinical isolates and isogenic beta-lactam-resistant mutants. Antimicrob Agents Chemother **2020**; 64:e02165-19.
423. Sader HS, Flamm RK, Carvalhaes CG, Castanheira M. Antimicrobial susceptibility of *Pseudomonas aeruginosa* to ceftazidime-avibactam, ceftolozane-tazobactam, piperacillin-tazobactam, and meropenem stratified by U.S. census divisions: results from the 2017 INFORM program. Antimicrob Agents Chemother **2018**; 62:e01587-18.
424. Karlowsky JA, Lob SH, Siddiqui F, et al. Activity of ceftolozane/tazobactam and imipenem/relebactam against Gram-negative clinical isolates collected in Mexico—SMART 2017–2021. JAC-Antimicrob Resist **2024**; 6:dlae077. doi:10.1093/jacamr/dlae077
425. Pfaller MA, Shortridge D, Sader HS, Castanheira M, Flamm RK. Ceftolozane/tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* causing healthcare-associated infections in the Asia-Pacific region (minus China, Australia and New Zealand): report from an antimicrobial surveillance programme (2013–2015). Int J Antimicrob Agents **2018**; 51:181–9.
426. Pfaller MA, Shortridge D, Sader HS, Gales A, Castanheira M, Flamm RK. Ceftolozane-tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* causing healthcare-associated infections in Latin America: report from an antimicrobial surveillance program (2013–2015). Braz J Infect Dis **2017**; 21:627–37.
427. Pfaller MA, Shortridge D, Sader HS, Flamm RK, Castanheira M. Ceftolozane-tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* causing healthcare-associated infections in Australia and New Zealand: report from an antimicrobial surveillance program (2013–2015). J Glob Antimicrob Resist **2017**; 10:186–94.
428. Shortridge D, Castanheira M, Pfaller MA, Flamm RK. Ceftolozane-tazobactam activity against *Pseudomonas aeruginosa* clinical isolates from U.S. hospitals: report from the PACTS antimicrobial surveillance program, 2012 to 2015. Antimicrob Agents Chemother **2017**; 61:e00465-17.
429. Pfaller MA, Bassetti M, Duncan LR, Castanheira M. Ceftolozane/tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginos*a causing urinary tract and intraabdominal infections in Europe: report from an antimicrobial surveillance programme (2012–15). J Antimicrob Chemother **2017**; 72:1386–95.
430. Sader HS, Castanheira M, Mendes RE, Flamm RK. Frequency and antimicrobial susceptibility of gram-negative bacteria isolated from patients with pneumonia hospitalized in ICUs of US medical centres (2015–17). J Antimicrob Chemother **2018**; 73:3053–9.
431. Sader HS, Carvalhaes CG, Streit JM, Doyle TB, Castanheira M. Antimicrobial activity of ceftazidime-avibactam, ceftolozane-tazobactam and comparators tested against *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* isolates from United States medical centers in 2016–2018. Microb Drug Resist **2021**; 27:342–9.
432. Sader HS, Castanheira M, Flamm RK, Farrell DJ, Jones RN. Antimicrobial activity of ceftazidime-avibactam against gram-negative organisms collected from U.S. medical centers in 2012. Antimicrob Agents Chemother **2014**; 58:1684–92.
433. Sader HS, Castanheira M, Mendes RE, Flamm RK, Farrell DJ, Jones RN. Ceftazidime-avibactam activity against multidrug-resistant *Pseudomonas aeruginosa* isolated in U.S. medical centers in 2012 and 2013. Antimicrob Agents Chemother **2015**; 59:3656–9.
434. Sader HS, Huband MD, Castanheira M, Flamm RK. *Pseudomonas aeruginosa* antimicrobial susceptibility results from four years (2012 to 2015) of the international network for optimal resistance monitoring program in the United States. Antimicrob Agents Chemother **2017**; 61:e02252-16.
435. Sader HS, Castanheira M, Flamm RK. Antimicrobial activity of ceftazidime-avibactam against gram-negative bacteria isolated from patients hospitalized with pneumonia in U.S. medical centers, 2011 to 2015. Antimicrob Agents Chemother **2017**; 61:e02083-16.
436. Sader HS, Castanheira M, Jones RN, Flamm RK. Antimicrobial activity of ceftazidime-avibactam and comparator agents when tested against bacterial

isolates causing infection in cancer patients (2013–2014). Diagn Microbiol Infect Dis **2017**; 87:261–5.
437. Sader HS, Castanheira M, Flamm RK, Jones RN. Antimicrobial activities of ceftazidime-avibactam and comparator agents against gram-negative organisms isolated from patients with urinary tract infections in U.S. medical centers, 2012 to 2014. Antimicrob Agents Chemother **2016**; 60:4355–60.
438. Sader HS, Castanheira M, Flamm RK, Huband MD, Jones RN. Ceftazidime-avibactam activity against aerobic gram negative organisms isolated from intra-abdominal infections in United States hospitals, 2012–2014. Surg Infect (Larchmt) **2016**; 17:473–8.
439. Huband MD, Castanheira M, Flamm RK, Farrell DJ, Jones RN, Sader HS. In vitro activity of ceftazidime-avibactam against contemporary *Pseudomonas aeruginosa* isolates from U.S. medical centers by census region, 2014. Antimicrob Agents Chemother **2016**; 60:2537–41.
440. Sader HS, Castanheira M, Farrell DJ, Flamm RK, Jones RN. Ceftazidime-avibactam activity when tested against ceftazidime-nonsusceptible *Citrobacter* spp., *Enterobacter* spp., *Serratia marcescens*, and *Pseudomonas aeruginosa* from Unites States medical centers (2011–2014). Diagn Microbiol Infect Dis **2015**; 83:389–94.
441. Sader HS, Castanheira M, Flamm RK, Mendes RE, Farrell DJ, Jones RN. *Ceftazidime/avibactam* tested against gram-negative bacteria from intensive care unit (ICU) and non-ICU patients, including those with ventilator-associated pneumonia. Int J Antimicrob Agents **2015**; 46:53–9.
442. Lob SH, DePestel DD, DeRyke CA, et al. Ceftolozane/tazobactam and imipenem/relebactam cross-susceptibility among clinical isolates of pseudomonas aeruginosa from patients with respiratory tract infections in ICU and non-ICU wards-SMART United States 2017–2019. Open Forum Infect Dis **2021**; 8:ofab320.
443. Lob SH, Hackel MA, Young K, Motyl MR, Sahm DF. Activity of imipenem/relebactam and comparators against gram-negative pathogens from patients with bloodstream infections in the United States and Canada—SMART 2018–2019. Diagn Microbiol Infect Dis **2021**; 100:115421.
444. Kuo SC, Wang YC, Tan MC, et al. In vitro activity of imipenem/relebactam, meropenem/vaborbactam, ceftazidime/avibactam, cefepime/zidebactam and other novel antibiotics against imipenem-non-susceptible Gram-negative bacilli from Taiwan. J Antimicrob Chemother **2021**; 76:2071–8.
445. Karlowsky JA, Lob SH, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem/relebactam against gram-negative bacilli from pediatric patients-study for monitoring antimicrobial resistance trends (SMART) global surveillance program 2015–2017. J Pediatric Infect Dis Soc **2021**; 10:274–81.
