

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

Pranita D. Tamma,¹ Samuel L. Aitken,² Robert A. Bonomo,³ Amy J. Mathers,⁴ David van Duin,⁵ & Cornelius J. Clancy⁶

Affiliations

¹Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

²Department of Pharmacy, University of Michigan Health, Ann Arbor, Michigan, USA

³Medical Service and Center for Antimicrobial Resistance and Epidemiology, Louis Stokes Cleveland Veterans Affairs Medical Center, University Hospitals Cleveland Medical Center and Departments of Medicine, Pharmacology, Molecular Biology, and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA

⁴Departments of Medicine and Pathology, University of Virginia, Charlottesville, Virginia, USA

⁵Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

⁶Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Corresponding Author: Pranita D. Tamma, MD, MHS, Johns Hopkins University School of Medicine, Department of Pediatrics, Baltimore, Maryland, USA; ptamma1@jhmi.edu

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

Running Title: AMR Treatment Guidance

Abstract

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

Methods: A panel of six infectious diseases specialists with expertise in managing antimicrobial-resistant infections formulated questions about the treatment of infections caused by ESBL-E, AmpC-E, CRE, DTR-*P. aeruginosa*, CRAB, and *S. maltophilia*. Because of differences in the epidemiology of resistance and availability of specific anti-infectives internationally, this document focuses on the treatment of infections in the United States.

Results: Preferred and alternative suggested treatment approaches are provided with accompanying rationales, assuming the causative organism has been identified and antibiotic susceptibility results are known. Approaches to empiric treatment, transitioning to oral therapy, duration of therapy, and other management considerations are also discussed briefly. Suggested approaches apply for both adult and pediatric populations, although suggested antibiotic dosages are provided only for adults.

Conclusions: The field of antimicrobial resistance is highly dynamic. Consultation with an infectious diseases specialist is recommended for the treatment of antimicrobial resistant infections. This document is current as of December 31, 2022 and will be updated periodically. The most current version of this document, including date of publication, is available at www.idsociety.org/practice-guideline/amr-guidance/.

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; 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); should not be considered inclusive of all available treatment approaches, or as a statement of the standard of care; do not mandate any particular course of medical care; and 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. While 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.

The guidance represents the proprietary and copyrighted property of IDSA. Copyright 2023 Infectious Diseases Society of America. All rights reserved. No part of this guidance may be reproduced, distributed, or transmitted in any form or by any means, including photocopying, recording, or other electronic or mechanical methods, without the prior written permission of IDSA. Permission is granted to physicians and health care providers solely to copy and use the guidance in their professional practices and clinical decision-making. No license or permission is granted to any person or entity, and prior written authorization by IDSA is required, to sell, distribute, or modify the guidance, or to make derivative works of or incorporate the guidance into any product, including but not limited to clinical decision support software or any other software product. Except for the permission granted above, any person or entity desiring to use the guidance in any way must contact IDSA for approval in accordance

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

with the terms and conditions of third-party use, in particular any use of the guidance in any software product.

Introduction

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

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

Guidance is presented in the form of answers to a series of clinical questions for each pathogen. Although brief descriptions of notable clinical trials, resistance mechanisms, and antimicrobial susceptibility testing (AST) methods are included, the document does not provide a comprehensive review of these topics. GRADE methodology was not employed. Due to differences in the molecular epidemiology of resistance and availability of specific antibiotics internationally, treatment recommendations are geared toward antimicrobial resistant infections in the United States. The content of this document is current as of December 31st, 2022. The most current version of this IDSA guidance document and corresponding date of publication is available at: www.idsociety.org/practice-guideline/amr-guidance.

Methodology

IDSA convened a panel of six actively practicing infectious diseases specialists with clinical and research expertise in the treatment of antimicrobial resistant bacterial infections. Through a series of virtual meetings, the panel developed commonly encountered treatment questions and corresponding suggested treatment approaches for each pathogen group. Answers include a brief discussion of the rationale supporting the suggested approaches. This guidance document applies to both adult and pediatric populations. Suggested antibiotic dosing for adults with antimicrobial resistant infections, assuming normal renal and hepatic function, are provided in [Table 1](#). Pediatric dosing is not provided.

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

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

	All other infections: 3 grams IV every 8 hours, infused over 3 hours
Ciprofloxacin	Cystitis: 400 milligrams IV every 12 hours or 500 milligrams PO every 12 hours All other infections: 400 milligrams IV every 8 hours OR 750 milligrams PO every 12 hours
Colistin	Refer to international consensus guidelines on polymyxins (Tsuji BT, et al. Pharmacotherapy. 2019; 39:10-39).
Eravacycline	1 mg/kg per dose IV every 12 hours
Ertapenem	1 gram IV every 24 hours, infused over 30 minutes
Fosfomycin	Uncomplicated cystitis: 3 grams PO as a single dose
Gentamicin	Uncomplicated cystitis: 5 mg/kg/dose IV as a single dose Pyelonephritis or complicated urinary tract infections: 7 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in Supplemental Material .
Imipenem-cilastatin	Uncomplicated cystitis: 500 mg IV every 6 hours, infused over 30 minutes All other infections: 500 mg IV every 6 hours, infused over 3 hours (if possible) Additional information in Supplemental Material .
Imipenem-cilastatin-relebactam	1.25 grams IV every 6 hours, infused over 30 minutes Additional information in Supplemental Material .
Levofloxacin	750 milligrams IV/PO every 24 hours
Meropenem	Uncomplicated cystitis: 1 grams IV every 8 hours, infused over 30 minutes All other infections: 2 grams IV every 8 hours, infused over 3 hours (if possible) Additional information in Supplemental Material .
Meropenem-vaborbactam	4 grams IV every 8 hours, infused over 3 hours
Minocycline	200 milligrams IV/PO every 12 hours
Nitrofurantoin	Macrocrystal/monohydrate (Macrobid®): 100 mg PO every 12 hours Oral suspension: 50 milligrams PO every 6 hours

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

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

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

General Management Recommendations

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

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

Empiric Therapy

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

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

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

Duration of Therapy and Transitioning to Oral Therapy

Recommendations on durations of therapy are not provided, but clinicians are advised that the duration of therapy should not differ for infections caused by organisms with resistant phenotypes compared to infections caused by more susceptible phenotypes. After AST results are available, it may become apparent that inactive antibiotic therapy was initiated empirically. This may impact the duration of therapy. For example, uncomplicated cystitis is typically a mild infection [4]. If an antibiotic not active against the causative organism was administered empirically for uncomplicated cystitis, but clinical improvement nonetheless occurred, it is generally not necessary to repeat a urine culture, change the antibiotic regimen, or extend the planned treatment course. However, for all other infections, if AST results indicate a potentially inactive agent was initiated empirically, a change to an active regimen for a full treatment course (dated from the start of active therapy) is recommended. Additionally, important host factors related to immune status, ability to attain source control, and general response to therapy should be considered when determining treatment durations for antimicrobial resistant infections, as with the treatment of any bacterial infection. Finally, whenever possible, transitioning to oral therapy should be considered, particularly if the following criteria are met: (1) susceptibility to an appropriate oral agent is demonstrated, (2) the patient is hemodynamically stable, (3) reasonable source control measures have occurred, and (4) concerns about insufficient intestinal absorption are not present [5].

Section 1: Extended-spectrum β -lactamase-Producing Enterobacterales

The incidence of ESBL-E identified in bacterial cultures in the United States increased by 53% from 2012 to 2017, in large part due to a greater number of community-acquired infections [6, 7]. ESBLs are enzymes that inactivate most penicillins, cephalosporins, and aztreonam. ESBL-E generally remain susceptible to carbapenems. ESBLs do not inactivate non- β -lactam agents (e.g., ciprofloxacin, trimethoprim-sulfamethoxazole [TMP-SMX], gentamicin). However, organisms carrying ESBL genes often harbor additional genes or mutations in genes that mediate resistance to a broad range of antibiotics.

Any gram-negative organism has the potential to harbor ESBL genes; however, they are most prevalent in *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*[8-10]. CTX-M enzymes, particularly CTX-M-15, are the most common ESBLs in the United States[10]. ESBLs other than CTX-M with unique hydrolyzing abilities are also present, including variants of narrow-spectrum TEM and SHV β -lactamases with amino acid substitutions, but they have undergone less rigorous clinical investigation than CTX-M enzymes [11-14]. Routine ESBL testing is not performed by most clinical microbiology laboratories [15, 16]. Rather, non-susceptibility to ceftriaxone (i.e., ceftriaxone minimum inhibitory concentrations [MICs] ≥ 2 $\mu\text{g/mL}$), is often used as a proxy for ESBL production, although this threshold has limitations with specificity as organisms not susceptible to ceftriaxone for reasons other than ESBL production may be falsely presumed to be ESBL-producers [17, 18]. For this guidance document, ESBL-E will refer to presumed or confirmed ESBL-producing *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*. Treatment 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. Single dose aminoglycosides and oral fosfomycin (for *E. coli* only) are also alternative treatments for uncomplicated cystitis caused by ESBL-E.

Rationale

Nitrofurantoin and TMP-SMX have been shown to be safe and effective options for uncomplicated cystitis, including uncomplicated ESBL-E cystitis [4, 19, 20]. Although carbapenems and the fluoroquinolones ciprofloxacin or levofloxacin are effective agents against ESBL-E cystitis [21, 22], their use for uncomplicated cystitis is discouraged when other safe and effective options are available. Limiting use of these agents preserves their activity for future infections when treatment options may be more restricted. Moreover, limiting their use reduces the risk of associated toxicities, particularly with the fluoroquinolones, which have been associated with an increased risk for prolonged QTc intervals, tendinitis and tendon rupture, aortic dissections, seizures, peripheral neuropathy, and *Clostridioides difficile* infections[23-26].

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

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

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

Two clinical outcomes studies, published more than 40 years ago, demonstrated that oral tetracyclines may be effective for the treatment of UTIs [33, 34]. Both of these studies, however, primarily focused on *P. aeruginosa*, an organism not susceptible to oral tetracyclines, questioning the impact that antibiotic therapy had on clinical cure. Doxycycline is primarily eliminated through the intestinal tract[35]. Its urinary excretion is limited. Until more convincing data demonstrating the clinical effectiveness of oral doxycycline for the treatment of ESBL-E cystitis are available, the panel suggests against use of doxycycline for this indication. The roles of piperacillin-tazobactam, cefepime, and the cephamycins for the treatment of uncomplicated cystitis are discussed in [Question 1.4](#), [Question 1.5](#), and [Question 1.6](#), respectively.

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

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

Rationale

TMP-SMX, ciprofloxacin, and levofloxacin are preferred treatment options for patients with ESBL-E pyelonephritis and cUTIs based on the ability of these agents to achieve adequate and sustained concentrations in the urine, clinical trial results, and clinical experience[36-38]. Carbapenems are also preferred agents, when resistance or toxicities prevent use of TMP-SMX or fluoroquinolones, or early in the treatment course if a patient is critically ill ([Question 1.3](#)). If a carbapenem is initiated and susceptibility to TMP-SMX, ciprofloxacin, or levofloxacin is demonstrated, transitioning to oral formulations of these agents is preferred over completing a treatment course with a carbapenem. Limiting use of carbapenem exposure will preserve their activity for future antimicrobial resistant infections.

In patients in whom the potential for nephrotoxicity is deemed acceptable, aminoglycosides (dosed based on therapeutic drug monitoring results) for a full treatment course are an alternative option for the treatment of ESBL-E pyelonephritis or cUTI [39, 40] ([Table 1, Supplemental Material](#)). Once-daily plazomicin was noninferior to meropenem in a clinical trial that included patients with pyelonephritis and cUTIs caused by Enterobacterales [41]. Individual aminoglycosides are equally effective if susceptibility is demonstrated. Of note, in January 2023 the Clinical Laboratory and Standards Institute (CLSI) revised the aminoglycoside breakpoints[16] ([Table 2](#)).

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

fosfomycin as an oral step-down agent for patients with pyelonephritis or cUTI, particularly when administered as a multidose regimen and after several days of preferred therapy. A clinical trial of 97 women with *E. coli* pyelonephritis (approximately half of patients had associated bacteremia) who received up to 5 days of IV therapy and were subsequently transitioned to either once-daily 3 g doses of oral fosfomycin or twice daily 500 mg doses of oral ciprofloxacin for 10 days of total antibiotic therapy identified similar clinical cure percentages in both groups (75% versus 65%, respectively)[42]. However, only approximately 6% of isolates were ESBL-producing, limiting generalizability to pyelonephritis caused by more drug-resistant phenotypes[42].

Fosfomycin is an alternative option for the treatment of prostatitis caused by ESBL-producing *E. coli* when preferred options (i.e., carbapenems, TMP-SMX, or fluoroquinolones) cannot be tolerated or do not test susceptible [43-48]. In an observational study, fosfomycin, dosed at 3 g orally daily for one week, followed by 3 g orally every 48 hours for 6 to 12 weeks, was associated with clinical cure in 36 (82%) of 44 males with chronic bacterial prostatitis [43]. Fosfomycin should be avoided for prostatitis caused by gram-negative organisms other than *E. coli* ([Question 1.1](#)).

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

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

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

Rationale

A carbapenem is recommended as first-line treatment of ESBL-E infections outside of the urinary tract, based primarily on data from a large clinical trial, as described below [49]. Meropenem, imipenem-cilastatin, or ertapenem are preferred agents; ertapenem offers a more convenient option for patients needing to continue carbapenem therapy in the outpatient setting when oral treatment options are not available. For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenems.

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

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

The clinical trial which established carbapenem therapy as the treatment of choice for ESBL-E bloodstream infections randomized 391 patients with ceftriaxone non-susceptible *E. coli* or *K. pneumoniae* (87% later confirmed to have ESBL genes) bloodstream infections to piperacillin-tazobactam 4.5 g IV every six hours or meropenem 1 g IV every eight hours, both as standard infusions (i.e., over 30 minutes). The primary outcome of 30-day mortality occurred in 12% and 4% of patients receiving piperacillin-tazobactam and meropenem, respectively [49]. Trial data were subsequently reanalyzed only including patients with clinical isolates against which piperacillin-tazobactam MICs were ≤ 16 $\mu\text{g}/\text{mL}$ by broth microdilution, the reference standard for AST [58]. Reanalyzing the data from 320 patients, 30-day mortality was observed in 11% versus 4% of those in the piperacillin-tazobactam and meropenem arms, respectively. Although the absolute risk difference was attenuated and no longer significant in the reanalysis (i.e., the 95% confidence interval ranged from -1% to 10%) [58], the panel still suggests carbapenem therapy as the preferred treatment of ESBL-producing bloodstream infections due to the notable direction of the risk difference. Comparable clinical trial data are not available for ESBL-E infections of other body sites. Nevertheless, the panel suggests extrapolating evidence for ESBL-E bloodstream infections to other common sites of infection, namely intra-abdominal infections, skin and soft tissue infections, and pneumonia. Similarly, although the trial evaluated meropenem, the panel suggests extending the findings to imipenem-cilastatin and ertapenem, with the latter limited to patients with normal serum albumin and patients who are not critically ill.