446. Karlowsky JA, Lob SH, Raddatz J, et al. In vitro activity of imipenem/relebactam and ceftolozane/tazobactam against clinical isolates of Gram-negative bacilli with difficult-to-treat resistance and multidrug-resistant phenotypes—SMART United States 2015–2017. Clin Infect Dis **2020**; 72:2112–20.
447. Lob SH, Hackel MA, Kazmierczak KM, et al. Invitro activity of imipenem-relebactam against gram-negative bacilli isolated from patients with lower respiratory tract infections in the United States in 2015—results from the SMART global surveillance program. Diagn Microbiol Infect Dis **2017**; 88:171–6.
448. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In-vitro activity of imipenem/relebactam and key beta-lactam agents against gram-negative bacilli isolated from lower respiratory tract infection samples of intensive care unit patients—SMART Surveillance United States 2015–2017. Int J Antimicrob Agents **2020**; 55:105841.
449. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem/relebactam against Enterobacteriaceae and *Pseudomonas aeruginosa* isolated from intraabdominal and urinary tract infection samples: SMART Surveillance United States 2015–2017. J Glob Antimicrob Resist **2020**; 21:223–8.
450. Karlowsky JA, Lob SH, Young K, Motyl MR, Sahm DF. Activity of imipenem-relebactam against multidrug-resistant *Pseudomonas aeruginosa* from the United States—SMART 2015–2017. Diagn Microbiol Infect Dis **2019**; 95:212–5.
451. Lob SH, Karlowsky JA, Young K, et al. Activity of imipenem/relebactam against MDR *Pseudomonas aeruginosa* in Europe: SMART 2015–17. J Antimicrob Chemother **2019**; 74:2284–8.
452. Karlowsky JA, Lob SH, Young K, Motyl MR, Sahm DF. Activity of imipenem/relebactam against *Pseudomonas aeruginosa* with antimicrobial-resistant phenotypes from seven global regions: SMART 2015–2016. J Glob Antimicrob Resist **2018**; 15:140–7.
453. Lob SH, Hoban DJ, Young K, Motyl MR, Sahm DF. Activity of imipenem/relebactam against gram-negative bacilli from global ICU and non-ICU wards: SMART 2015–2016. J Glob Antimicrob Resist **2018**; 15:12–19.
454. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem-relebactam against clinical isolates of Gram-negative bacilli isolated in hospital laboratories in the United States as part of the SMART 2016 program. Antimicrob Agents Chemother **2018**; 62:e00169-18.
455. Karlowsky JA, Lob SH, Kazmierczak KM, et al. In vitro activity of imipenem/relebactam against gram-negative ESKAPE pathogens isolated in 17 European countries: 2015 SMART surveillance programme. J Antimicrob Chemother **2018**; 73:1872–9.
456. Lob SH, Hackel MA, Kazmierczak KM, et al. In vitro activity of imipenem-relebactam against gram-negative ESKAPE pathogens isolated by clinical laboratories in the United States in 2015 (results from the SMART global surveillance program). Antimicrob Agents Chemother **2017**; 61:e02209-16.
457. Zhang H, Jia P, Zhu Y, et al. Susceptibility to imipenem/relebactam of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates from Chinese intra-abdominal, respiratory and urinary tract infections: SMART 2015 to 2018. Infect Drug Resist **2021**; 14:3509–18.
458. Pogue JM, Kaye KS, Veve MP, et al. Ceftolozane/tazobactam vs polymyxin or aminoglycoside-based regimens for the treatment of drug-resistant *Pseudomonas aeruginosa*. Clin Infect Dis **2020**; 71:304–10.
459. Chen J, Liang Q, Chen X, et al. Ceftazidime/avibactam versus polymyxin B in the challenge of carbapenem-resistant *Pseudomonas aeruginosa* infection. Infect Drug Resist **2022**; 15:655–67.
460. Almangour TA, Aljabri A, Al Musawa M, et al. Ceftolozane-tazobactam vs. colistin for the treatment of infections due to multidrug-resistant *Pseudomonas aeruginosa*: a multicentre cohort study. J Glob Antimicrob Resist **2022**; 28: 288–94.
461. Holger DJ, Rebold NS, Alosaimy S, et al. Impact of ceftolozane-tazobactam vs. best alternative therapy on clinical outcomes in patients with multidrug-resistant and extensively drug-resistant *Pseudomonas aeruginosa* lower respiratory tract infections. Infect Dis Ther **2022**; 11:1965–80.
462. Hakeam HA, Askar G, Al Sulaiman K, et al. Treatment of multidrug-resistant *Pseudomonas aeruginosa* bacteremia using ceftolozane-tazobactam-based or colistin-based antibiotic regimens: a multicenter retrospective study. J Infect Public Health **2022**; 15:1081–88.
463. Caffrey AR, Appaneal HJ, Liao JX, et al. The comparative effectiveness of ceftolozane/tazobactam versus aminoglycoside- or polymyxin-based regimens in multi-drug-resistant *Pseudomonas aeruginosa* infections. Antibiotics (Basel) **2022**; 11:626.
464. Mazuski JE, Gasink LB, Armstrong J, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. Clin Infect Dis **2016**; 62:1380–9.
465. Lucasti C, Hershberger E, Miller B, et al. Multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. Antimicrob Agents Chemother **2014**; 58:5350–7.
466. Lucasti C, Vasile L, Sandesc D, et al. Phase 2, dose-ranging study of relebactam with imipenem-cilastatin in subjects with complicated intra-abdominal infection. Antimicrob Agents Chemother **2016**; 60:6234–43.
467. Titov I, Wunderink RG, Roquilly A, et al. A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 study). Clin Infect Dis **2020**; 70:1799–808.
468. Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis **2015**; 60:1462–71.
469. Stone GG, Newell P, Gasink LB, et al. Clinical activity of ceftazidime/avibactam against MDR Enterobacteriaceae and Pseudomonas aeruginosa: pooled data from the ceftazidime/avibactam phase III clinical trial programme. J Antimicrob Chemother **2018**; 73:2519–23.
470. Almangour TA, Ghonem L, Alassiri D, et al. Ceftolozane-tazobactam versus ceftazidime-avibactam for the treatment of infections caused by multidrug-resistant *Pseudomonas aeruginosa*: a multicenter cohort study. Antimicrob Agents Chemother **2023**; 67:e0040523.
471. Piccica M, Spinicci M, Botta A, et al. Cefiderocol use for the treatment of infections by carbapenem-resistant gram-negative bacteria: an Italian multicentre real-life experience. J Antimicrob Chemother **2023**; 78:2752–61.
472. Meschiari M, Volpi S, Faltoni M, et al. Real-life experience with compassionate use of cefiderocol for difficult-to-treat resistant *Pseudomonas aeruginosa* (DTR-P) infections. JAC Antimicrob Resist **2021**; 3:dlab188.
473. Adamkova V, Marekovic I, Szabo J, et al. Antimicrobial activity of ceftazidime-avibactam and comparators against *Pseudomonas aeruginosa* and Enterobacterales collected in Croatia, Czech Republic, Hungary, Poland,

Latvia and Lithuania: ATLAS surveillance program, 2019. Eur J Clin Microbiol Infect Dis **2022**; 41:989–96.