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

Data from observational studies support the use of oral step-down therapy for Enterobacterales bloodstream infections, including those caused by antimicrobial resistant isolates, after appropriate clinical milestones are achieved [60, 61]. Based on the known bioavailability and sustained serum concentrations of oral TMP-SMX and fluoroquinolones, these agents should be treatment considerations for patients with ESBL-E infections if (1) susceptibility to one of these agents is demonstrated, (2) the patient is hemodynamically stable, (3) reasonable source control has occurred, and (4) concerns about insufficient intestinal absorption are not present [5].

Clinicians should avoid oral step-down to nitrofurantoin, fosfomycin, amoxicillin-clavulanate, doxycycline, or omadacycline for ESBL-E bloodstream infections. Nitrofurantoin and fosfomycin achieve poor serum concentrations. Amoxicillin-clavulanate and doxycycline achieve unreliable serum concentrations.

Omadacycline is a tetracycline derivative with an oral formulation that has limited in vitro activity against ESBL-producing Enterobacterales isolates and has an unfavorable PK/PD profile for the treatment of Enterobacterales infections[62, 63]. Like other tetracyclines, omadacycline efficacy is associated with the 24-hour area under the curve to MIC ratio (AUC/MIC). In in vitro models, an AUC/MIC ratio of ~38 is needed to achieve at least a one-log kill (a standard pharmacodynamic target) for *E. coli*[63]. Standard oral omadacycline dosing achieves a 24-hour AUC of ~13mg*hr/L[64], suggesting limited activity of omadacycline against Enterobacterales, which have an MIC₅₀ of 0.5 µg/mL (i.e., AUC/MIC ratio of ~26)[65]. The panel does not suggest omadacycline for the treatment of ESBL-E infections.

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

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

Rationale

Piperacillin-tazobactam demonstrates in vitro activity against a number of ESBL-E[66]. There are several concerns regarding tazobactam's ability to function as an effective β -lactamase inhibitor. First, piperacillin-tazobactam MIC testing may be inaccurate and/or poorly reproducible when ESBL enzymes are present, or in the presence of other β -lactamase enzymes such as OXA-1, making it unclear if an isolate that tests susceptible to this agent is indeed susceptible [58, 67-70]. Second, in vitro data indicate that with increased bacterial inoculum (e.g., abscesses), piperacillin-tazobactam may no longer be effective against ESBL-E when compared to meropenem; however, the clinical implications of these findings are unclear[71-73]. Additionally, the effectiveness of tazobactam may be diminished by organisms with increased expression of ESBL enzymes or by the presence of multiple ESBL or other β -lactamases[74]. Finally, there are ESBL enzymes that are inhibitor resistant (i.e., not inhibited by β -lactamase inhibitors)[75, 76].

If piperacillin-tazobactam was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary, as uncomplicated cystitis often resolves on its own. At least three observational studies have compared the efficacy of piperacillin-tazobactam

and carbapenems for the treatment of ESBL-E pyelonephritis or cUTI [77-79]. The most robust observational study included 186 hospitalized patients from five hospitals with pyelonephritis or cUTI caused by *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*, with confirmation of the presence of ESBL genes in all isolates. This study identified no difference in the resolution of clinical symptoms or 30-day mortality between the groups [77]. A randomized, open-label clinical trial investigating this question was also conducted [80]. The trial included 66 patients with ESBL-producing *E. coli* pyelonephritis or cUTI (with confirmation of the presence of ESBL genes) randomized to either piperacillin-tazobactam 4.5 g IV every six hours or ertapenem 1 g IV every 24 hours. Clinical success was similar between both groups at 94% for piperacillin-tazobactam and 97% for ertapenem. These studies suggest non-inferiority between piperacillin-tazobactam and carbapenems for pyelonephritis or cUTIs.

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

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

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

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

Rationale

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

If cefepime was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary, as uncomplicated cystitis often resolves on its own. Limited data are available evaluating the role of cefepime versus carbapenems for ESBL-E pyelonephritis and cUTIs [80, 96]. A clinical trial evaluating the treatment of molecularly confirmed ESBL-E pyelonephritis and cUTI was terminated early because of a high clinical failure signal with cefepime (2 g IV every 12 hours), despite all isolates having cefepime MICs of 1-2 µg/mL [80]. It is unknown if results would have been more favorable with every 8-hour cefepime dosing. Until larger, more robust comparative effectiveness studies are available to inform the role of cefepime, the panel suggests avoiding cefepime for the treatment of ESBL-E pyelonephritis or cUTI.

Observational studies and a subgroup analysis of 23 patients in a clinical trial that compared cefepime and carbapenems for the treatment of invasive ESBL-E infections demonstrated either no difference in outcomes or poorer outcomes with cefepime [97-101].

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

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 ceftazidime or ceftolozane are available and optimal dosing has been defined.

Rationale

The cephamycins are cephalosporins generally able to withstand hydrolysis from ESBL enzymes[102, 103]. The cephamycins available in the United States are ceftazidime and ceftolozane which are both IV agents. At least eight retrospective observational studies have compared the clinical outcomes of patients with ESBL-E infections—generally UTIs or bloodstream infections with urinary sources—treated with cephamycins versus carbapenems [104-111]. Six of the eight investigations found no difference in clinical outcomes[104, 106-108, 110, 111], while two studies demonstrated poorer outcomes with cephamycins[105]. One of the two studies included 57 patients with *K. pneumoniae* bloodstream infections; 14-day mortality was 55% and 39% in the cephamycin and carbapenem arms, respectively[105]. The second study was the largest published to date, including 380 patients with *E. coli* and *K. pneumoniae* bloodstream infections, and 30-day mortality was 29% versus 13% in the cephamycin and carbapenem arms, respectively [109]. Importantly, all eight studies included diverse sources of infection, had notable selection bias, and used a variety of cephamycins with differences in dosing, duration, and frequency of administration.

The panel does not suggest cephamycins for the treatment of ESBL-E infections, including ESBL-E uncomplicated cystitis. Many of the cephamycins investigated in observational studies are not available in the United States. Limited numbers of patients received ceftazidime or ceftolozane in published studies [107, 111, 112]. The panel believes more clinical data associated with these agents for the treatment of ESBL-E infections is necessary before advocating for their use—including optimal dosing and frequency of administration—especially in light of the two observational studies suggesting poorer clinical outcomes with cephamycin use. Data

suggest more favorable outcomes with high-dose, continuous infusion ceftazidime (i.e., 6 g per day infused continuously) [111, 112], but this is challenging to administer. As both ceftazidime and ceftazidime/avibactam are only available IV and have relatively short half-lives, there does not appear to be a feasibility advantage with use of these agents over preferred agents for the treatment of ESBL-E infections.

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

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

Rationale

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

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

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

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

Section 2: AmpC β -Lactamase-Producing Enterobacterales

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

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

For the other two mechanisms (i.e., stable chromosomal de-repression or constitutively expressed *ampC* genes), AmpC production is always increased. Isolates with either of these two mechanisms are expected to test non-susceptible to ceftriaxone, cefotaxime, and/or ceftazidime. As such, infections by these organisms generally pose less of a treatment dilemma than infections caused by isolates with inducible *ampC* expression. Regarding the first of these two mechanisms, some Enterobacterales isolates (e.g., certain *Escherichia coli* and *Shigella* spp.) contain mutations in promoters or attenuators of *ampC* or other related genes (e.g., *ampD*, *ampR*, *ampG*), stably de-repressing gene expression [132]. For the second mechanism,

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

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

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

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

Rationale

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

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

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

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

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

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

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

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

Rationale

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

Cefepime has the advantage of both being a weak inducer of *ampC* and of withstanding hydrolysis by AmpC β -lactamases because of the formation of stable acyl enzyme complexes [155, 156]. Therefore, cefepime is generally an effective agent for the treatment of AmpC-E infections [157]. TMP-SMX, fluoroquinolones, aminoglycosides, tetracyclines, and other non- 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 to high risk of clinically significant AmpC production due to an inducible *ampC* gene?

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

Rationale

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

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

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

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

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

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

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

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

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

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

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

Rationale

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

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

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

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

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

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

Rationale

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

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

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

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

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

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

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

Rationale

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

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

The role of TMP-SMX or fluoroquinolones for the treatment of AmpC-E infections outside of the urinary tract has not been formally evaluated in clinical trials or robust observational studies. However, neither TMP-SMX nor fluoroquinolones are substrates for AmpC hydrolysis. Oral step-down therapy with TMP-SMX or fluoroquinolones have been shown to be reasonable treatment considerations for Enterobacterales bloodstream infections, including those caused by AmpC-E, after appropriate clinical milestones are achieved [60, 61].

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

Section 3: Carbapenem-Resistant Enterobacterales

CRE account for more than 13,000 infections and contribute to greater than 1,000 deaths in the United States annually [188]. The CDC defines CRE as members of the Enterobacterales order resistant to at least one carbapenem antibiotic or producing a carbapenemase enzyme [189]. Resistance to at least one carbapenem other than imipenem is required for bacteria generally not susceptible to imipenem (e.g., *Proteus* spp., *Morganella* spp., *Providencia* spp.) [189]. For the purposes of this guidance document, CRE refers to organisms displaying resistance to either meropenem or imipenem, or those Enterobacterales isolates producing carbapenemase enzymes ([Question 3.1](#)).

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

The most common carbapenemases in the United States are *K. pneumoniae* carbapenemases (KPCs), which are not limited to *K. pneumoniae* isolates. Other notable carbapenemases that have been identified in the United States include New Delhi metallo- β -lactamases (NDMs), Verona integron-encoded metallo- β -lactamases (VIMs), imipenem-hydrolyzing metallo- β -lactamases (IMPs), and oxacillinases (e.g., OXA-48-like) [193, 194]. Knowledge of whether a CRE isolate is carbapenemase-producing and, if it is, the specific carbapenemase produced is important in guiding treatment decisions.

Phenotypic tests such as the modified carbapenem inactivation method differentiate carbapenemase and non-carbapenemase-producing CRE [195]. Molecular testing can identify specific carbapenemase gene families (e.g., differentiating *bla*_{KPC} from *bla*_{OXA-48-like} genes). Carbapenemase phenotypic and/or genotypic testing are performed by a minority of clinical microbiology laboratories, but the panel strongly encourages all clinical microbiology

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

laboratories to pursue carbapenemase testing to inform optimal treatment decisions.

Treatment suggestions for CRE infections listed below assume that in vitro activity of preferred and alternative antibiotics has been demonstrated.

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

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

Rationale

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

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

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

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

Rationale

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

A single dose of an aminoglycoside is an alternative option for CRE uncomplicated cystitis. Aminoglycosides are almost exclusively eliminated by the renal route in their active form. A single IV dose is generally effective for cystitis, with minimal toxicity [27]. Individual aminoglycosides are equally effective if susceptibility is demonstrated. In general, higher percentages of CRE clinical isolates are susceptible to amikacin and plazomicin than to other aminoglycosides [196, 197]. Plazomicin may remain active against isolates resistant to other aminoglycosides [198].

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

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

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

Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are alternative options for uncomplicated CRE cystitis. They are designated alternative agents to preserve their activity for more invasive CRE infections. Data are insufficient to favor one agent over the others but all of these agents are reasonable treatment options based on published comparative effectiveness studies [117, 201-205].

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

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

Rationale

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

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

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

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

Suggested approach: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for infections outside of the urinary tract caused by CRE, when carbapenemase testing results are either not available or negative. For patients with CRE infections who within the previous 12 months have received medical care in countries with a relatively high prevalence of metallo- β -lactamase-producing organisms or who have previously had a clinical or surveillance culture where a metallo- β -lactamase-producing isolate was identified, preferred treatment options include the combination of ceftazidime-avibactam plus aztreonam, or cefiderocol as monotherapy, while awaiting AST results to the novel β -lactam agents and carbapenemase testing results.

Rationale

The CDC characterized over 42,000 CRE isolates collected from between 2017-2019 and found that approximately 35% of CRE clinical or surveillance isolates in the United States carry one of the main five carbapenemase genes [191]. Of these 35% of isolates, the specific prevalence by carbapenemase gene family is as follows: *bla*_{KPC} (86%), *bla*_{NDM} (9%), *bla*_{VIM} (<1%), *bla*_{IMP} (1%), or *bla*_{OXA-48-like} (4%) [191]. A separate cohort of 1,040 clinical and surveillance CRE isolates from across the United States demonstrated that 59% of isolates were carbapenemase producing, with the distribution of carbapenemase genes relatively similar: *bla*_{KPC} (92%), *bla*_{NDM} (3%), *bla*_{VIM} (<1%), *bla*_{IMP} (<1%), and *bla*_{OXA-48-like} (3%) [192].

Ceftazidime-avibactam has activity against most KPC- and OXA-48-like-producing CRE isolates [206, 207]. Meropenem-vaborbactam and imipenem-cilastatin-relebactam are active against most Enterobacterales that produce KPC enzymes but not those that produce OXA-48-like carbapenemases[208-216]. Neither ceftazidime-avibactam, meropenem-vaborbactam, nor imipenem-cilastatin-relebactam have activity against metallo- β -lactamase (e.g., NDM) producing Enterobacterales. As described above, the vast majority of CRE clinical isolates in the

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

Cefiderocol is suggested as an alternative treatment option for CRE infections outside of the urine. Cefiderocol is a synthetic conjugate composed of a cephalosporin moiety and a catechol-type siderophore, which binds to iron and facilitates bacterial cell entry using active iron transporters [219]. Once inside the periplasmic space, the cephalosporin moiety dissociates from iron and binds primarily to PBP3 to inhibit bacterial cell wall synthesis [220]. Cefiderocol is highly likely to be active against CRE clinical isolates as it exhibits activity against Enterobacterales producing any of the five major carbapenemase enzymes, as well as CRE isolates not producing carbapenemases [217, 221]. In an effort to preserve cefiderocol activity for infections caused by pathogens where other β -lactam agents may have little to no activity, such as those caused by metallo- β -lactamase-producing Enterobacterales or by non-fermenting gram-negative organisms, the panel suggests cefiderocol as an alternative agent for infections caused by non-metallo- β -lactamase producing CRE. Patients with CRE infections who have received medical care in countries with a relatively high prevalence of metallo- β -lactamase-producing CRE within the previous 12 months [222] or who previously had a clinical or surveillance culture where metallo- β -lactamase-producing organisms were identified have a high likelihood of being infected with metallo- β -lactamase-producing Enterobacterales. For such patients (if carbapenemase results are not yet available), preferred treatment options include the combination of ceftazidime-avibactam plus aztreonam, or cefiderocol as monotherapy ([Question 3.6](#)).