474. Nichols WW, de Jonge BL, Kazmierczak KM, Karlowsky JA, Sahm DF. In vitro susceptibility of global surveillance isolates of *Pseudomonas aeruginosa* to ceftazidime-avibactam (INFORM 2012 to 2014). Antimicrob Agents Chemother **2016**; 60:4743–9.
475. Kazmierczak KM, Rabine S, Hackel M, et al. Multiyear, multinational survey of the incidence and global distribution of metallo-beta-lactamase-producing Enterobacteriaceae and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother **2016**; 60:1067–78.
476. Lee M, Abbey T, Biagi M, Wenzler E. Activity of aztreonam in combination with ceftazidime-avibactam against serine- and metallo-beta-lactamase-producing *Pseudomonas aeruginosa*. Diagn Microbiol Infect Dis **2021**; 99:115227.
477. Sempere A, Vinado B, Los-Arcos I, et al. Ceftazidime-avibactam plus aztreonam for the treatment of infections by VIM-type-producing gram-negative bacteria. Antimicrob Agents Chemother **2022**; 66:e0075122.
478. Mularoni A, Mezzatesta ML, Pilato M, et al. Combination of aztreonam, ceftazidime-avibactam and amikacin in the treatment of VIM-1 *Pseudomonas aeruginosa* ST235 osteomyelitis. Int J Infect Dis **2021**; 108:510–12.
479. Skoglund E, Abodakpi H, Rios R, et al. In vivo resistance to ceftolozane/tazobactam in *Pseudomonas aeruginosa* arising by AmpC- and non-AmpC-mediated pathways. Case Rep Infect Dis **2018**; 2018:9095203.
480. Berrazeg M, Jeannot K, Ntsogo Enguene VY, et al. Mutations in beta-lactamase AmpC increase resistance of *Pseudomonas aeruginosa* isolates to antipseudomonal cephalosporins. Antimicrob Agents Chemother **2015**; 59:6248–55.
481. Fraile-Ribot PA, Cabot G, Mulet X, et al. Mechanisms leading to in vivo ceftolozane/tazobactam resistance development during the treatment of infections caused by MDR *Pseudomonas aeruginosa*. J Antimicrob Chemother **2018**; 73: 658–63.
482. MacVane SH, Pandey R, Steed LL, Kreiswirth BN, Chen L. Emergence of ceftolozane-tazobactam-resistant pseudomonas aeruginosa during treatment is mediated by a single AmpC structural mutation. Antimicrob Agents Chemother **2017**; 61:e01183-17.
483. So W, Shurko J, Galega R, Quilitz R, Greene JN, Lee GC. Mechanisms of high-level ceftolozane/tazobactam resistance in Pseudomonas aeruginosa from a severely neutropenic patient and treatment success from synergy with tobramycin. J Antimicrob Chemother **2019**; 74:269–71.
484. Zamudio R, Hijazi K, Joshi C, Aitken E, Oggioni MR, Gould IM. Phylogenetic analysis of resistance to ceftazidime/avibactam, ceftolozane/tazobactam and carbapenems in piperacillin/tazobactam-resistant *Pseudomonas aeruginosa* from cystic fibrosis patients. Int J Antimicrob Agents **2019**; 53:774–80.
485. Cabot G, Bruchmann S, Mulet X, et al. *Pseudomonas aeruginosa* ceftolozane-tazobactam resistance development requires multiple mutations leading to overexpression and structural modification of AmpC. Antimicrob Agents Chemother **2014**; 58:3091–9.
486. Diaz-Canestro M, Perianez L, Mulet X, et al. Ceftolozane/tazobactam for the treatment of multidrug resistant *Pseudomonas aeruginosa*: experience from the Balearic Islands. Eur J Clin Microbiol Infect Dis **2018**; 37:2191–200.
487. Boulant T, Jousset AB, Bonnin RA, et al. A 2.5-years within-patient evolution of a *Pseudomonas aeruginosa* with in vivo acquisition of ceftolozane-tazobactam and ceftazidime-avibactam resistance upon treatment. Antimicrob Agents Chemother **2019**; 63:e01637-19.
488. Haidar G, Philips NJ, Shields RK, et al. Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: clinical effectiveness and evolution of resistance. Clin Infect Dis **2017**; 65:110–20.
489. Rubio AM, Kline EG, Jones CE, et al. In vitro susceptibility of multidrug-resistant *Pseudomonas aeruginosa* following treatment-emergent resistance to ceftolozane-tazobactam. Antimicrob Agents Chemother **2021**; 65: e00084-21.
490. Tamma PD, Beisken S, Bergman Y, et al. Modifiable risk factors for the emergence of ceftolozane-tazobactam resistance. Clin Infect Dis **2020**; 73:e4599–606.
491. Khil PP, Dulanto Chiang A, Ho J, et al. Dynamic emergence of mismatch repair deficiency facilitates rapid evolution of ceftazidime-avibactam resistance in *Pseudomonas aeruginosa* acute infection. mBio **2019**; 10:e01822-19.
492. Lahiri SD, Walkup GK, Whiteaker JD, et al. Selection and molecular characterization of ceftazidime/avibactam-resistant mutants in *Pseudomonas aeruginosa* strains containing derepressed AmpC. J Antimicrob Chemother **2015**; 70: 1650–8.
493. Shields RK, Stellfox ME, Kline EG, Samanta P, Van Tyne D. Evolution of imipenem-relebactam resistance following treatment of multidrug-resistant *Pseudomonas aeruginosa* pneumonia. Clin Infect Dis **2022**; 75:710–14.
494. Gomis-Font MA, Cabot G, Lopez-Arguello S, et al. Comparative analysis of in vitro dynamics and mechanisms of ceftolozane/tazobactam and imipenem/relebactam resistance development in *Pseudomonas aeruginosa* XDR high-risk clones. J Antimicrob Chemother **2022**; 77:957–68.
495. Shields RK, Kline EG, Squires KM, Van Tyne D, Doi Y. In vitro activity of cefiderocol against *Pseudomonas aeruginosa* demonstrating evolved resistance to novel beta-lactam/beta-lactamase inhibitors. JAC Antimicrob Resist **2023**; 5: dlad107.
496. Streling AP, Al Obaidi MM, Lainhart WD, et al. Evolution of cefiderocol non-susceptibility in *Pseudomonas aeruginosa* in a patient without previous exposure to the antibiotic. Clin Infect Dis **2021**; 73:e4472–4.
497. Simner PJ, Beisken S, Bergman Y, Posch AE, Cosgrove SE, Tamma PD. Cefiderocol activity against clinical *Pseudomonas aeruginosa* isolates exhibiting ceftolozane-tazobactam resistance. Open Forum Infect Dis **2021**; 8:ofab311.
498. Gomis-Font MA, Sastre-Femenia MA, Taltavull B, Cabot G, Oliver A. In vitro dynamics and mechanisms of cefiderocol resistance development in wild-type, mutator and XDR *Pseudomonas aeruginosa*. J Antimicrob Chemother **2023**; 78:1785–94.
499. Tsai YV, Bookstaver PB, Kohn J, et al. The prevalence of gram-negative bacteria with difficult-to-treat resistance and utilization of novel beta-lactam antibiotics in the southeastern United States. Antimicrob Steward Healthc Epidemiol **2024**; 4:e35.
500. Corbella L, Boan J, San-Juan R, et al. Effectiveness of ceftazidime-avibactam for the treatment of infections due to *Pseudomonas aeruginosa*. Int J Antimicrob Agents **2022**; 59:106517.
501. Gallagher JC, Satlin MJ, Elabor A, et al. Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: a multicenter study. Open Forum Infect Dis **2018**; 5:ofy280.
502. Kwa A, Kasiakou SK, Tam VH, Falagas ME. Polymyxin B: similarities to and differences from colistin (polymyxin E). Expert Rev Anti Infect Ther **2007**; 5: 811–21.
503. Akajagbor DS, Wilson SL, Shere-Wolfe KD, Dakum P, Charurat ME, Gilliam BL. Higher incidence of acute kidney injury with intravenous colistimethate sodium compared with polymyxin B in critically ill patients at a tertiary care medical center. Clin Infect Dis **2013**; 57:1300–3.
504. Phe K, Lee Y, McDaneld PM, et al. In vitro assessment and multicenter cohort study of comparative nephrotoxicity rates associated with colistimethate versus polymyxin B therapy. Antimicrob Agents Chemother **2014**; 58:2740–6.
505. Tuon FF, Rigatto MH, Lopes CK, Kamei LK, Rocha JL, Zavascki AP. Risk factors for acute kidney injury in patients treated with polymyxin B or colistin methanesulfonate sodium. Int J Antimicrob Agents **2014**; 43:349–52.
506. Rigatto MH, Oliveira MS, Perdigao-Neto LV, et al. Multicenter prospective cohort study of renal failure in patients treated with colistin versus polymyxin B. Antimicrob Agents Chemother **2016**; 60:2443–9.
507. Oliveira MS, Prado GV, Costa SF, Grinbaum RS, Levin AS. Polymyxin B and colistimethate are comparable as to efficacy and renal toxicity. Diagn Microbiol Infect Dis **2009**; 65:431–4.
508. 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**; 117:1335–47.
509. 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**; 41:754–7.
510. 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**; 103:707–13.
511. 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**; 55:118–25.
512. 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**; 49:523–30.
513. Kang CH, Tsai CM, Wu TH, et al. Colistin inhalation monotherapy for ventilator-associated pneumonia of *Acinetobacter baumannii* in prematurity. Pediatr Pulmonol **2014**; 49:381–8.
514. 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**; 37:314–20.
515. 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:e12278.
516. 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**; 144:1768–75.
517. 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: 1238–44.
518. 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:e304.
519. 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.
520. 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**; 6:26.
521. 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**; 9:555–67.
522. 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**; 102:407–12.
523. 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**; 18:872–7.
524. 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.
525. 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: 323–31.
526. Doshi NM, Cook CH, Mount KL, et al. Adjunctive aerosolized colistin for multidrug resistant gram-negative pneumonia in the critically ill: a retrospective study. BMC Anesthesiol **2013**; 13:45.
527. 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**; 9:153–60.
528. 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**; 62:39–47.
529. 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**; 16:1230–6.
530. 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:R53–9.
531. 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: 522–7.
532. 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**; 25:596–9.
533. 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**; 18:870–6.
534. Motaouakkil S, Charra B, Hachimi A, et al. Colistin and rifampicin in the treatment of nosocomial infections from multiresistant *Acinetobacter baumannii*. J Infect **2006**; 53:274–8.
535. 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.
536. 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**; 65:2645–9.
537. 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**; 151:1239–46.
538. 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**; 20:330–40.
539. Qin JP, Huang HB, Zhou H, Zhu Y, Xu Y, Du B. Amikacin nebulization for the adjunctive therapy of gram-negative pneumonia in mechanically ventilated patients: a systematic review and meta-analysis of randomized controlled trials. Sci Rep **2021**; 11:6969.
540. 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**; 58:7331–9.
541. Rouby JJ, Bouhemad B, Monsel A, et al. Aerosolized antibiotics for ventilator-associated pneumonia: lessons from experimental studies. Anesthesiology **2012**; 117:1364–80.
542. Wenzler E, Fraidenburg DR, Scardina T, Danziger LH. Inhaled antibiotics for gram-negative respiratory infections. Clin Microbiol Rev **2016**; 29:581–632.
543. 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**; 8:27.
544. 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:e61–111.
545. 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**; 39:10–39.
546. 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**; 23:629–39.
547. Maselli DJ, Keyt H, Restrepo MI. Inhaled antibiotic therapy in chronic respiratory diseases. Int J Mol Sci **2017**; 18:1062.
548. 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.
549. 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**; 21:46.
550. Vijayakumar S, Biswas I, Veeraraghavan B. Accurate identification of clinically important *Acinetobacter* spp.: an update. Future Sci OA **2019**; 5:FSO395.
551. 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**; 258:72–7.
552. Penwell WF, Shapiro AB, Giacobbe RA, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. Antimicrob Agents Chemother **2015**; 59:1680–9.
553. 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:e01576-17.
554. 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**; 68:2786–91.
555. 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.
556. Bonomo RA, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. Clin Infect Dis **2006**; 43(Suppl 2):S49–56.
557. 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**; 73:3346–54.
558. 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:e01268-16.
559. 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:e01680-20.
560. 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**; 10:880.
561. 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**; 47:479–82.
562. 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**; 22:67–77.
563. 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**; 39:38–43.
564. Assimakopoulos SF, Karamouzos 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**; 27:11–16.
565. 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.
566. 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**; 21:319.
567. Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii*-calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). Lancet Infect Dis **2023**; 23:1072–84.
568. Kaye KS, Marchaim D, Thamlikitkul V, et al. Colistin monotherapy versus combination therapy for carbapenem-resistant organisms. NEJM Evid **2023**; 2: 10.1056/evidoa2200131.
569. 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**; 18:391–400.
570. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant Acinetobacter baumannii infections. Antimicrob Agents Chemother **2014**; 58:5598–601.
571. 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**; 57:349–58.
572. 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**; 141:1214–22.
573. 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.
574. Iovleva A, Mustapha MM, Griffith MP, et al. Carbapenem-resistant *Acinetobacter baumannii* in U.S. hospitals: diversification of circulating lineages and antimicrobial resistance. mBio **2022**; 13:e0275921.
575. Wang M, Ge L, Chen L, et al. Clinical outcomes and bacterial characteristics of carbapenem-resistant *Acinetobacter baumannii* among patients from different global regions. Clin Infect Dis **2023**; 78:248–58.
576. Karlowsky JA, Hackel MA, McLeod SM, Miller AA. In vitro activity of sulbactam-durlobactam against global isolates of *Acinetobacter baumannii*-calcoaceticus complex collected from 2016 to 2021. Antimicrob Agents Chemother **2022**; 66:e0078122.
577. Bhavnani SM, Rubino CM, Hammel JP, et al. Population pharmacokinetics, pharmacodynamic/pharmacokinetic attainment and clinical pharmacokinetic/pharmacodynamic analyses for sulbactam-durlobactam to support dose selection for the treatment of *Acinetobacter baumannii*-calcoaceticus infections [Abstract LB2306]. In ID Week 2022, Washington DC .