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

Previously, it was considered standard practice to administer extended-infusion meropenem in combination with a second agent, frequently polymyxins or aminoglycosides, for

the treatment of infections caused by CRE isolates with meropenem MICs as high as 8-16 µg/mL [223]. PK/PD data suggested that extended-infusion meropenem may remain active against infections caused by organisms with carbapenem MICs in this range [224-226]. However, subsequent observational and trial data indicate increased mortality and excess nephrotoxicity associated with polymyxin or aminoglycoside-based regimens relative to newer β-lactam-β-lactamase inhibitor agents for the treatment of CRE infections [227-238]. Therefore, the panel advises against the use of extended-infusion carbapenems with or without the addition of a second agent for the treatment of CRE infections.

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

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

Rationale

Preferred agents for KPC-producing infections include meropenem-vaborbactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam [206, 208-213, 239, 240]. Although all three agents are preferred agents for the treatment of KPC-producing infections, the panel slightly favors meropenem-vaborbactam, followed by ceftazidime-avibactam, and then imipenem-cilastatin-relebactam, based on available data regarding clinical outcomes and emergence of resistance. These agents are associated with improved clinical outcomes and reduced toxicity compared to other regimens commonly used to treat KPC-producing infections, which are often polymyxin-based [227-236, 239]. Clinical trials comparing these agents to each other for the treatment of KPC-producing infections are not available.

An observational study compared the clinical outcomes of patients who received either meropenem-vaborbactam or ceftazidime-avibactam for at least 72 hours for the treatment of CRE infections [241]. Carbapenemase status was largely unavailable. Clinical cure and 30-day mortality between the 26 patients who received meropenem-vaborbactam and 105 patients who received ceftazidime-avibactam were at 85% and 61% (limited to patients with isolates exhibiting susceptibility to the agent administered) and 12% and 19%, respectively. Although these differences were not statistically significant, they numerically favor meropenem-vaborbactam. Of patients who experienced recurrent CRE infections, 0% (0 of 3) of patients receiving meropenem-vaborbactam and 20% (3 of 15) patients receiving ceftazidime-avibactam had subsequent CRE isolates that developed resistance to initial therapy. This study had a number of important limitations: likely selection bias due to its observational nature, relatively small numbers of patients, heterogenous sites of CRE infection, more than half of patients had

polymicrobial infections, and more than half of patients received additional antibiotic therapy. These limitations notwithstanding, this study suggests that both meropenem-vaborbactam and ceftazidime-avibactam are reasonable treatment options for KPC-producing infections, although the emergence of resistance may be more common with ceftazidime-avibactam ([Question 3.8](#)). At least two groups that have published their clinical experiences with the use of ceftazidime-avibactam and meropenem-vaborbactam similarly found that patients who received meropenem-vaborbactam had a slightly higher likelihood of clinical cure and survival and a lower risk of emergence of resistance than patients treated with ceftazidime-avibactam[242-245].

Limited clinical data are available for imipenem-cilastatin-relebactam compared with the other novel β -lactam- β -lactamase inhibitor agents. A clinical trial including patients with infections caused by gram-negative organisms not susceptible to imipenem assigned patients to receive either imipenem-cilastatin-relebactam versus imipenem-cilastatin and colistin [230]. Of patients with Enterobacterales infections, 40% (2 of 5 patients) and 100% (2 of 2 patients) experienced a favorable clinical response with imipenem-cilastatin-relebactam and imipenem-cilastatin in combination with colistin, respectively [230]. It is difficult to draw meaningful conclusions from these data given the small numbers. However, in vitro activity of imipenem-cilastatin-relebactam against CRE [215, 246-249], clinical experience with imipenem-cilastatin, and the stability of relebactam as a β -lactamase inhibitor [250] suggest imipenem-cilastatin-relebactam is likely to be effective for CRE infections if it tests susceptible.

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

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

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

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

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

Rationale

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

An observational study of 102 adults with bloodstream infections caused by metallo- β -lactamase-producing Enterobacterales compared the outcomes of 52 patients receiving ceftazidime-avibactam in combination with aztreonam versus 50 patients receiving a combination of other agents, primarily polymyxin or tigecycline-based therapy [256]. Thirty-day mortality was 19% for the ceftazidime-avibactam/aztreonam group and 44% for the alternate arm, highlighting the potential clinical benefit with the former. Strategies for administering the combination of ceftazidime-avibactam and aztreonam are reviewed in [Table 1 and Supplemental Material](#) [267-269]. Patients should be monitored closely for elevations in liver enzymes[270]. In rare situations where cefiderocol or combination therapy with ceftazidime-avibactam and aztreonam is not possible (e.g., allergy or intolerance), combination therapy

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

A second preferred option for the treatment of NDM and other metallo- β -lactamase-producing Enterobacterales is cefiderocol. Surveillance data indicate that NDM-producing Enterobacterales isolates have a higher cefiderocol MIC₉₀ than isolates producing serine β -lactamases, although this is not always associated with frank cefiderocol resistance [221, 273]. Cefiderocol was active against 58% of 12 international NDM-producing CRE isolates [221]. A separate cohort found that cefiderocol was active against 83% of 29 NDM-producing CRE isolates[217]. Two clinical trials including patients with metallo- β -lactamase producing infections (not limited to the Enterobacterales) found that clinical cure occurred in 71% (17 of 24) and 40% (4 of 10) of patients receiving cefiderocol versus alternate therapy (primarily polymyxin-based therapy), respectively[257]. Day 28 mortality occurred in 13% (3 of 24) and 50% (5 of 10) of patients, respectively[257]. Clinical outcomes data comparing ceftazidime-avibactam in combination with aztreonam versus cefiderocol are not available.

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

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

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

Rationale

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

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

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

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

Rationale

As with most antibiotic agents, treatment with any β -lactam agents active against CRE (i.e., ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol) increases the likelihood that subsequent isolates causing infection will no longer be effectively treated with these agents. The most data on the emergence of resistance of novel agents to CRE focuses on KPC-producing isolates. The emergence of resistance to ceftazidime-avibactam most commonly occurs because of mutations in the *bla*_{KPC} gene translating to amino acid changes in the KPC carbapenemase [279-300]. Changes in permeability and efflux are the primary drivers of the emergence of resistance to meropenem-vaborbactam [210, 244, 288, 292, 301-306] and imipenem-cilastatin-relebactam [307-309]. Increases in *bla*_{KPC} copy numbers have been associated with resistance to all of these agents[310-312].

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

Estimates of the emergence of resistance after clinical exposure to ceftazidime-avibactam and meropenem-vaborbactam are approximately 10-20% [231, 235, 245, 283] and 3% [241, 244, 323], respectively. The most data are available for ceftazidime-avibactam, in part because it was the first of the novel β -lactam agents active against CRE to receive approval from the United States Food and Drug Administration (FDA). Limited data exist on the

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

The panel recommends always repeating AST for the newer β -lactams when a patient previously infected with a CRE presents with a sepsis-like picture suggestive of a new or relapsed infection. Furthermore, if a patient was recently treated with ceftazidime-avibactam and presents with a sepsis-like condition, the panel suggests considering use of a different novel β -lactam agent at least until culture and AST data are available. For example, if a patient with a KPC-producing bloodstream infection received a treatment course of ceftazidime-avibactam one month earlier and presents to medical care with symptoms suggestive of infection, consider administering an agent such as meropenem-vaborbactam until organism and AST results are available.

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

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

Rationale

Tetracycline derivatives function independent of the presence or type of carbapenemase. More specifically, both carbapenemase-producing (e.g., KPC, NDM, OXA-48-like carbapenemases) and non-carbapenemase-producing CRE may test susceptible to these agents [209, 217, 324]. The tetracycline-derivative agents achieve rapid tissue distribution following administration, resulting in limited urine and serum concentrations [325]. Therefore, the panel suggests avoiding their use for urinary and bloodstream infections. Tigecycline or eravacycline can be considered as alternative options for intra-abdominal infections, skin and soft tissue infections, osteomyelitis, and respiratory infections when optimal dosing is used ([Table 1](#)).

Tigecycline has more published experience available for the treatment of CRE infections compared with eravacycline [326-329]. A meta-analysis of 15 clinical trials suggested that tigecycline monotherapy is associated with higher mortality than alternative regimens used for the treatment of pneumonia, not exclusively limited to pneumonia caused by the Enterobacterales [330]. Subsequent investigations have demonstrated that when high-dose tigecycline is prescribed (200 mg IV as a single dose followed 100 mg IV every 12 hours) mortality differences between tigecycline and comparator agents may no longer be evident [331-333]. Thus, if tigecycline is prescribed for the treatment of CRE infections, the panel recommends that high-dosages be administered [334] ([Table 1](#)).

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

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

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

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

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

Rationale

Observational and clinical data indicate increased mortality and excess nephrotoxicity associated with polymyxin-based regimens relative to comparator agents [227-235]. Concerns about the clinical effectiveness of polymyxins and accuracy of polymyxin susceptibility testing led the CLSI to eliminate a susceptible category for colistin and polymyxin B [16]. The panel suggests that these agents be avoided for the treatment of CRE infections, with the exception of colistin as an alternative agent against CRE cystitis. Polymyxin B should not be used as treatment for CRE cystitis, due to its predominantly nonrenal clearance [200].

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

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

Rationale

Although empiric combination antibiotic therapy increases the likelihood that at least one active therapeutic agent for patients at risk for CRE infections is being administered, data do not indicate that continued combination therapy—once the β -lactam agent has demonstrated in vitro activity—offers any additional benefit [343]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [343].

Randomized trial data are not available comparing the novel β -lactam agents as monotherapy and as a component of combination therapy (e.g., ceftazidime-avibactam versus ceftazidime-avibactam and tobramycin). An observational study compared the clinical outcomes of 165 patients receiving ceftazidime-avibactam and 412 patients receiving ceftazidime-avibactam plus a second agent for the treatment of KPC-producing infections [242]. Thirty-day mortality was essentially identical at approximately 25% in both study arms.

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

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

The CDC reports that 32,600 cases of multidrug-resistant (MDR)-*P. aeruginosa* infections occurred in patients hospitalized in the United States in 2017, resulting in 2,700 deaths [188]. MDR- *P. aeruginosa* is defined as *P. aeruginosa* not susceptible to at least one antibiotic in at least three antibiotic classes for which *P. aeruginosa* susceptibility is generally expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems [344]. In 2018, the concept of “difficult-to-treat” resistance was proposed [345]. In this guidance document, DTR is defined as *P. aeruginosa* exhibiting non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.

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

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

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

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

Suggested approach: When *P. aeruginosa* isolates test susceptible to both traditional non-carbapenem β -lactam agents (i.e., 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 agent as high-dose extended-infusion therapy is suggested, and repeat AST is encouraged. For critically ill patients or those with poor source control with *P. aeruginosa* isolates resistant to carbapenems but susceptible to traditional β -lactams, use of a novel β -lactam agent that tests susceptible (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam) is also a reasonable treatment approach.

Rationale

In general, when a *P. aeruginosa* isolate tests susceptible to multiple traditional β -lactam agents (i.e., piperacillin-tazobactam, ceftazidime, cefepime, aztreonam), fluoroquinolones (i.e., ciprofloxacin, levofloxacin), or carbapenems, the panel prefers an agent from the former two 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 (e.g., meropenem or imipenem-cilastatin MICs ≥ 4 $\mu\text{g/mL}$) but susceptible to other traditional non-carbapenem β -lactam agents ([Table 2](#)) constitute approximately 20% to 60% of carbapenem-resistant *P. aeruginosa* isolates [354-360]. This phenotype is generally due to lack of or limited production of OprD, which normally facilitates entry of carbapenem agents into *P. aeruginosa*, with or without overexpression of efflux pumps [356-359]. Comparative effectiveness studies to guide treatment decisions for infections caused by *P. aeruginosa* resistant to carbapenems but susceptible to traditional non-carbapenem β -lactams are not available. When confronted with these scenarios, the panel suggests AST to confirm antibiotic MICs. If the isolate remains

susceptible to a traditional non-carbapenem β -lactam (e.g., cefepime) on repeat testing, the panel's preferred approach is to administer the non-carbapenem agent as high-dose extended-infusion therapy (e.g., cefepime 2 g IV every 8 hours, infused over at least 3 hours); ([Table 1](#)).

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

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

Suggested approach: Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are the preferred treatment options for uncomplicated cystitis caused by DTR-*P. aeruginosa*. A single-dose of tobramycin or amikacin is an alternative treatment for uncomplicated cystitis caused by DTR-*P. aeruginosa*.

Rationale

Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for uncomplicated DTR-*P. aeruginosa* cystitis, based on clinical trials showing non-inferiority of these agents to common comparator agents for the treatment of UTIs [117, 203-205, 361]. Data are insufficient to favor one of these agents over the others for the treatment of uncomplicated cystitis, and available trials generally do not include patients infected by pathogens with DTR phenotypes. Additional information comparing these agents is described in [Question 4.4](#). The suggested approach for the treatment of uncomplicated cystitis caused by DTR-*P. aeruginosa* isolates confirmed to produce metallo- β -lactamase enzymes (e.g., *bla*_{VIM}) is reviewed in [Question 4.5](#).

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

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

Colistin, but not polymyxin B, is an alternate consideration for treating DTR-*P. aeruginosa* cystitis as it converts to its active form in the urinary tract [199]. Clinicians should remain cognizant of the associated risk of nephrotoxicity. The panel does not recommend the use of oral fosfomicin for DTR-*P. aeruginosa* cystitis as it is associated with a high likelihood of clinical failure [19, 363]. This is in part due to the presence of the *fosA* gene, which is intrinsic to *P. aeruginosa* [28].

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

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

Rationale

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

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

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

Rationale

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

Summarizing international surveillance data, ceftolozane-tazobactam [364, 366, 367, 369-379, 390], ceftazidime-avibactam [365, 378-390], and imipenem-cilastatin-relebactam [247, 249, 307, 390-405] are active against approximately 76%, 74%, and 69% of carbapenem-resistant *P. aeruginosa* isolates, respectively, with lower percent susceptibilities exhibited by isolates from patients with cystic fibrosis [419, 420]. Available surveillance data generally represent time periods before the novel agents were used clinically and likely overestimate susceptibility percentages observed in clinical practice. Regional differences in susceptibility estimates across the newer agents exist. The panel suggests always obtaining AST results for DTR-*P. aeruginosa* infections to guide treatment decisions.

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

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

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

of ceftazidime-avibactam against comparators are lacking. However, pooled data from five trials explored differences in clinical responses for patients with MDR-*P. aeruginosa* infections receiving ceftazidime-avibactam versus more traditional regimens with a favorable clinical response observed in 57% (32 of 56 patients) versus 54% (21 of 39) of patients in the two treatment arms, respectively [424]. Only 66% of isolates were susceptible to ceftazidime-avibactam making interpretation of the results challenging [424]. A clinical trial including 24 patients infected with imipenem-non-susceptible *P. aeruginosa* identified a favorable clinical response in 81% of patients receiving imipenem-cilastatin-relebactam compared to 63% receiving imipenem-cilastatin in combination with colistin [230]. While not achieving statistical significance, potentially due to the small sample size, the numerical differences suggest improved outcomes with use of imipenem-cilastatin-relebactam over more traditional regimens.

Cefiderocol is suggested as an alternative treatment option for DTR-*P. aeruginosa* infections outside of the urine. Combining data from 1,500 carbapenem-non-susceptible *P. aeruginosa* isolates in surveillance studies, over 97% of isolates exhibited susceptibility to cefiderocol (i.e., MICs ≤ 4 $\mu\text{g/mL}$) [115, 183, 221, 425-429]. Similar to the novel β -lactam- β -lactamase inhibitors, percent susceptibility to cefiderocol is likely to be reduced after widespread use of this agent.

A clinical trial compared the outcomes of patients with infections due to carbapenem-resistant organisms treated with cefiderocol versus alternative therapy, which largely consisted of polymyxin-based therapy [205]. The trial included 22 unique patients with 29 carbapenem-resistant *P. aeruginosa* infections [430]. Mortality at the end of therapy was 18% in both the cefiderocol and alternative therapy arms for patients infected with *P. aeruginosa*. This trial suggests that cefiderocol performs as well as agents that were previously the mainstay of treatment against DTR-*P. aeruginosa* in the past (i.e., combinations of extended-infusion meropenem, polymyxins, and aminoglycosides) but may not be associated with improved outcomes, as has been observed with some of the newer β -lactam- β -lactamase inhibitors [230, 406]. Despite the high DTR-*P. aeruginosa* susceptibility to cefiderocol, the panel suggests

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

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

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

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

Rationale

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

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

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

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

avibactam and aztreonam have activity against <10% of metallo- β -lactamase-producing *P. aeruginosa*[435].

Question 4.6: What is the likelihood of the emergence of resistance of DTR-*P. aeruginosa* isolates to the newer β -lactam agents when used to treat DTR-*P. aeruginosa* infections?

Suggested approach: The emergence of resistance is a concern with all β -lactams used to treat DTR-*P. aeruginosa* infections. Available data suggest the frequency may be the highest for ceftolozane-tazobactam and ceftazidime-avibactam.

Rationale

As with most antibiotic agents, treatment of DTR-*P. aeruginosa* with any of the newer β -lactam agents (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol) increases the likelihood that subsequent infections will no longer be effectively treated with these agents. The emergence of resistance to ceftolozane-tazobactam most commonly occurs because of amino acid substitutions, insertions, or deletions in PDCs [368, 422, 437-448]. These alterations occur most commonly in or adjacent to a particular region of the PDC known as the “omega loop.” Similarly, acquired resistance of *P. aeruginosa* to ceftazidime-avibactam is most frequently the result of alterations in PDCs [437, 439, 440, 442, 445, 447-450].

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

Based on available data thus far, the emergence of resistance of *P. aeruginosa* to novel β -lactams appears most concerning for ceftolozane-tazobactam and ceftazidime-avibactam. Cross-resistance between these agents is high because of structural similarities. In a cohort of 28 patients with DTR-*P. aeruginosa* infections treated with ceftolozane-tazobactam, 50% of patients were infected with subsequent DTR-*P. aeruginosa* isolates no longer susceptible to ceftolozane-tazobactam [448]. Remarkably, over 80% of patients with index isolates susceptible

to ceftazidime-avibactam had subsequent isolates with high-level resistance to ceftazidime-avibactam after ceftolozane-tazobactam exposure, and in the absence of ceftazidime-avibactam exposure. Another cohort study including 23 patients with index and subsequent *P. aeruginosa* isolates after ceftolozane-tazobactam described a similar experience [447]. Treatment-emergent PDC changes were identified in 79% of paired isolates.

Limited data on the frequency of emergence of resistance to imipenem-cilastatin-relebactam exist. However, one report identified the emergence of non-susceptibility to this agent in 26% (5 of 19) of patients receiving imipenem-cilastatin-relebactam for the treatment of *P. aeruginosa* infections[451]. Similarly, estimates of the frequency of the emergence of resistance of *P. aeruginosa* to cefiderocol since its clinical introduction are incomplete but in a clinical trial, three of 12 carbapenem-resistant isolates had at least 4-fold increases in cefiderocol MICs (though not necessarily frank resistance) after exposure to this agent [205].

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

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

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

Rationale

Although empiric combination antibiotic therapy (e.g., the addition of tobramycin to a β -lactam agent) to broaden the likelihood of at least one active agent for patients at risk for DTR-*P. aeruginosa* infections is reasonable, data do not indicate that continued combination therapy—once the β -lactam agent has demonstrated in vitro activity—offers any additional benefit over monotherapy with the β -lactam antibiotic [343]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [343].

Clinical trials comparing ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol as monotherapy and as a component of combination therapy are not available (e.g., ceftazidime-avibactam versus ceftazidime-avibactam and tobramycin). Based on toxicities associated with aminoglycosides and polymyxins and previous clinical outcomes data not demonstrating a benefit with the use of combination therapy for *P. aeruginosa* infections[343], the panel does not suggest that combination therapy be routinely administered for DTR-*P. aeruginosa* infections when susceptibility to a preferred β -lactam agent has been demonstrated.

If no preferred agent demonstrates activity against DTR-*P. aeruginosa*, tobramycin (if susceptibility is demonstrated) can be considered in combination with either ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol, preferentially selecting the β -lactam agent for which the MIC is closest to its susceptibility breakpoint. For example, if ceftolozane-tazobactam and ceftazidime-avibactam MICs against a DTR-*P. aeruginosa* isolate are both >128/4 mcg/mL (highly resistant) and the imipenem-cilastatin-relebactam MIC is 4/4 μ g/mL (intermediate category), imipenem-cilastatin-

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

If tobramycin does not test susceptible, polymyxin B can be considered in combination with a novel β -lactam. Polymyxin B is preferred over colistin for non-urinary tract infections because (1) it is not administered as a prodrug and therefore can achieve more reliable plasma concentrations than colistin, and (2) it has a reduced risk of nephrotoxicity, although limitations across studies preclude accurate determination of the differential risk of nephrotoxicity [455-460].

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

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

Rationale

There have been conflicting findings for the clinical effectiveness of nebulized antibiotics for the treatment of gram-negative pneumonia in observational studies [461-488]. At least three clinical trials investigated the outcomes of patients with gram-negative ventilator-associated pneumonia comparing nebulized antibiotics versus placebo. All three trials allowed for the use of systemic antibiotics, at the discretion of the treating clinician. In brief, one trial compared the outcomes of 100 adults with pneumonia (34% caused by *P. aeruginosa*) treated with nebulized colistin versus placebo [489]; a second trial compared the outcomes of 142 adults with pneumonia (22% caused by *P. aeruginosa*) treated with nebulized amikacin/fosfomycin versus placebo [490]; and the third trial compared the outcomes of 508 adults with pneumonia (32% caused by *P. aeruginosa*) treated with nebulized amikacin versus placebo [491]. None of the three clinical trials demonstrated improved clinical outcomes or a survival benefit with the use of nebulized antibiotics compared with placebo for the treatment of ventilator-associated pneumonia, including in a subgroup analyses of patients with drug-resistant pathogens [489-491]. A meta-analysis of 13 trials including 1,733 adults with ventilator-associated pneumonia indicated that the addition of nebulized antibiotics was associated with at least partial resolution of clinical symptoms of infection compared to the control group; however, there was significant heterogeneity among the pathogens involved and the definition of clinical response across studies[492]. No survival benefit, reduction in intensive care unit length of stay, or reduction in ventilator days was observed in patients receiving nebulized antibiotics[492].

Reasons for the lack of clear clinical benefit with nebulized antibiotics in available trials are unclear. In a PK/PD modeling study, aerosolized delivery of the prodrug of colistin to

critically ill patients achieved high active drug levels in epithelial lining fluid of the lungs [493]. However, it is likely that nebulized antibiotics do not achieve sufficient penetration and/or distribution throughout lung tissue to exert significant bactericidal activity [494], likely due in part to the use of parenteral formulations not specifically designed for inhalation in suboptimal delivery devices such as jet nebulizers [495, 496]. Professional societies have expressed conflicting views regarding the role of nebulized antibiotics as adjunctive therapy to IV antibiotics [497-499]. The panel suggests against the use of nebulized antibiotics as adjunctive therapy for DTR-*P. aeruginosa* pneumonia due to the lack of benefit observed in clinical trials, concerns regarding unequal distribution in infected lungs, and concerns for respiratory complications such as bronchoconstriction with use of aerosolized antibiotics [500].

Section 5: Carbapenem-Resistant *Acinetobacter baumannii*

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

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

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

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

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

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

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

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

Rationale

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

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

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

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

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

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

Rationale

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

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

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

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

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

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

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

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

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

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

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

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

Rationale

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

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

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

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

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

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

The antibiotic sulbactam-durlobactam completed phase 3 clinical studies but is not currently FDA-approved at the end date for which data were reviewed for preparation of this document (December 31, 2022)[566]. The proposed dosing of sulbactam-durlobactam provides insights into ampicillin-sulbactam dosing for CRAB infections. Pre-clinical and clinical studies

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

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

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

Rationale

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

The panel advises against polymyxin monotherapy for the following reasons: First, concentrations of polymyxins in serum achieved with conventional dosing strategies are highly variable and may be inadequate for effective bactericidal activity [200]. Second, dosages required to treat systemic infections approach the threshold for nephrotoxicity making the therapeutic window narrow (i.e., ~2 µg/mL may be required to achieve 1-log₁₀ reduction in bacterial growth, but this is also the threshold associated with nephrotoxicity) [573]. Third, the activity of IV polymyxins in pulmonary epithelial lining fluid is suboptimal and generally does not result in adequate bacterial killing in the lungs [574-576]. Finally, there are several reports of clinical failure and resistance emergence during polymyxin monotherapy [572, 577-580].

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

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

Rationale

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

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

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

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

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

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

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

Suggested approach: Ceftiderocol 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 ceftiderocol is used to treat CRAB infections, the panel suggests prescribing the agent as part of a combination regimen.

Rationale

Ceftiderocol is the only novel FDA-approved β -lactam agent with in vitro activity against CRAB isolates. International surveillance studies indicate that approximately 95% of CRAB isolates are susceptible to ceftiderocol using the CLSI susceptibility criteria ≤ 4 $\mu\text{g/mL}$ ([Table 2](#))[220, 273, 427, 428, 603, 604]. Determining CRAB susceptibility to ceftiderocol is challenging, in part due to variable iron concentrations in media. Moreover, MIC results are not always reproducible across methods, with heteroresistance often observed[605, 606]. The percent free time above the MIC of ceftiderocol required for a 1- \log_{10} reduction in *A. baumannii* was higher than for Enterobacterales, *P. aeruginosa*, or *S. maltophilia* in a murine lung infection model[603].

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

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

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

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

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

Rationale

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

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

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

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

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

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

Last updated December 31st, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

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

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

Suggested approach: 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 [461-488]. At least three trials evaluated the outcomes of patients with gram-negative ventilator-associated pneumonia comparing nebulized antibiotics versus placebo. All three trials allowed for the use of systemic antibiotics, at the discretion of the treating clinician. In brief, one trial compared the outcomes of 100 adults with pneumonia (65% caused by *A. baumannii*) treated with nebulized colistin versus placebo [489]; a second trial compared the outcomes of 142 adults with pneumonia (20% caused by *A. baumannii*) treated with nebulized amikacin/fosfomycin versus placebo [490]; and the third trial compared the outcomes of 508 adults with pneumonia (29% caused by *A. baumannii*) treated with nebulized amikacin versus placebo [491]. None of the three clinical trials demonstrated improved clinical outcomes or a survival benefit with the use of nebulized antibiotics compared with placebo for the treatment of ventilator-associated pneumonia, including in subgroup analyses of drug-resistant pathogens [489-491].

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

Reasons for the lack of clinical benefit in these trials are unclear. In a PK/PD modeling study, aerosolized delivery of the prodrug of colistin to critically ill patients achieved high active

drug levels in epithelial lining fluid of the lungs [493]. However, it is likely that nebulized antibiotics do not achieve sufficient penetration and/or distribution throughout lung tissue to exert significant bactericidal activity [494], likely due in part to the use of parenteral formulations not specifically designed for inhalation in suboptimal delivery devices such as jet nebulizers [495, 496]. Professional societies have expressed conflicting views regarding the role of nebulized antibiotics as adjunctive therapy to IV antibiotics [497-499]. The panel suggests against the use of nebulized antibiotics as adjunctive therapy for CRAB pneumonia, due to the lack of benefit observed in clinical trials, concerns regarding unequal distribution in infected lungs, and concerns for respiratory complications such as bronchoconstriction patients receiving aerosolized antibiotics [500].