578. Iovleva A, Mcelheny C, Fowler, et al. In vitro activity of sulbactam-durlobactam (SUL-DUR) against colistin-resistant and/or cefiderocol-non-susceptible, carbapenem-resistant *Acinetobacter baumannii* collected in US hospitals. ECCMID 2023, Cophenhagen Denmark.
579. Choi JY, Park YS, Cho CH, et al. Synergic in-vitro activity of imipenem and sulbactam against *Acinetobacter baumannii*. Clin Microbiol Infect **2004**; 10: 1098–101.
580. Tanudra A, McLeod S, Miller A, Tommasi R, O'Donell J. Sulbactam-durlobactam (SUL-DUR) in vitro dose response studies with and without imipenem or meropenem carbapenemase-producing *Acinetobacter baumannii* utilizing the hollow-fiber infection model. ECCMID 2022, Lisbon, Portugal, Poster 02037.
581. Fernandez-Cuenca F, Martinez-Martinez L, Conejo MC, Ayala JA, Perea EJ, Pascual A. Relationship between beta-lactamase production, outer membrane protein and penicillin-binding protein profiles on the activity of carbapenems against clinical isolates of *Acinetobacter baumannii*. J Antimicrob Chemother **2003**; 51:565–74.
582. O'Donnell J, Tanudra A, Chen A, Miller AA, McLeod SM, Tommasi R. In vitro pharmacokinetics/pharmacodynamics of the beta-lactamase inhibitor, durlobactam, in combination with sulbactam against *Acinetobacter baumannii*-calcoaceticus complex. Antimicrob Agents Chemother **2024**; 68:e0031223.
583. Findlay J, Poirel L, Bouvier M, Nordmann P. In vitro activity of sulbactam-durlobactam against carbapenem-resistant *Acinetobacter baumannii* and mechanisms of resistance. J Glob Antimicrob Resist **2022**; 30:445–50.
584. Noguchi JK, Gill MA. Sulbactam: a beta-lactamase inhibitor. Clin Pharm **1988**; 7:37–51.
585. Jaruratanasirikul S, Nitchot W, Wongpoowarak W, Samaeng M, Nawakitrangsan M. Population pharmacokinetics and Monte Carlo simulations of sulbactam to optimize dosage regimens in patients with ventilator-associated pneumonia caused by *Acinetobacter baumannii*. Eur J Pharm Sci **2019**; 136: 104940.
586. Jaruratanasirikul S, Wongpoowarak W, Aeinlang N, Jullangkoon M. Pharmacodynamics modeling to optimize dosage regimens of sulbactam. Antimicrob Agents Chemother **2013**; 57:3441–4.
587. Gill CM, Santini D, Takemura M, et al. In vivo efficacy & resistance prevention of cefiderocol in combination with ceftazidime/avibactam, ampicillin/sulbactam or meropenem using human-simulated regimens versus *Acinetobacter baumannii*. J Antimicrob Chemother **2023**; 78:983–90.
588. Yokoyama Y, Matsumoto K, Ikawa K, et al. Pharmacokinetic/pharmacodynamic evaluation of sulbactam against *Acinetobacter baumannii* in in vitro and murine thigh and lung infection models. Int J Antimicrob Agents **2014**; 43:547–52.
589. Housman ST, Hagihara M, Nicolau DP, Kuti JL. In vitro pharmacodynamics of human-simulated exposures of ampicillin/sulbactam, doripenem and tigecycline alone and in combination against multidrug-resistant *Acinetobacter baumannii*. J Antimicrob Chemother **2013**; 68:2296–304.
590. O'Donnell JP, Bhavnani SM. The pharmacokinetics/pharmacodynamic relationship of durlobactam in combination with sulbactam in in vitro and in vivo infection model systems versus *Acinetobacter baumannii*-calcoaceticus complex. Clin Infect Dis **2023**; 76(Suppl 2):S202–9.
591. Abouelhassan Y, Nicolau DP, Abdelraouf K. Defining optimal sulbactam regimens for treatment of *Acinetobacter baumannii* pneumonia and impact of blaOXA-23 on efficacy. J Antimicrob Chemother **2024**; 79:2306–16.
592. Clinical and Laboratory Standards Institute. *Acinetobacter baumannii* Ampicillin/Sulbactam Breakpoint Working Group Presentation. Presented 22 January 2024. Available at: https://app.smartsheet.com/b/publish?EQBCT=d95488fe530f46799bcc71ed48ce4029. Accessed 19 February 2024.
593. Jaruratanasirikul S, Wongpoowarak W, Wattanavijitkul T, et al. Population pharmacokinetics and pharmacodynamics modeling to optimize dosage regimens of sulbactam in critically ill patients with severe sepsis caused by *Acinetobacter baumannii*. Antimicrob Agents Chemother **2016**; 60:7236–44.
594. McLeod SM, Moussa SH, Hackel MA, Miller AA. In vitro activity of sulbactam-durlobactam against *Acinetobacter baumannii*-calcoaceticus complex isolates collected globally in 2016 and 2017. Antimicrob Agents Chemother **2020**; 64: e02534-19.
595. 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**; 54:2235–8.
596. 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.
597. Viana GF, Saalfeld SM, Moreira RR, et al. Can ampicillin/sulbactam resistance in *Acinetobacter baumannii* be predicted accurately by disk diffusion? J Glob Antimicrob Resist **2013**; 1:221–3.
598. Fernandez-Cuenca F, Tomas M, Caballero-Moyano FJ, et al. Reporting antimicrobial susceptibilities and resistance phenotypes in *Acinetobacter* spp: a nationwide proficiency study. J Antimicrob Chemother **2018**; 73:692–7.

599. Shields RK, Paterson DL, Tamma PD. Navigating available treatment options for carbapenem-resistant *Acinetobacter baumannii*-calcoaceticus complex infections. Clin Infect Dis **2023**; 76(Suppl 2):S179–93.
600. Khalili H, Shojaei L, Mohammadi M, Beigmohammadi MT, Abdollahi A, Doomanlou M. Meropenem/colistin versus meropenem/ampicillin-sulbactam in the treatment of carbapenem-resistant pneumonia. J Comp Eff Res **2018**; 7: 901–11.
601. Mosaed R, Haghighi M, Kouchak M, et al. Interim study: comparison of safety and efficacy of levofloxacin plus colistin regimen with levofloxacin plus high dose ampicillin/sulbactam infusion in treatment of ventilator-associated pneumonia due to multi drug resistant *Acinetobacter*. Iran J Pharm Res **2018**; 17(Suppl2):206–13.
602. Pourheidar E, Haghighi M, Kouchek M, et al. Comparison of intravenous ampicillin-sulbactam plus nebulized colistin with intravenous colistin plus nebulized colistin in treatment of ventilator associated pneumonia caused by multi drug resistant *Acinetobacter baumannii*: randomized open label trial. Iran J Pharm Res Fall **2019**; 18(Suppl1):269–81.
603. 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**; 9:17127.
604. 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**; 60:4047–54.
605. Bowers DR, Cao H, Zhou J, et al. Assessment of minocycline and polymyxin B combination against *Acinetobacter baumannii*. Antimicrob Agents Chemother **2015**; 59:2720–5.
606. 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**; 54:1085–91.
607. 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**; 11:319–25.
608. 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**; 46:827–30.
609. 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**; 57:5104–11.
610. 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.