1 **Section 6: *Stenotrophomonas maltophilia***

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

8 *S. maltophilia* infections pose management challenges very similar to those of CRAB
9 infections. First, although *S. maltophilia* has the potential to cause serious disease, it is often
10 unclear if *S. maltophilia* represents a colonizing organism or a true pathogen, particularly in
11 patients with underlying pulmonary conditions such as cystic fibrosis or ventilator dependency
12 [623-627]. *S. maltophilia* is often recovered as a component of a polymicrobial infection –
13 further challenging the need for targeted *S. maltophilia* therapy [619, 628]. Importantly, *S.*
14 *maltophilia* can be a true pathogen that causes considerable morbidity and mortality in the
15 hematologic malignancy population primarily due to hemorrhagic pneumonia or bacteremia
16 [629-635].

17 Second, treatment selection is hampered by the impressive number of antimicrobial
18 resistance genes and gene mutations carried by *S. maltophilia* isolates [619, 621, 636]. An L1
19 metallo β -lactamase and L2 serine β -lactamase render most conventional β -lactams ineffective
20 against *S. maltophilia*. L1 hydrolyzes penicillins, cephalosporins, and carbapenems, but not
21 aztreonam. L2 has extended cephalosporin activity as well as the ability to hydrolyze aztreonam
22 [619]. *S. maltophilia* exhibits intrinsic resistance to aminoglycosides via chromosomal
23 aminoglycoside acetyl transferase enzymes [637]. Furthermore, *S. maltophilia* can accumulate
24 multidrug efflux pumps that reduce the activity of TMP-SMX, tetracyclines, and
25 fluoroquinolones, and chromosomal *Smqnr* genes that further reduce the effectiveness of
26 fluoroquinolones [638-641].

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

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

42 There are no CLSI susceptibility criteria established for the polymyxins [16, 645].
43 Incomplete *S. maltophilia* growth inhibition often occurs in polymyxin wells, suggestive of
44 heteroresistance. Challenges exist in both the accuracy and reproducibility of polymyxin MICs
45 [646, 647]. The panel does not suggest polymyxins for the treatment of *S. maltophilia*
46 infections. This guidance document focuses on the treatment of moderate-severe *S. maltophilia*
47 infections.

48

49

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

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

57 **Rationale**

58 In situations of *S. maltophilia* infection, either of two approaches are suggested. Firstly,
59 combination therapy with at least two active agents (i.e., TMP-SMX, minocycline/tigecycline,
60 cefiderocol, or levofloxacin) is suggested at least until clinical improvement is observed,
61 primarily because of the limited clinical data supporting any individual agent ([Questions 6.2 to](#)
62 [6.5](#)). Alternatively, the combination of ceftazidime-avibactam and aztreonam can be considered
63 in situations of significant clinical instability, when clinical failure with other agents occurs, or if
64 there is intolerance to other agents ([Question 6.6](#)).

65 In vitro data are conflicting but several investigations suggest synergy between agents
66 with activity against *S. maltophilia* including minocycline, cefiderocol, and fluoroquinolones
67 [648-651]. Clinical outcomes data comparing monotherapy and combination therapy are
68 similarly conflicting and limited to observational studies plagued with concerns such as
69 selection bias, small sample sizes, and significant heterogeneity in patient, microbial, and
70 treatment characteristics [652-654]. As this document focuses on moderate-severe disease due
71 to *S. maltophilia*, the panel favors combination therapy to increase the likelihood that at least
72 one active agent is being administered.

73

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

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

78 **Rationale**

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

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

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

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

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

113 Acknowledging the paucity of clinical data supporting this suggestion, the panel still
114 considers TMP-SMX a preferred treatment option for *S. maltophilia* infections, given the long-
115 standing experience with its use and no clear clinical failure signals. As described in [Question](#)
116 [6.1](#), when prescribing TMP-SMX for *S. maltophilia* infections, the addition of a second agent
117 (e.g., minocycline/tigecycline, cefiderocol, levofloxacin), at least until clinical improvement is
118 observed, is suggested.

119

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

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

129 **Rationale**

130 Tetracycline derivatives generally have low MICs when tested against *S. maltophilia*
131 [651, 670-673]. Surveillance studies report that minocycline and tigecycline have activity
132 against approximately 70-90% of *S. maltophilia* isolates, with a lower (and hence, more
133 favorable) MIC₉₀ generally observed for minocycline [651, 670-673]. Amongst tetracycline
134 derivatives, CLSI susceptibility criteria are only available for minocycline [16]. Greater than 90%
135 target attainment is achieved with minocycline dosages of 100 mg IV every 12 hours compared
136 to approximately 75% target attainment with tigecycline dosed at 100 mg IV every 12 hours
137 [671]. Both minocycline and tigecycline have extensive penetration into lung tissue [674-677].

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

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

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

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

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

171

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

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

176 **Rationale**

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

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

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

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

201 **Rationale**

202 *S. maltophilia* isolates frequently harbor *Smqnr* resistance determinants that interfere
203 with fluoroquinolone binding to gyrase and topoisomerase, leading to increased
204 fluoroquinolone MICs [621, 638]. Fluoroquinolone MICs may increase further as a result of
205 overexpression of multidrug-resistant efflux pumps [655, 692-694]. Baseline susceptibility
206 percentages of *S. maltophilia* to levofloxacin vary from approximately 30% to 80% in
207 surveillance studies [650, 651, 673, 695]. Several studies have shown that *S. maltophilia* isolates
208 that test susceptible to levofloxacin can develop elevated levofloxacin MICs during therapy
209 [661, 664, 666, 696]. CLSI susceptibility criteria exist for levofloxacin against *S. maltophilia*, but
210 not for ciprofloxacin or moxifloxacin [16]. In January 2023, the CLSI elected to include a
211 comment suggesting levofloxacin should be used only as a component of combination therapy
212 for the treatment of *S. maltophilia* infections[16].

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

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

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

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

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

258

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

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

264 **Rationale**

265 The combination of ceftazidime-avibactam and aztreonam can be used to overcome the
266 activity of both the L1 and L2 β -lactamases intrinsic to *S. maltophilia* [621, 704-709]. The L1
267 metallo- β -lactamase hydrolyzes ceftazidime but not aztreonam. The L2 serine β -lactamase
268 hydrolyzes ceftazidime and aztreonam but is inactivated by avibactam. Therefore, the
269 combination of ceftazidime-avibactam and aztreonam enables aztreonam to bypass
270 inactivation and successfully reach its target PBPs of *S. maltophilia*. Despite limited available
271 clinical data with this combination for the treatment of *S. maltophilia* infections [706, 710, 711],
272 the combination of ceftazidime-avibactam and aztreonam [267, 269] is a reasonable treatment
273 option for moderate to severe infections, such as pneumonia or bloodstream infections in the
274 hematologic malignancy population, as well as in situations where intolerance or resistance to
275 other agents precludes their use. Strategies for administering the combination of ceftazidime-
276 avibactam and aztreonam are reviewed in [Table 1 and Supplemental Material](#) [267-269].
277 Patients should be monitored closely for elevations in liver enzymes[270]. Although several
278 groups have described methods used to test susceptibility with this combination of agents[259-
279 266], the CLSI does not currently endorse a specific approach to test in vitro activity with this
280 combination[16].

281

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

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

287 **Rationale**

288 The panel does not suggest prescribing ceftazidime for the treatment of *S. maltophilia*
289 infections, as intrinsic L1 and L2 β -lactamases are expected to render it ineffective. Almost 30-
290 40% of *S. maltophilia* isolates test susceptible to ceftazidime using CLSI interpretive criteria;
291 however, due to insufficient data to reevaluate ceftazidime breakpoints, “susceptibility” is likely
292 not reflective of clinical success [673, 695]. Ceftazidime MICs against *S. maltophilia* may be
293 inaccurate and non-reproducible using AST methods commonly employed by clinical
294 microbiology laboratories, potentially related to the presence of inactivating β -lactamases [643,
295 644]. Avibactam (i.e., ceftazidime-avibactam) is not likely to expand the activity of ceftazidime
296 against *S. maltophilia*, in the absence of aztreonam. In vitro models suggest ceftazidime is
297 unable to substantively prevent *S. maltophilia* growth [651]. Comparative effectiveness studies
298 evaluating the role of ceftazidime against *S. maltophilia* infections are virtually non-existent
299 [712]. Local clinical microbiology laboratories and antibiotic stewardship teams are encouraged
300 to convey the likely ineffectiveness of ceftazidime against *S. maltophilia* to clinicians, even
301 when it tests susceptible.

302

303 Conclusions

304 The field of AMR is dynamic and rapidly evolving, and the treatment of antimicrobial
305 resistant infections will continue to challenge clinicians. As newer antibiotics against resistant
306 pathogens are incorporated into clinical practice, we are learning more about their
307 effectiveness and propensity to resistance. This treatment guidance focusing on ESBL-E, AmpC-
308 E, CRE, and DTR-*P. aeruginosa*, CRAB, and *S. maltophilia* will be updated approximately annually
309 and is available at: <https://www.idsociety.org/practice-guideline/amr-guidance/>.

310

311

312

313

314

315

316

317

318

319

320

321

322

323

324

325

326

Notes

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

Conflict of Interest Summary: The following list includes what has been reported to IDSA. To provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guidance topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the Board of Directors liaison to the Standards and Practice Guidelines Committee and, if necessary, the Conflicts of Interest and Ethics Committee. The assessment of disclosed relationships for possible conflicts of interests is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). IDSA requests panel members to disclose activities and financial relationships/investments related to consultant/advisory roles, promotional speakers bureau, stocks/bonds, honoraria, expert testimony, ownership interest, research grants, organizational benefits, intellectual property, other numeration, activities with other organizations, and relevant financial interest of family members. Readers of this guidance should be mindful of this when the list of disclosures is reviewed. **S.L.A.** serves as a scientific advisor for Shionogi, Basilea Pharmaceutica, and GSK; served as a scientific advisor for Entasis Therapeutics, Merck, Paratek Pharmaceuticals, The Medicines Company, Zavante, Shionogi, Cempra, Theravance, bioMérieux, F2G, and AstraZeneca; received research funding from Melinta Therapeutics and Merck; served as a speaker at a non-branded CME-accredited satellite symposium at the MAD-ID meeting funded by an unrestricted educational grant from Melinta Therapeutics; serves as President-Elect for the Society of Infectious Diseases Pharmacists (SIDP); served as Chair for the SIDP Guidelines Committee and as a faculty member for the Infectious Diseases Board Certification Preparatory Course-American Society of Health-System Pharmacists; serves as

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

Last updated December 31, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Table 2. 2023 Clinical and Laboratory Standards Institute Susceptibility Interpretive Criteria for Select Gram-Negative Organisms and Select Antibiotic Combinations as Suggested in the IDSA AMR Guidance Document¹

Antibiotic	Enterobacterales (µg/mL)	<i>Pseudomonas aeruginosa</i> (µg/mL)	<i>Acinetobacter baumannii</i> (µg/mL)	<i>Stenotrophomonas maltophilia</i> (µg/mL)
Amikacin	≤4	≤16 ²	--	--
Ampicillin-sulbactam	--	--	≤8/4	--
Aztreonam	≤4	≤8	--	--
Cefepime	≤2 ³	≤8	--	--
Cefiderocol	≤4	≤4	≤4	≤1
Ceftazidime	≤4	≤8	--	--
Ceftazidime-avibactam	≤8/4	≤8/4	--	--
Ceftolozane-tazobactam	≤2/4	≤4/4	--	--
Ciprofloxacin	≤0.25	≤0.5	--	--
Colistin or Polymyxin B	-- ⁴	-- ⁴	-- ⁴	--
Doxycycline	≤4	--	--	--
Ertapenem	≤0.5	--	--	--
Fosfomicin	≤64 ⁵	--	--	--
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	≤4
Nitrofurantoin	≤32	--	--	--
Piperacillin-tazobactam	≤8/4 ⁶	≤16/4	--	--
Plazomicin	≤2	--	--	--
Tigecycline	-- ⁷	--	-- ⁸	-- ⁸
Trimethoprim-sulfamethoxazole	≤2/38	--	--	≤2/38
Tobramycin	≤2	≤1	--	--

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

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

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

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

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

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

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

⁸ Neither CLSI nor FDA susceptibility criteria are available.

Last updated December 31, 2022, and posted online at <https://www.idsociety.org/practice-guideline/amr-guidance/>. Please check website for most updated version of this guidance.

References

1. Antimicrobial Resistance C. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* **2022**; 399(10325): 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. Sears CL, File TM, Alexander BD, et al. Charting the Path Forward: Development, Goals and Initiatives of the 2019 Infectious Diseases of America Strategic Plan. *Clin Infect Dis* **2019**; 69(12): e1-e7.
4. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* **2011**; 52(5): e103-20.
5. 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(10): ofab434.
6. Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients, 2012-2017. *N Engl J Med* **2020**; 382(14): 1309-19.
7. Duffy N, Karlsson M, Reses HE, et al. Epidemiology of extended-spectrum beta-lactamase-producing Enterobacterales in five US sites participating in the Emerging Infections Program, 2017. *Infect Control Hosp Epidemiol* **2022**; 43(11): 1586-94.
8. Tamma PD, Sharara SL, Pana ZD, et al. Molecular Epidemiology of Ceftriaxone Non-Susceptible Enterobacterales Isolates in an Academic Medical Center in the United States. *Open Forum Infect Dis* **2019**; 6(8): ofz353.
9. 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(6).
10. 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(2): ofad038.
11. Bush K, Bradford PA. Epidemiology of beta-Lactamase-Producing Pathogens. *Clin Microbiol Rev* **2020**; 33(2): e00047-e19.
12. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrob Agents Chemother* **2010**; 54(3): 969-76.
13. Castanheira M, Farrell SE, Krause KM, Jones RN, Sader HS. Contemporary diversity of beta-lactamases among Enterobacteriaceae in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent beta-lactamase groups. *Antimicrob Agents Chemother* **2014**; 58(2): 833-8.
14. Castanheira M, Simner PJ, Bradford PA. Extended-spectrum beta-lactamases: an update on their characteristics, epidemiology and detection. *JAC Antimicrob Resist* **2021**; 3(3): dlab092.