611. Lenhard JR, Nation RL, Tsuji BT. Synergistic combinations of polymyxins. Int J Antimicrob Agents **2016**; 48:607–13.
612. 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**; 35:194–9.
613. 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**; 63:351–61.
614. 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**; 59:181–90.
615. 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**; 138:650–5.
616. Poulakou G, Kontopidou FV, Paramythiotou E, et al. Tigecycline in the treatment of infections from multi-drug resistant gram-negative pathogens. J Infect **2009**; 58:273–84.
617. 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**; 42:37–42.
618. 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**; 24:908.e1–7.
619. 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:e0150642.
620. 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**; 23:345–9.
621. 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:e52349.
622. Kuo LC, Lai CC, Liao CH, et al. Multidrug-resistant *Acinetobacter baumannii* bacteraemia: clinical features, antimicrobial therapy and outcome. Clin Microbiol Infect **2007**; 13:196–8.
623. 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**; 30:448–52.
624. 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**; 9:476–85.
625. 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**; 26:325–31.
626. 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.
627. Batirel A, Balkan II, 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**; 33:1311–22.
628. Amat T, Gutierrez-Pizarraya 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**; 24:630–4.
629. 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**; 69:3119–26.
630. 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**; 69:769–76.
631. 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**; 58:851–8.
632. 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**; 22:352–8.
633. Nation RL, Velkov T, Li J. Colistin and polymyxin B: peas in a pod, or chalk and cheese? Clin Infect Dis **2014**; 59:88–94.
634. Qureshi ZA, Hittle LE, O'Hara JA, et al. Colistin-resistant *Acinetobacter baumannii*: beyond carbapenem resistance. Clin Infect Dis **2015**; 60:1295–303.
635. Bakthavatchalam YD, Veeraraghavan B. Challenges, issues and warnings from CLSI and EUCAST working group on polymyxin susceptibility testing. J Clin Diagn Res **2017**; 11:DL03–4.
636. 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**; 70:3291–7.
637. 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: 462–8.
638. 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**; 46:1946–52.
639. Nation RL, Rigatto MHP, Falci DR, Zavascki AP. Polymyxin acute kidney injury: dosing and other strategies to reduce toxicity. Antibiotics (Basel) **2019**; 8:24.
640. Fluit AC, Florijn A, Verhoef J, Milatovic D. Presence of tetracycline resistance determinants and susceptibility to tigecycline and minocycline. Antimicrob Agents Chemother **2005**; 49:1636–8.
641. 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**; 43:738–44.
642. 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**; 71:76–82.

643. 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.
644. Allen JC. Minocycline. Ann Intern Med **1976**; 85:482–7.
645. 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:e01809-20.
646. 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**; 85:352–5.
647. 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: e01154-19.
648. 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.
649. Chan JD, Graves JA, Dellit TH. Antimicrobial treatment and clinical outcomes of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Intensive Care Med **2010**; 25:343–8.
650. 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.
651. Wood GC, Hanes SD, Boucher BA, Croce MA, Fabian TC. Tetracyclines for treating multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Intensive Care Med **2003**; 29:2072–6.
652. Livermore DM, Mushtaq S, Warner M, Woodford N. In vitro activity of eravacycline against carbapenem-resistant Enterobacteriaceae and *Acinetobacter baumannii*. Antimicrob Agents Chemother **2016**; 60:3840–4.
653. 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:e00931-17.
654. 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**; 68:140–51.
655. Xie J, Roberts JA, Alobaid AS, et al. Population pharmacokinetics of tigecycline in critically ill patients with severe infections. Antimicrob Agents Chemother **2017**; 61:e00345-17.
656. 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**; 51:62–64.
657. 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**; 59:1802–5.
658. Alosaimy S, Morrisette T, Lagnf AM, et al. Clinical outcomes of eravacycline in patients treated predominately for carbapenem-resistant *Acinetobacter baumannii*. Microbiol Spectr **2022**; 10:e0047922.
659. Scott CJ, Zhu E, Jayakumar RA, Shan G, Viswesh V. Efficacy of eravacycline versus best previously available therapy for adults with pneumonia due to difficult-to-treat resistant (DTR) *Acinetobacter baumannii*. Ann Pharmacother **2022**; 56:1299–307.
660. Morrisette T, Alosaimy S, Lagnf AM, et al. Real-world, multicenter case series of patients treated with oral omadacycline for resistant gram-negative pathogens. Infect Dis Ther **2022**; 11:1715–23.
661. Karlowsky JA, Hackel MA, Takemura M, Yamano Y, Echols R, Sahm DF. In vitro susceptibility of gram-negative pathogens to cefiderocol in five consecutive annual multinational SIDERO-WT surveillance studies, 2014 to 2019. Antimicrob Agents Chemother **2022**; 66:e0199021.
662. Morris CP, Bergman Y, Tekle T, Fissel JA, Tamma PD, Simner PJ. Cefiderocol antimicrobial susceptibility testing against multidrug-resistant gram-negative bacilli: a comparison of disk diffusion to broth microdilution. J Clin Microbiol **2020**; 59:e01649-20.
663. Stracquadanio S, Bonomo C, Marino A, et al. *Acinetobacter baumannii* and cefiderocol, between cidality and adaptability. Microbiol Spectr **2022**; 10:e0234722.
664. Simner PJ, Palavecino EL, Satlin MJ, et al. Potential of inaccurate cefiderocol susceptibility results: a CLSI AST subcommittee advisory. J Clin Microbiol **2023**; 61: e0160022.
665. 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:e01022-17.
666. Stainton SM, Monogue ML, Tsuji M, Yamano Y, Echols R, Nicolau DP. Efficacy of humanized cefiderocol exposures over 72 hours against a diverse group of gram-negative isolates in the neutropenic murine thigh infection model. Antimicrob Agents Chemother **2019**; 63:e01040-18.
667. Matsumoto S, Singley CM, Hoover J, et al. Efficacy of cefiderocol against carbapenem-resistant gram-negative bacilli in immunocompetent-rat respiratory tract infection models recreating human plasma pharmacokinetics. Antimicrob Agents Chemother **2017**; 61:e00700-17.
668. 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: e02031-18.
669. 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**; 21:213–25.
670. Falcone M, Tiseo G, Leonildi A, et al. Cefiderocol-compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother **2022**; 66:e0214221.
671. Russo A, Bruni A, Gulli S, et al. Efficacy of cefiderocol- vs colistin-containing regimen for treatment of bacteraemic ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii* in patients with COVID-19. Int J Antimicrob Agents **2023**; 62:106825.
672. Pascale R, Pasquini Z, Bartoletti M, et al. Cefiderocol treatment for carbapenem-resistant *Acinetobacter baumannii* infection in the ICU during the COVID-19 pandemic: a multicentre cohort study. JAC Antimicrob Resist **2021**; 3:dlab174.
673. Giannella M, Verardi S, Karas A, et al. Carbapenem-resistant *Acinetobacter* spp, infection in critically ill patients with limited treatment options: a descriptive study of cefiderocol therapy during the COVID-19 pandemic. Open Forum Infect Dis **2023**; 10:ofad329.
674. Heil EL, Claeys KC, Kline EG, et al. Early initiation of three-drug combinations for the treatment of carbapenem-resistant *A. baumannii* among COVID-19 patients. J Antimicrob Chemother **2023**; 78:1034–40.