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(2): 358-61.
16. Clinical and Laboratory Standards Institute. M100: Performance Standards for Antimicrobial Susceptibility Testing. 33 ed. Wayne, PA, **2023**.
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(2): dlab019.
18. Mathers AJ, Lewis JS, 2nd. CON: Testing for ESBL production is unnecessary for ceftriaxone-resistant Enterobacterales. *JAC Antimicrob Resist* **2021**; 3(2): 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(17): 1781-9.
20. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med* **2007**; 167(20): 2207-12.
21. Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. *JAMA* **2005**; 293(8): 949-55.
22. Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. *JAMA* **2012**; 307(6): 583-9.
23. Tanne JH. FDA adds "black box" warning label to fluoroquinolone antibiotics. *BMJ* **2008**; 337: a816.
24. 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(5): 2326-32.
25. 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(1): 11-8.
26. 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(9): 1254-60.
27. Goodlet KJ, Benhalima FZ, Nailor MD. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? *Antimicrob Agents Chemother* **2018**; 63(1): e02165-18.
28. Ito R, Mustapha MM, Tomich AD, et al. Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal *fosA* Gene. *mBio* **2017**; 8(4): e00749-17.
29. Elliott ZS, Barry KE, Cox HL, et al. The Role of *fosA* in Challenges with Fosfomycin Susceptibility Testing of Multispecies *Klebsiella pneumoniae* Carbapenemase-Producing Clinical Isolates. *J Clin Microbiol* **2019**; 57(10): e00634-19.
30. 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(3): 1023-6.
31. 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(1).
 32. 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(12): 1457-64.
 33. Mukerji AC, Sharma MM, Taneja OP, Saxena SN, Bhatnagar RK, Ghosh-Ray B. A clinical trial of alpha-6-deoxyxytetracycline (doxycycline) in the treatment of urinary tract infections. *Chemotherapy* **1969**; 14(2): 77-85.
 34. 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.
 35. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylicyclines. *J Antimicrob Chemother* **2006**; 58(2): 256-65.
 36. 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(9840): 484-90.
 37. 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(3): 499-507.
 38. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. *JAMA* **2000**; 283(12): 1583-90.
 39. 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(8): 2307-13.
 40. 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(4): 407-38.
 41. Wagenlehner FME, Cloutier DJ, Komirenko AS, et al. Once-Daily Plazomicin for Complicated Urinary Tract Infections. *N Engl J Med* **2019**; 380(8): 729-40.
 42. 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(2): 221-9.
 43. Karaiskos I, Galani L, Sakka V, et al. Oral fosfomycin for the treatment of chronic bacterial prostatitis. *J Antimicrob Chemother* **2019**; 74(5): 1430-7.
 44. Grayson ML, Macesic N, Trevillyan J, et al. Fosfomycin for Treatment of Prostatitis: New Tricks for Old Dogs. *Clin Infect Dis* **2015**; 61(7): 1141-3.

45. 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(4): e101-5.
46. Kwan ACF, Beahm NP. Fosfomycin for bacterial prostatitis: a review. *Int J Antimicrob Agents* **2020**; 56(4): 106106.
47. 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(11).
48. 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(1): 105935.
49. Harris PNA, Tambyah PA, Lye DC, et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. *JAMA* **2018**; 320(10): 984-94.
50. Zhanel GG, Wiebe R, Dilay L, et al. Comparative review of the carbapenems. *Drugs* **2007**; 67(7): 1027-52.
51. 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(11): 3108-11.
52. 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(2): 277-84.
53. 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(5): 432-6.
54. 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(1): 54-8.
55. 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(1): 150-3.
56. 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(4): 1222-7.
57. 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(4): 340-4.
58. 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**.

59. 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**.
60. Tamma PD, Conley AT, Cosgrove SE, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. *JAMA Intern Med* **2019**; 179(3): 316-23.
61. Punjabi C, Tien V, Meng L, Deresinski S, Holubar M. Oral Fluoroquinolone or Trimethoprim-sulfamethoxazole vs. beta-lactams as Step-Down Therapy for Enterobacteriaceae Bacteremia: Systematic Review and Meta-analysis. *Open Forum Infect Dis* **2019**; 6(10): ofz364.
62. Iregui A, Landman D, Quale J. Activity of Omadacycline and Other Tetracyclines Against Contemporary Gram-Negative Pathogens from New York City Hospitals. *Microb Drug Resist* **2021**; 27(2): 190-5.
63. Noel AR, Attwood M, Bowker KE, MacGowan AP. In vitro pharmacodynamics of omadacycline against *Escherichia coli* and *Acinetobacter baumannii*. *J Antimicrob Chemother* **2021**; 76(3): 667-70.
64. Rodvold KA, Burgos RM, Tan X, Pai MP. Omadacycline: A Review of the Clinical Pharmacokinetics and Pharmacodynamics. *Clin Pharmacokinet* **2020**; 59(4): 409-25.
65. Pfaller MA, Huband MD, Shortridge D, Flamm RK. Surveillance of omadacycline activity tested against clinical isolates from the USA: report from the SENTRY Antimicrobial Surveillance Program, 2019. *J Glob Antimicrob Resist* **2021**; 27: 337-51.
66. Bush K, Macalintal C, Rasmussen BA, Lee VJ, Yang Y. Kinetic interactions of tazobactam with beta-lactamases from all major structural classes. *Antimicrob Agents Chemother* **1993**; 37(4): 851-8.
67. Livermore DM, Andrews JM, Hawkey PM, et al. Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly? *J Antimicrob Chemother* **2012**; 67(7): 1569-77.
68. 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.
69. Paterson DL, Henderson A, Harris PNA. Current evidence for therapy of ceftriaxone-resistant Gram-negative bacteremia. *Curr Opin Infect Dis* **2020**; 33(1): 78-85.
70. 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(2): 326-33.
71. Burgess DS, Hall RG, 2nd. In vitro killing of parenteral beta-lactams against standard and high inocula of extended-spectrum beta-lactamase and non-ESBL producing *Klebsiella pneumoniae*. *Diagn Microbiol Infect Dis* **2004**; 49(1): 41-6.
72. 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(11): O831-9.
73. 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(12): 3548-54.

74. Papp-Wallace KM, Bethel CR, Caillon J, et al. Beyond Piperacillin-Tazobactam: Cefepime and AAI101 as a Potent beta-Lactam-beta-Lactamase Inhibitor Combination. *Antimicrob Agents Chemother* **2019**; 63(5): e00105-19.
75. Chaibi EB, Sirot D, Paul G, Labia R. Inhibitor-resistant TEM beta-lactamases: phenotypic, genetic and biochemical characteristics. *J Antimicrob Chemother* **1999**; 43(4): 447-58.
76. Canton R, Morosini MI, de la Maza OM, de la Pedrosa EG. IRT and CMT beta-lactamases and inhibitor resistance. *Clin Microbiol Infect* **2008**; 14 Suppl 1: 53-62.
77. 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**.
78. Dizbay M, Ozger HS, Karasahin O, Karasahin EF. Treatment efficacy and superinfection rates in complicated urinarytract infections treated with ertapenem or piperacillin tazobactam. *Turk J Med Sci* **2016**; 46(6): 1760-4.
79. 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(4): 410-5.
80. 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(1): 404.
81. 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(7): 4159-69.
82. 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.
83. 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(4): e0153696.
84. 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(9): 1319-25.
85. 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(3): 222-6.
86. 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(2): 167-74.

87. 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(1): 611.
88. 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.
89. 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(2): 305-11.
90. 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.
91. 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(8): 981-5.
92. 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(7): 972-80.
93. Bitterman R, Paul M, Leibovici L, Mussini C. PipEracillin Tazobactam Versus mERoPENem for Treatment of Bloodstream Infections Caused by Cephalosporin-resistant Enterobacteriaceae (PETERPEN). <https://clinicaltrials.gov/ct2/show/NCT03671967>. Accessed December 31, 2022.
94. 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(5): 522-4.
95. 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(2): 470-8.
96. 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(1): 155-8.
97. Wang R, Cosgrove SE, Tschudin-Sutter S, et al. Cefepime Therapy for Cefepime-Susceptible Extended-Spectrum beta-Lactamase-Producing Enterobacteriaceae Bacteremia. *Open Forum Infect Dis* **2016**; 3(3): ofw132.
98. Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. *Clin Infect Dis* **2013**; 56(4): 488-95.
99. Chopra T, Marchaim D, Veltman J, et al. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-beta-lactamase-

- producing *Klebsiella pneumoniae* and *Escherichia coli*. *Antimicrob Agents Chemother* **2012**; 56(7): 3936-42.
100. Zanetti G, Bally F, Greub G, et al. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Antimicrob Agents Chemother* **2003**; 47(11): 3442-7.
 101. Lee NY, Lee CC, Li CW, et al. Cefepime Therapy for Monomicrobial *Enterobacter cloacae* Bacteremia: Unfavorable Outcomes in Patients Infected by Cefepime-Susceptible Dose-Dependent Isolates. *Antimicrob Agents Chemother* **2015**; 59(12): 7558-63.
 102. Lepeule R, Leflon-Guibout V, Vanjak D, et al. Clinical spectrum of urine cultures positive for ESBL-producing *Escherichia coli* in hospitalized patients and impact on antibiotic use. *Med Mal Infect* **2014**; 44(11-12): 530-4.
 103. 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(1): e0022621.
 104. 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(5): 1074-7.
 105. 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.
 106. 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(3): e159-63.
 107. Pilimis 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(8): 1263-5.
 108. 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(9): 5107-13.
 109. 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. *International Journal of Antimicrobial Agents* **2015**; 46(6): 610-5.
 110. 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(1): 427.
 111. 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(1): 121-9.

112. 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(1): 90.
113. Bush K, Bradford PA. Interplay between beta-lactamases and new beta-lactamase inhibitors. *Nat Rev Microbiol* **2019**; 17(5): 295-306.
114. 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(1).
115. Karlowsky JA, Hackel MA, Tsuji M, Yamano Y, Echols R, Sahm DF. In Vitro Activity of Cefiderocol, a Siderophore Cephalosporin, Against Gram-Negative Bacilli Isolated by Clinical Laboratories in North America and Europe in 2015-2016: SIDERO-WT-2015. *Int J Antimicrob Agents* **2019**; 53(4): 456-66.
116. Karlowsky JA, Biedenbach DJ, Kazmierczak KM, Stone GG, Sahm DF. Activity of Ceftazidime-Avibactam against Extended-Spectrum- and AmpC beta-Lactamase-Producing Enterobacteriaceae Collected in the INFORM Global Surveillance Study from 2012 to 2014. *Antimicrob Agents Chemother* **2016**; 60(5): 2849-57.
117. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis* **2016**; 16(6): 661-73.
118. 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(6).
119. 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(6).
120. Fratoni AJ, Colmerauer JL, Linder KE, Nicolau DP, Kuti JL. A Retrospective Case Series of Concomitant Carbapenem and Valproic Acid Use: Are Best Practice Advisories Working? *J Pharm Pract* **2021**: 8971900211063301.
121. Karlowsky JA, Lob SH, Young K, Motyl MR, Sahm DF. Activity of ceftolozane/tazobactam against Gram-negative isolates from patients with lower respiratory tract infections - SMART United States 2018-2019. *BMC Microbiol* **2021**; 21(1): 74.
122. 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(1): 268-72.

123. 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(4): 1166-77.
124. Paterson DL, Bassetti M, Motyl M, et al. Ceftolozane/tazobactam for hospital-acquired/ventilator-associated bacterial pneumonia due to ESBL-producing Enterobacterales: a subgroup analysis of the ASPECT-NP clinical trial. *J Antimicrob Chemother* **2022**; 77(9): 2522-31.
125. Bassetti M, Vena A, Giacobbe DR, et al. Ceftolozane/Tazobactam for Treatment of Severe ESBL-Producing Enterobacterales Infections: A Multicenter Nationwide Clinical Experience (CEFTABUSE II Study). *Open Forum Infect Dis* **2020**; 7(5): ofaa139.
126. Arakawa S, Kawahara K, Kawahara M, et al. The efficacy and safety of tazobactam/ceftolozane in Japanese patients with uncomplicated pyelonephritis and complicated urinary tract infection. *J Infect Chemother* **2019**; 25(2): 104-10.
127. Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ, Antibacterial Resistance Leadership G. A Primer on AmpC beta-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. *Clin Infect Dis* **2019**; 69(8): 1446-55.
128. Jacoby GA. AmpC beta-lactamases. *Clin Microbiol Rev* **2009**; 22(1): 161-82.
129. Eliopoulos GM. Induction of beta-lactamases. *J Antimicrob Chemother* **1988**; 22 Suppl A: 37-44.
130. Bennett PM, Chopra I. Molecular basis of beta-lactamase induction in bacteria. *Antimicrob Agents Chemother* **1993**; 37(2): 153-8.
131. Jacobson KL, Cohen SH, Inciardi JF, et al. The relationship between antecedent antibiotic use and resistance to extended-spectrum cephalosporins in group I beta-lactamase-producing organisms. *Clin Infect Dis* **1995**; 21(5): 1107-13.
132. Honore N, Nicolas MH, Cole ST. Inducible cephalosporinase production in clinical isolates of *Enterobacter cloacae* is controlled by a regulatory gene that has been deleted from *Escherichia coli*. *EMBO J* **1986**; 5(13): 3709-14.
133. Philippon A, Arlet G, Jacoby GA. Plasmid-determined AmpC-type beta-lactamases. *Antimicrob Agents Chemother* **2002**; 46(1): 1-11.
134. Lindberg F, Westman L, Normark S. Regulatory components in *Citrobacter freundii* ampC beta-lactamase induction. *Proc Natl Acad Sci U S A* **1985**; 82(14): 4620-4.
135. Underwood S, Avison MB. *Citrobacter koseri* and *Citrobacter amalonaticus* isolates carry highly divergent beta-lactamase genes despite having high levels of biochemical similarity and 16S rRNA sequence homology. *J Antimicrob Chemother* **2004**; 53(6): 1076-80.
136. Petrella S, Clermont D, Casin I, Jarlier V, Sougakoff W. Novel class A beta-lactamase Sed-1 from *Citrobacter sedlakii*: genetic diversity of beta-lactamases within the *Citrobacter* genus. *Antimicrob Agents Chemother* **2001**; 45(8): 2287-98.
137. Matsen JM, Blazevic DJ, Ryan JA, Ewing WH. Characterization of indole-positive *Proteus mirabilis*. *Appl Microbiol* **1972**; 23(3): 592-4.
138. Choi SH, Lee JE, Park SJ, et al. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC beta-lactamase: implications for antibiotic use. *Antimicrob Agents Chemother* **2008**; 52(3): 995-1000.

139. Chow JW, Fine MJ, Shlaes DM, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* **1991**; 115(8): 585-90.
140. Kaye KS, Cosgrove S, Harris A, Eliopoulos GM, Carmeli Y. Risk factors for emergence of resistance to broad-spectrum cephalosporins among Enterobacter spp. *Antimicrob Agents Chemother* **2001**; 45(9): 2628-30.
141. Hilty M, Sendi P, Seiffert SN, et al. Characterisation and clinical features of Enterobacter cloacae bloodstream infections occurring at a tertiary care university hospital in Switzerland: is cefepime adequate therapy? *Int J Antimicrob Agents* **2013**; 41(3): 236-49.
142. Tamma PD, Girdwood SC, Gopaul R, et al. The use of cefepime for treating AmpC beta-lactamase-producing Enterobacteriaceae. *Clin Infect Dis* **2013**; 57(6): 781-8.
143. Kohlmann R, Bahr T, Gatermann SG. Species-specific mutation rates for ampC derepression in Enterobacteriales with chromosomally encoded inducible AmpC beta-lactamase. *J Antimicrob Chemother* **2018**; 73(6): 1530-6.
144. 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.
145. Seoane A, Francia MV, Garcia Lobo JM. Nucleotide sequence of the ampC-ampR region from the chromosome of Yersinia enterocolitica. *Antimicrob Agents Chemother* **1992**; 36(5): 1049-52.
146. Girlich D, Naas T, Bellais S, Poirel L, Karim A, Nordmann P. Heterogeneity of AmpC cephalosporinases of Hafnia alvei clinical isolates expressing inducible or constitutive ceftazidime resistance phenotypes. *Antimicrob Agents Chemother* **2000**; 44(11): 3220-3.
147. Sanders CC, Bradford PA, Ehrhardt AF, et al. Penicillin-binding proteins and induction of AmpC beta-lactamase. *Antimicrob Agents Chemother* **1997**; 41(9): 2013-5.
148. Weber DA, Sanders CC. Diverse potential of beta-lactamase inhibitors to induce class I enzymes. *Antimicrob Agents Chemother* **1990**; 34(1): 156-8.
149. Livermore DM, Oakton KJ, Carter MW, Warner M. Activity of ertapenem (MK-0826) versus Enterobacteriaceae with potent beta-lactamases. *Antimicrob Agents Chemother* **2001**; 45(10): 2831-7.
150. 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(2): 339-45.
151. 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(7): e0218589.
152. Endimiani A, Doi Y, Bethel CR, et al. Enhancing resistance to cephalosporins in class C beta-lactamases: impact of Gly214Glu in CMY-2. *Biochemistry* **2010**; 49(5): 1014-23.
153. 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(3): 1151-6.
154. 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(2).

155. Hancock RE, Bellido F. Antibacterial in vitro activity of fourth generation cephalosporins. *J Chemother* **1996**; 8 Suppl 2: 31-6.
156. Negri MC, Baquero F. In vitro selective concentrations of cefepime and ceftazidime for AmpC beta-lactamase hyperproducer *Enterobacter cloacae* variants. *Clin Microbiol Infect* **1999**; 5 Suppl 1: S25-S8.
157. Harris PN, Wei JY, Shen AW, et al. Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by *Enterobacter*, *Citrobacter* or *Serratia* species: a systematic review with meta-analysis. *J Antimicrob Chemother* **2016**; 71(2): 296-306.
158. 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.
159. 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(5): 1289-93.
160. Barnaud G, Benzerara Y, Gravisse J, et al. Selection during cefepime treatment of a new cephalosporinase variant with extended-spectrum resistance to cefepime in an *Enterobacter aerogenes* clinical isolate. *Antimicrob Agents Chemother* **2004**; 48(3): 1040-2.
161. Song W, Moland ES, Hanson ND, Lewis JS, Jorgensen JH, Thomson KS. Failure of cefepime therapy in treatment of *Klebsiella pneumoniae* bacteremia. *J Clin Microbiol* **2005**; 43(9): 4891-4.
162. Limaye AP, Gautam RK, Black D, Fritsche TR. Rapid emergence of resistance to cefepime during treatment. *Clin Infect Dis* **1997**; 25(2): 339-40.
163. Charrel RN, Pages JM, De Micco P, Mallea M. Prevalence of outer membrane porin alteration in beta-lactam-antibiotic-resistant *Enterobacter aerogenes*. *Antimicrob Agents Chemother* **1996**; 40(12): 2854-8.
164. Philippon A, Arlet G, Labia R, Iorga BI. Class C beta-Lactamases: Molecular Characteristics. *Clin Microbiol Rev* **2022**; 35(3): e0015021.
165. Siedner MJ, Galar A, Guzman-Suarez BB, et al. Cefepime vs other antibacterial agents for the treatment of *Enterobacter* species bacteremia. *Clin Infect Dis* **2014**; 58(11): 1554-63.
166. Tan SH, Ng TM, Chew KL, et al. Outcomes of treating AmpC-producing *Enterobacterales* bacteraemia with carbapenems vs. non-carbapenems. *Int J Antimicrob Agents* **2020**; 55(2): 105860.
167. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum beta-lactamase Producing *Enterobacterales* (ESBL-E), Carbapenem-Resistant *Enterobacterales* (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P. *aeruginosa*). *Clin Infect Dis* **2021**; 72(7): e169-e83.
168. 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(10): 5058-64.

169. Cheng MP, Lee RS, Cheng AP, et al. Beta-Lactam/Beta-Lactamase Inhibitor Therapy for Potential AmpC-Producing Organisms: A Systematic Review and Meta-Analysis. *Open Forum Infect Dis* **2019**; 6(7): ofz248.
170. 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(5): 560-8.
171. 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(3): 410-4.
172. 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.
173. Derrick C, Bookstaver PB, Lu ZK, et al. Multicenter, Observational Cohort Study Evaluating Third-Generation Cephalosporin Therapy for Bloodstream Infections Secondary to *Enterobacter*, *Serratia*, and *Citrobacter* Species. *Antibiotics (Basel)* **2020**; 9(5).
174. 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.
175. 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(1): 107.
176. Nukaga M, Papp-Wallace KM, Hoshino T, et al. Probing the Mechanism of Inactivation of the FOX-4 Cephamecinase by Avibactam. *Antimicrob Agents Chemother* **2018**; 62(5).
177. Cheng L, Nelson BC, Mehta M, et al. Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC beta-Lactamase-Producing Enterobacteriaceae. *Antimicrob Agents Chemother* **2017**; 61(6): e00276-17.
178. Stewart AG, Paterson DL, Young B, et al. Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC β -Lactamase-Producing *Enterobacter* spp, *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp, or *Serratia marcescens*: A Pilot Multicenter Randomized Controlled Trial (MERINO-2). *Open Forum Infect Dis* **2021**; 8(8): ofab387.
179. Zhanel GG, Lawrence CK, Adam H, et al. Imipenem-Relebactam and Meropenem-Vaborbactam: Two Novel Carbapenem-beta-Lactamase Inhibitor Combinations. *Drugs* **2018**; 78(1): 65-98.
180. Tselepis L, Langley GW, Aboklaish AF, et al. In vitro efficacy of imipenem-relebactam and cefepime-AAI101 against a global collection of ESBL-positive and carbapenemase-producing Enterobacteriaceae. *Int J Antimicrob Agents* **2020**; 56(1): 105925.
181. 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**.

182. 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**.
183. 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(1): 115012.
184. Tato M, Garcia-Castillo M, Bofarull AM, Canton R, Group CS. In vitro activity of ceftolozane/tazobactam against clinical isolates of *Pseudomonas aeruginosa* and Enterobacteriaceae recovered in Spanish medical centres: Results of the CENIT study. *International Journal of Antimicrobial Agents* **2015**; 46(5): 502-10.
185. Robin F, Auzou M, Bonnet R, et al. In Vitro Activity of Ceftolozane-Tazobactam against *Enterobacter cloacae* Complex Clinical Isolates with Different beta-Lactam Resistance Phenotypes. *Antimicrob Agents Chemother* **2018**; 62(9): e00675-18.
186. Stewart AG, Harris PNA, Chatfield MD, Littleford R, Paterson DL. Ceftolozane-tazobactam versus meropenem for definitive treatment of bloodstream infection due to extended-spectrum beta-lactamase (ESBL) and AmpC-producing Enterobacterales ("MERINO-3"): study protocol for a multicentre, open-label randomised non-inferiority trial. *Trials* **2021**; 22(1): 301.
187. Fox MT, Melia MT, Same RG, Conley AT, Tamma PD. A Seven-Day Course of TMP-SMX May Be as Effective as a Seven-Day Course of Ciprofloxacin for the Treatment of Pyelonephritis. *Am J Med* **2017**; 130(7): 842-5.
188. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019, **2019**.
189. Centers for Disease Control and Prevention. Facility Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE): November 2015 Update - CRE Toolkit, **2015**.
190. 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(2): 385-95.
191. 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).
192. 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**.
193. Aitken SL, Tarrand JJ, Deshpande LM, et al. High Rates of Nonsusceptibility to Ceftazidime-avibactam and Identification of New Delhi Metallo-beta-lactamase Production in Enterobacteriaceae Bloodstream Infections at a Major Cancer Center. *Clin Infect Dis* **2016**; 63(7): 954-8.
194. Senchyna F, Gaur RL, Sandlund J, et al. Diversity of resistance mechanisms in carbapenem-resistant Enterobacteriaceae at a health care system in Northern California, from 2013 to 2016. *Diagn Microbiol Infect Dis* **2019**; 93(3): 250-7.

195. Tamma PD, Simner PJ. Phenotypic Detection of Carbapenemase-Producing Organisms from Clinical Isolates. *J Clin Microbiol* **2018**; 56(11): e01140-18.
196. Sutherland CA, Verastegui JE, Nicolau DP. In vitro potency of amikacin and comparators against *E. coli*, *K. pneumoniae* and *P. aeruginosa* respiratory and blood isolates. *Ann Clin Microbiol Antimicrob* **2016**; 15(1): 39.
197. Castanheira M, Davis AP, Mendes RE, Serio AW, Krause KM, Flamm RK. In Vitro Activity of Plazomicin against Gram-Negative and Gram-Positive Isolates Collected from U.S. Hospitals and Comparative Activities of Aminoglycosides against Carbapenem-Resistant Enterobacteriaceae and Isolates Carrying Carbapenemase Genes. *Antimicrob Agents Chemother* **2018**; 62(8): e00313-18.
198. Castanheira M, Sader HS, Mendes RE, Jones RN. Activity of Plazomicin Tested against Enterobacterales Isolates Collected from U.S. Hospitals in 2016-2017: Effect of Different Breakpoint Criteria on Susceptibility Rates among Aminoglycosides. *Antimicrob Agents Chemother* **2020**; 64(5).
199. Sorli L, Luque S, Li J, et al. Colistin for the treatment of urinary tract infections caused by extremely drug-resistant *Pseudomonas aeruginosa*: Dose is critical. *J Infect* **2019**; 79(3): 253-61.
200. Sandri AM, Landersdorfer CB, Jacob J, et al. Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens. *Clin Infect Dis* **2013**; 57(4): 524-31.
201. Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. *Clin Infect Dis* **2016**; 63(6): 754-62.
202. Kaye KS, Bhowmick T, Metallidis S, et al. Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. *JAMA* **2018**; 319(8): 788-99.
203. Portsmouth S, van Veenhuizen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* **2018**; 18(12): 1319-28.
204. Sims M, Mariyanovski V, McLeroth P, et al. Prospective, randomized, double-blind, Phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections. *J Antimicrob Chemother* **2017**; 72(9): 2616-26.
205. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis* **2021**; 21(2): 226-40.
206. de Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. In Vitro Susceptibility to Ceftazidime-Avibactam of Carbapenem-Nonsusceptible Enterobacteriaceae Isolates Collected during the INFORM Global Surveillance Study (2012 to 2014). *Antimicrob Agents Chemother* **2016**; 60(5): 3163-9.

207. Spiliopoulou I, Kazmierczak K, Stone GG. In vitro activity of ceftazidime/avibactam against isolates of carbapenem-non-susceptible Enterobacteriaceae collected during the INFORM global surveillance programme (2015-17). *J Antimicrob Chemother* **2020**; 75(2): 384-91.
208. 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**.
209. Castanheira M, Doyle TB, Kantro V, Mendes RE, Shortridge D. Meropenem-Vaborbactam Activity against Carbapenem-Resistant Enterobacterales Isolates Collected in U.S. Hospitals during 2016 to 2018. *Antimicrob Agents Chemother* **2020**; 64(2).
210. 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(2): 144-50.
211. Johnston BD, Thuras P, Porter SB, et al. Activity of Imipenem-Relebactam against Carbapenem-Resistant Escherichia coli Isolates from the United States in Relation to Clonal Background, Resistance Genes, Coresistance, and Region. *Antimicrob Agents Chemother* **2020**; 64(5).
212. 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**: AAC0228820.
213. Castanheira M, Doyle TB, Hubler C, Sader HS, Mendes RE. Ceftazidime-avibactam activity against a challenge set of carbapenem-resistant Enterobacterales: Ompk36 L3 alterations and beta-lactamases with ceftazidime hydrolytic activity lead to elevated MIC values. *Int J Antimicrob Agents* **2020**; 56(1): 106011.
214. Haidar G, Clancy CJ, Chen L, et al. Identifying Spectra of Activity and Therapeutic Niches for Ceftazidime-Avibactam and Imipenem-Relebactam against Carbapenem-Resistant Enterobacteriaceae. *Antimicrob Agents Chemother* **2017**; 61(9).
215. Canver MC, Satlin MJ, Westblade LF, et al. Activity of Imipenem-Relebactam and Comparator Agents against Genetically Characterized Isolates of Carbapenem-Resistant Enterobacteriaceae. *Antimicrob Agents Chemother* **2019**; 63(9).
216. Galani I, Souli M, Nafplioti K, et al. In vitro activity of imipenem-relebactam against non-MBL carbapenemase-producing Klebsiella pneumoniae isolated in Greek hospitals in 2015-2016. *Eur J Clin Microbiol Infect Dis* **2019**; 38(6): 1143-50.
217. 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* **2022**: 1-6.
218. Zhang HL, Gontjes KJ, Han JH, et al. Characterization of resistance to newer antimicrobials among carbapenem-resistant Klebsiella pneumoniae in the post-acute-care setting. *Infect Control Hosp Epidemiol* **2022**: 1-4.