675. Nutman A, Lellouche J, Temkin E, et al. Colistin plus meropenem for carbapenem-resistant gram-negative infections: in vitro synergism is not associated with better clinical outcomes. Clin Microbiol Infect **2020**; 26:1185–91.
676. Lesho E, Wortmann G, Moran K, Craft D. Fatal Acinetobacter baumannii infection with discordant carbapenem susceptibility. Clin Infect Dis **2005**; 41:758–9.
677. Jones RN, Sader HS, Fritsche TR, Rhomberg PR. Carbapenem susceptibility discords among *Acinetobacter* isolates. Clin Infect Dis **2006**; 42:158.
678. 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**; 30:354–60.
679. Wehrli W. Rifampin: mechanisms of action and resistance. Rev Infect Dis **1983**; 5(Suppl 3):S407–11.
680. Luna B, Trebosc V, Lee B, et al. A nutrient-limited screen unmasks rifabutin hyperactivity for extensively drug-resistant *Acinetobacter baumannii*. Nat Microbiol **2020**; 5:1134–43.
681. 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:e02204-20.
682. 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**; 75:3552–62.
683. 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:ofaa460.
684. Rothstein DM. Rifamycins, alone and in combination. Cold Spring Harb Perspect Med **2016**; 6:a027011.
685. Mojica MF, Humphries R, Lipuma JJ, et al. Clinical challenges treating *Stenotrophomonas maltophilia* infections: an update. JAC Antimicrob Resist **2022**; 4:dlac040.
686. Brooke JS. Stenotrophomonas maltophilia: an emerging global opportunistic pathogen. Clin Microbiol Rev **2012**; 25:2–41.
687. Groschel MI, Meehan CJ, Barilar I, et al. The phylogenetic landscape and nosocomial spread of the multidrug-resistant opportunist *Stenotrophomonas maltophilia*. Nat Commun **2020**; 11:2044.
688. 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:e00405-19.

689. Isom CM, Fort B, Anderson GG. Evaluating metabolic pathways and biofilm formation in *Stenotrophomonas maltophilia*. J Bacteriol **2022**; 204:e0039821.
690. Paez JI, Costa SF. Risk factors associated with mortality of infections caused by *Stenotrophomonas maltophilia*: a systematic review. J Hosp Infect **2008**; 70: 101–8.
691. Osawa K, Shigemura K, Kitagawa K, Tokimatsu I, Fujisawa M. Risk factors for death from *Stenotrophomonas maltophilia* bacteremia. J Infect Chemother **2018**; 24:632–6.
692. 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**; 4:1103–9.
693. Jeon YD, Jeong WY, Kim MH, et al. Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia. Medicine (Baltimore) **2016**; 95: e4375.
694. 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**; 29:605–8.
695. 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.
696. 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: e0079321.
697. Micozzi A, Venditti M, Monaco M, et al. Bacteremia due to *Stenotrophomonas maltophilia* in patients with hematologic malignancies. Clin Infect Dis **2000**; 31:705–11.
698. 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**; 47:837–45.
699. Safdar A, Rolston KV. *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. Clin Infect Dis **2007**; 45: 1602–9.
700. 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**; 38:285–95.
701. 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**; 48:74–9.
702. Araoka H, Fujii T, Izutsu K, et al. Rapidly progressive fatal hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in hematologic malignancy. Transpl Infect Dis **2012**; 14:355–63.
703. Crossman LC, Gould VC, Dow JM, et al. The complete genome, comparative and functional analysis of *Stenotrophomonas maltophilia* reveals an organism heavily shielded by drug resistance determinants. Genome Biol **2008**; 9:R74.
704. Okazaki A, Avison MB. Aph(3')-IIc, an aminoglycoside resistance determinant from *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother **2007**; 51: 359–60.
705. Gordon NC, Wareham DW. Novel variants of the Smqnr family of quinolone resistance genes in clinical isolates of *Stenotrophomonas maltophilia*. J Antimicrob Chemother **2010**; 65:483–9.
706. Alonso A, Martinez JL. Cloning and characterization of SmeDEF, a novel multidrug efflux pump from *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother **2000**; 44:3079–86.
707. Bostanghadiri N, Ghalavand Z, Fallah F, et al. Characterization of phenotypic and genotypic diversity of *Stenotrophomonas maltophilia* strains isolated from selected hospitals in Iran. Front Microbiol **2019**; 10:1191.
708. Sanchez MB, Martinez JL. The efflux pump SmeDEF contributes to trimethoprim-sulfamethoxazole resistance in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother **2015**; 59:4347–8.
709. Guerci P, Bellut H, Mokhtari M, et al. Outcomes of *Stenotrophomonas maltophilia* hospital-acquired pneumonia in intensive care unit: a nationwide retrospective study. Crit Care **2019**; 23:371.
710. Barnhill AE, Brewer MT, Carlson SA. Adverse effects of antimicrobials via predictable or idiosyncratic inhibition of host mitochondrial components. Antimicrob Agents Chemother **2012**; 56:4046–51.
711. 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.
712. 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.
713. 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**; 51:39–43.
714. 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**; 142:602–7.
715. 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:e00559-20.
716. 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:e0152132.
717. 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**; 74:2055–9.
718. 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.
719. 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**; 22:508–12.
720. Chen L, Hua J, Hong S, et al. Assessment of the relative benefits of monotherapy and combination therapy approaches to the treatment of hospital-acquired *Stenotrophomonas maltophilia* pneumonia: a multicenter, observational, real-world study. Ann Intensive Care **2023**; 13:47.
721. 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: 380–6.
722. Yamano Y. In vitro activity of cefiderocol against a broad range of clinically important gram-negative bacteria. Clin Infect Dis **2019**; 69(Suppl 7):S544–51.
723. Gill CM, Abdelraouf K, Oota M, et al. Discrepancy in sustained efficacy and resistance emergence under human-simulated exposure of cefiderocol against Stenotrophomonas maltophilia between in vitro chemostat and in vivo murine infection models. J Antimicrob Chemother **2021**; 76:2615–21.
724. Werth BJ, Ashford NK, Penewit K, et al. Evolution of cefiderocol resistance in *Stenotrophomonas maltophilia* using in vitro serial passage techniques. JAC Antimicrob Resist **2022**; 4:dlac011.
725. 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.
726. Nakamura R, Oota M, Matsumoto S, Sato T, Yamano Y. In vitro activity and in vivo efficacy of cefiderocol against *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother **2021**; 65:e01436-20.
727. Petraitis V, Petraitiene R, Kavaliauskas P, et al. Efficacy of cefiderocol in experimental *Stenotrophomonas maltophilia* pneumonia in persistently neutropenic rabbits. Antimicrob Agents Chemother **2022**; 66:e0061822.
728. Heil EL, Tamma PD. Cefiderocol: the Trojan horse has arrived but will Troy fall? Lancet Infect Dis **2021**; 21:153–5.
729. Fratoni AJ, Kuti JL, Nicolau DP. Optimised cefiderocol exposures in a successfully treated critically ill patient with polymicrobial *Stenotrophomonas maltophilia* bacteraemia and pneumonia receiving continuous venovenous haemodiafiltration. Int J Antimicrob Agents **2021**; 58:106395.
730. Hsu AJ, Simner PJ, Bergman Y, Mathers AJ, Tamma PD. Successful treatment of persistent *Stenotrophomonas maltophilia* bacteremia with cefiderocol in an infant. Open Forum Infect Dis **2023**; 10:ofad174.
731. Falcone M, Tiseo G, Nicastro M, et al. Cefiderocol as rescue therapy for *Acinetobacter baumannii* and other carbapenem-resistant gram-negative infections in intensive care unit patients. Clin Infect Dis **2021**; 72:2021–4.
732. Zappulo E, Grimaldi F, Paolillo R, et al. Successful treatment of MDR *Stenotrophomonas maltophilia*-associated pneumonia with cefiderocol-based regimen in a patient with hematological malignancy. Ann Hematol **2022**; 101: 2805–6.
733. Koirala A, Krishnappa B, Banh C, Brandenburg U, Findlay M, Williams PCM. Successful use of cefiderocol to treat a multidrug-resistant *Stenotrophomonas maltophilia* ventilator-associated pneumonia in an extremely preterm neonate. Pediatr Infect Dis J **2023**; 42:1012–6.

734. 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: e01437-20.
735. 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:e00297-20.
736. 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:e00777-17.
737. 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**; 60:5130–4.
738. 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**; 21:60.
739. 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:e01433-20.
740. 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: e00010-19.
741. 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.
742. 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**; 43:146–9.
743. De Almeida Torres N, Morales Junior R, Bueno Lopes LF, Zeigler R, Everson Uip D. Synergistic combination of aztreonam and ceftazidime/avibactam against resistant *Stenotrophomonas maltophilia* on pancreatitis. J Infect Dev Ctries **2023**; 17:881–5.
744. 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:e01603-19.
745. 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**; 47:846–51.
746. Pfaller MA, Shortridge D, Carvalhaes CG, Castanheira M. Trends in the susceptibility of U.S. *Acinetobacter baumannii*-calcoaceticus species complex and *Stenotrophomonas maltophilia* isolates to minocycline, 2014–2021. Microbiol Spectr **2023**; 11:e0198123.
747. Fratoni AJ, Nicolau DP, Kuti JL. Minocycline pharmacodynamics against *Stenotrophomonas maltophilia* in the neutropenic murine infection model: implications for susceptibility breakpoints. J Antimicrob Chemother **2022**; 77: 1052–60.
748. Hand E, Davis H, Kim T, Duhon B. Monotherapy with minocycline or trimethoprim/sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. J Antimicrob Chemother **2016**; 71:1071–5.
749. Jacobson S, Junco Noa L, Wallace MR, Bowman MC. Clinical outcomes using minocycline for *Stenotrophomonas maltophilia* infections. J Antimicrob Chemother **2016**; 71:3620.
750. Tekce YT, Erbay A, Cabadak H, Sen S. Tigecycline as a therapeutic option in *Stenotrophomonas maltophilia* infections. J Chemother **2012**; 24:150–4.
751. Zha L, Zhang D, Pan L, et al. Tigecycline in the treatment of ventilator-associated pneumonia due to *Stenotrophomonas maltophilia*: a multicenter retrospective cohort study. Infect Dis Ther **2021**; 10:2415–29.
752. Hevia EC, Wooten L, Carr AL. Trimethoprim/sulfamethoxazole vs minocycline for the treatment of nonurinary monomicrobial *Stenotrophomonas maltophilia* infections in hospitalized patients. Ann Pharmacother **2024**; 58: 698–704.
753. 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.
754. 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:ofaa141.
755. Al-Jasser AM. *Stenotrophomonas maltophilia* resistant to trimethoprim-sulfamethoxazole: an increasing problem. Ann Clin Microbiol Antimicrob **2006**; 5:23.
756. Toleman MA, Bennett PM, Bennett DM, Jones RN, Walsh TR. Global emergence of trimethoprim/sulfamethoxazole resistance in *Stenotrophomonas maltophilia* mediated by acquisition of sul genes. Emerg Infect Dis **2007**; 13: 559–65.
757. Lasko MJ, Gethers ML, Tabor-Rennie JL, Nicolau DP, Kuti JL. In vitro time-kill studies of trimethoprim/sulfamethoxazole against *Stenotrophomonas maltophilia* versus *Escherichia coli* using cation-adjusted Mueller-Hinton broth and ISO-sensitest broth. Antimicrob Agents Chemother **2022**; 66:e0216721.
758. Lasko MJ, Tabor-Rennie JL, Nicolau DP, Kuti JL. Trimethoprim/sulfamethoxazole pharmacodynamics against *Stenotrophomonas maltophilia* in the in vitro chemostat model. J Antimicrob Chemother **2022**; 77:3187–93.
759. Sarzynski SH, Warner S, Sun J, et al. Trimethoprim-sulfamethoxazole versus levofloxacin for *Stenotrophomonas maltophilia* infections: a retrospective comparative effectiveness study of electronic health records from 154 US hospitals. Open Forum Infect Dis **2022**; 9:ofab644.
760. 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**; 25:546–54.
761. Nys C, Cherabuddi K, Venugopalan V, Klinker KP. Clinical and microbiologic outcomes in patients with monomicrobial *Stenotrophomonas maltophilia* infections. Antimicrob Agents Chemother **2019**; 63:e00788-19.
762. 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**; 58:581–3.
763. Watson L, Esterly J, Jensen AO, Postelnick M, Aguirre A, McLaughlin M. Sulfamethoxazole/trimethoprim versus fluoroquinolones for the treatment of *Stenotrophomonas maltophilia* bloodstream infections. J Glob Antimicrob Resist **2018**; 12:104–6.
764. Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. Antimicrob Agents Chemother **2014**; 58:176–82.
765. Lai JJ, Siu LK, Chang FY, et al. Appropriate antibiotic therapy is a predictor of outcome in patients with *Stenotrophomonas maltophilia* blood stream infection in the intensive care unit. J Microbiol Immunol Infect **2023**; 56:624–33.
766. Dao BD, Barreto JN, Wolf RC, Dierkhising RA, Plevak MF, Tosh PK. Serum peak sulfamethoxazole concentrations demonstrate difficulty in achieving a target range: a retrospective cohort study. Curr Ther Res Clin Exp **2014**; 76:104–9.
767. Zhang L, Li XZ, Poole K. Multiple antibiotic resistance in *Stenotrophomonas maltophilia*: involvement of a multidrug efflux system. Antimicrob Agents Chemother **2000**; 44:287–93.
768. 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.
769. 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**; 21:464–7.
770. 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**; 54:2735–7.
771. 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:ofaa008.
772. Baek JH, Kim CO, Jeong SJ, et al. Clinical factors associated with acquisition of resistance to levofloxacin in *Stenotrophomonas maltophilia*. Yonsei Med J **2014**; 55:987–93.
773. 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: e0156690.
774. 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**; 48:946–53.
775. 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**; 45:115–7.
776. 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**; 46:3997–9.
777. 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**; 77:164–8.
778. 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.
779. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med **2017**; 177:1308–15.
780. Falagas ME, Valkimadi PE, Huang YT, Matthaiou DK, Hsueh PR. Therapeutic options for *Stenotrophomonas maltophilia* infections beyond co-trimoxazole: a systematic review. J Antimicrob Chemother **2008**; 62:889–94.