219. McCreary EK, Heil EL, Tamma PD. New Perspectives on Antimicrobial Agents: Cefiderocol. *Antimicrob Agents Chemother* **2021**; 65(8): e0217120.
220. Ito A, Sato T, Ota M, et al. In Vitro Antibacterial Properties of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacteria. *Antimicrob Agents Chemother* **2018**; 62(1).
221. 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(2): 177-84.
222. Boyd SE, Livermore DM, Hooper DC, Hope WW. Metallo-beta-Lactamases: Structure, Function, Epidemiology, Treatment Options, and the Development Pipeline. *Antimicrob Agents Chemother* **2020**; 64(10).
223. Daikos GL, Tsaousi S, Tzouveleki 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(4): 2322-8.
224. 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(1): 142-50.
225. 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(10): 1116-23.
226. 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(10): 1171-8.
227. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia. *Antimicrob Agents Chemother* **2017**; 61(8).
228. van Duin D, Lok JJ, Earley M, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. *Clin Infect Dis* **2018**; 66(2): 163-71.
229. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. *Infect Dis Ther* **2018**; 7(4): 439-55.
230. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections. *Clin Infect Dis* **2020**; 70(9): 1799-808.
231. 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(3): 775-83.

232. 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.
233. 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.
234. 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(1): 772.
235. Tumbarello M, Treccarichi EM, Corona A, et al. Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by *Klebsiella pneumoniae* Carbapenemase-producing *K. pneumoniae*. *Clin Infect Dis* **2019**; 68(3): 355-64.
236. 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**.
237. Chen Y, Huang HB, Peng JM, Weng L, Du B. Efficacy and Safety of Ceftazidime-Avibactam for the Treatment of Carbapenem-Resistant Enterobacteriales Bloodstream Infection: a Systematic Review and Meta-Analysis. *Microbiol Spectr* **2022**; 10(2): e0260321.
238. Wilson GM, Fitzpatrick MA, Suda KJ, et al. Comparative effectiveness of antibiotic therapy for carbapenem-resistant Enterobacteriales (CRE) bloodstream infections in hospitalized US veterans. *JAC Antimicrob Resist* **2022**; 4(5): dlac106.
239. 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(3): ofaa051.
240. Maraki S, Mavromanolaki VE, Magkafouraki E, et al. Epidemiology and in vitro activity of ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, eravacycline, plazomicin, and comparators against Greek carbapenemase-producing *Klebsiella pneumoniae* isolates. *Infection* **2022**; 50(2): 467-74.
241. Ackley R, Roshdy D, Meredith J, et al. Meropenem-Vaborbactam versus Ceftazidime-Avibactam for Treatment of Carbapenem-Resistant Enterobacteriaceae Infections. *Antimicrob Agents Chemother* **2020**; 64(5).
242. Tumbarello M, Raffaelli F, Giannella M, et al. Ceftazidime-avibactam use for KPC-Kp infections: a retrospective observational multicenter study. *Clin Infect Dis* **2021**.
243. 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(1): dlac022.
244. Shields RK, McCreary EK, Marini RV, et al. Early experience with meropenem-vaborbactam for treatment of carbapenem-resistant Enterobacteriaceae infections. *Clin Infect Dis* **2019**.
245. 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(5).
246. Kulengowski B, Burgess DS. Imipenem/relebactam activity compared to other antimicrobials against non-MBL-producing carbapenem-resistant Enterobacteriaceae from an academic medical center. *Pathog Dis* **2019**; 77(4).
247. Walkty A, Karlowsky JA, Baxter MR, et al. In vitro activity of imipenem-relebactam against various resistance phenotypes/genotypes of Enterobacteriales and *Pseudomonas aeruginosa* isolated from patients across Canada as part of the CANWARD study, 2016-2019. *Diagn Microbiol Infect Dis* **2021**; 101(1): 115418.
248. Yang TY, Hsieh YJ, Kao LT, et al. Activities of imipenem-relebactam combination against carbapenem-nonsusceptible Enterobacteriaceae in Taiwan. *J Microbiol Immunol Infect* **2021**.
249. 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(2): 207-17.
250. Papp-Wallace KM, Barnes MD, Alsop J, et al. Relebactam Is a Potent Inhibitor of the KPC-2 beta-Lactamase and Restores Imipenem Susceptibility in KPC-Producing Enterobacteriaceae. *Antimicrob Agents Chemother* **2018**; 62(6).
251. Shaw E, Rombauts A, Tubau F, et al. Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing *Klebsiella pneumoniae* infection. *J Antimicrob Chemother* **2018**; 73(4): 1104-6.
252. Hobson CA, Bonacorsi S, Fahd M, et al. Successful Treatment of Bacteremia Due to NDM-1-Producing *Morganella morganii* with Aztreonam and Ceftazidime-Avibactam Combination in a Pediatric Patient with Hematologic Malignancy. *Antimicrob Agents Chemother* **2019**; 63(2).
253. 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**.
254. Sieswerda E, van den Brand M, van den Berg RB, et al. Successful rescue treatment of sepsis due to a pandrug-resistant, NDM-producing *Klebsiella pneumoniae* using aztreonam powder for nebulizer solution as intravenous therapy in combination with ceftazidime/avibactam. *J Antimicrob Chemother* **2020**; 75(3): 773-5.
255. Benchetrit L, Mathy V, Armand-Lefevre L, Bouadma L, Timsit JF. Successful treatment of septic shock due to NDM-1-producing *Klebsiella pneumoniae* using ceftazidime/avibactam combined with aztreonam in solid organ transplant recipients: report of two cases. *Int J Antimicrob Agents* **2020**; 55(1): 105842.
256. 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 Enterobacteriales. *Clin Infect Dis* **2021**; 72(11): 1871-8.
257. 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(6): 1081-4.

258. 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**; e0075122.
259. Sreenivasan P, Sharma B, Kaur S, et al. In-vitro susceptibility testing methods for the combination of ceftazidime-avibactam with aztreonam in metallo-beta-lactamase producing organisms: Role of combination drugs in antibiotic resistance era. *J Antibiot (Tokyo)* **2022**; 75(8): 454-62.
260. Marshall S, Hujer AM, Rojas LJ, et al. Can Ceftazidime-Avibactam and Aztreonam Overcome beta-Lactam Resistance Conferred by Metallo-beta-Lactamases in Enterobacteriaceae? *Antimicrob Agents Chemother* **2017**; 61(4).
261. Bhatnagar A, Ransom EM, Machado MJ, et al. Assessing the in vitro impact of ceftazidime on aztreonam/avibactam susceptibility testing for highly resistant MBL-producing Enterobacteriales. *J Antimicrob Chemother* **2021**; 76(4): 979-83.
262. 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(1): 47-54.
263. Avery LM, Nicolau DP. Assessing the in vitro activity of ceftazidime/avibactam and aztreonam among carbapenemase-producing Enterobacteriaceae: Defining the zone of hope. *Int J Antimicrob Agents* **2018**; 52(5): 688-91.
264. Sahu C, Pal S, Patel SS, Singh S, Gurjar M, Ghoshal U. Phenotypic synergy testing of ceftazidime-avibactam with aztreonam in a university hospital having high number of metallo-beta-lactamase producing bacteria. *Infect Dis (Lond)* **2020**; 52(11): 801-7.
265. Khan A, Erickson SG, Pettaway C, Arias CA, Miller WR, Bhatti MM. Evaluation of Susceptibility Testing Methods for Aztreonam and Ceftazidime-Avibactam Combination Therapy on Extensively Drug-Resistant Gram-Negative Organisms. *Antimicrob Agents Chemother* **2021**; 65(11): e0084621.
266. 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(1): 115227.
267. Lodise TP, Smith NM, O'Donnell N, et al. Determining the optimal dosing of a novel combination regimen of ceftazidime/avibactam with aztreonam against NDM-1-producing Enterobacteriaceae using a hollow-fibre infection model. *J Antimicrob Chemother* **2020**; 75(9): 2622-32.
268. 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(4): 1025-31.
269. 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(12): e0093622.
270. 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(12): e0093522.

271. 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(2): 115674.
272. 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(3).
273. Dobias J, Denervaud-Tendon V, Poirel L, Nordmann P. Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens. *Eur J Clin Microbiol Infect Dis* **2017**; 36(12): 2319-27.
274. De la Calle C, Rodriguez O, Morata L, et al. Clinical characteristics and prognosis of infections caused by OXA-48 carbapenemase-producing Enterobacteriaceae in patients treated with ceftazidime-avibactam. *Int J Antimicrob Agents* **2019**; 53(4): 520-4.
275. 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(9): 1173-82.
276. 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**.
277. 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**: e0110022.
278. Boyd SE, Holmes A, Peck R, Livermore DM, Hope W. OXA-48-Like beta-Lactamases: Global Epidemiology, Treatment Options, and Development Pipeline. *Antimicrob Agents Chemother* **2022**; 66(8): e0021622.
279. Humphries RM, Yang S, Hemarajata P, et al. First Report of Ceftazidime-Avibactam Resistance in a KPC-3-Expressing *Klebsiella pneumoniae* Isolate. *Antimicrob Agents Chemother* **2015**; 59(10): 6605-7.
280. 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(8): 2279-86.
281. Livermore DM, Warner M, Jamrozny D, et al. In vitro selection of ceftazidime-avibactam resistance in Enterobacteriaceae with KPC-3 carbapenemase. *Antimicrob Agents Chemother* **2015**; 59(9): 5324-30.
282. Shields RK, Chen L, Cheng S, et al. Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne blaKPC-3 Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections. *Antimicrob Agents Chemother* **2017**; 61(3).
283. 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(12): 1615-8.

284. 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(7).
285. 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(3).
286. 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(11): 3211-6.
287. 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(5).
288. 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(3).
289. 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(1): 124 e1- e4.
290. 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.
291. 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.
292. 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(4): 516 e1- e4.
293. Hemarajata P, Humphries RM. Ceftazidime/avibactam resistance associated with L169P mutation in the omega loop of KPC-2. *J Antimicrob Chemother* **2019**; 74(5): 1241-3.
294. Raisanen K, Koivula I, Ilmavirta H, et al. Emergence of ceftazidime-avibactam-resistant *Klebsiella pneumoniae* during treatment, Finland, December 2018. *Euro Surveill* **2019**; 24(19).
295. 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-, Ceftriaxone-, or Aztreonam-Avibactam. *Antimicrob Agents Chemother* **2017**; 61(8).
296. 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(4): e0241421.
297. 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.
298. 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.
299. 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(4): e0095522.
300. 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(2).
301. 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(11).
302. 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(12).
303. 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(8): 4856-60.
304. 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(10): 2789-96.
305. 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(9): 5454-8.
306. 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(1).
307. 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(8): 5029-31.
308. 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(7): 877-81.
309. 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(6): 1570-7.
310. Papp-Wallace KM, Mack AR, Taracila MA, Bonomo RA. Resistance to Novel beta-Lactam-beta-Lactamase Inhibitor Combinations: The "Price of Progress". *Infect Dis Clin North Am* **2020**; 34(4): 773-819.

311. 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(5).
312. 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(5): e0019122.
313. Frohlich C, Sorum V, Tokuriki N, Johnsen PJ, Samuelsen O. Evolution of beta-lactamase-mediated cefiderocol resistance. *J Antimicrob Chemother* **2022**; 77(9): 2429-36.
314. Karakonstantis S, Rousaki M, Kritsotakis EI. Cefiderocol: Systematic Review of Mechanisms of Resistance, Heteroresistance and In Vivo Emergence of Resistance. *Antibiotics (Basel)* **2022**; 11(6).
315. 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: S251. Poster presented at: IDWeek 2018, San Francisco, CA, 3–7 October . Poster 696.
316. 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. **2018**: Poster presented at: American Society of Microbiology Annual Meeting, Atlanta, GA, 6–11 June 2018. Poster Saturday-619.
317. 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. June 6–11, 2018. Poster 619.
318. 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**.
319. 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(6): 1650-1.
320. 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(8): e0031122.
321. 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(3): e0267021.
322. 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(1).
323. 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(8): ofab371.
324. 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(10).
325. Falagas ME, Karageorgopoulos DE, Dimopoulos G. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of tigecycline. *Curr Drug Metab* **2009**; 10(1): 13-21.
326. Solomkin J, Evans D, Slepavicius A, et al. Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. *JAMA Surg* **2017**; 152(3): 224-32.
327. 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.
328. 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.
329. 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(1): 508.
330. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J Antimicrob Chemother* **2011**; 66(9): 1963-71.
331. Zha L, Pan L, Guo J, French N, Villanueva EV, Tefsen B. Effectiveness and Safety of High Dose Tigecycline for the Treatment of Severe Infections: A Systematic Review and Meta-Analysis. *Adv Ther* **2020**; 37(3): 1049-64.
332. Chen Z, Shi X. Adverse events of high-dose tigecycline in the treatment of ventilator-associated pneumonia due to multidrug-resistant pathogens. *Medicine (Baltimore)* **2018**; 97(38): e12467.
333. De Pascale G, Montini L, Pennisi M, et al. High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. *Crit Care* **2014**; 18(3): R90.
334. 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(11): e3126.
335. 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(3).
336. Solomkin JS, Gardovskis J, Lawrence K, et al. IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs Meropenem in the Treatment of Complicated Intraabdominal Infections. *Clin Infect Dis* **2019**; 69(6): 921-9.
337. Alosaimy S, Molina KC, Claeys KC, et al. Early Experience With Eravacycline for Complicated Infections. *Open Forum Infect Dis* **2020**; 7(5): ofaa071.
338. 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: S143. Poster presented at: IDWeek 2017, San Diego, CA, 4–8 October 8. Poster 364.
339. 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.
340. Pfaller MA, Huband MD, Shortridge D, Flamm RK. Surveillance of Omadacycline Activity Tested against Clinical Isolates from the United States and Europe as Part of the 2016 SENTRY Antimicrobial Surveillance Program. *Antimicrob Agents Chemother* **2018**; 62(4).
341. Pfaller MA, Huband MD, Shortridge D, Flamm RK. Surveillance of Omadacycline Activity Tested against Clinical Isolates from the United States and Europe: Report from the SENTRY Antimicrobial Surveillance Program, 2016 to 2018. *Antimicrob Agents Chemother* **2020**; 64(5).
342. Dong D, Zheng Y, Chen Q, et al. In vitro activity of omadacycline against pathogens isolated from Mainland China during 2017-2018. *Eur J Clin Microbiol Infect Dis* **2020**; 39(8): 1559-72.
343. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. *Clin Microbiol Rev* **2012**; 25(3): 450-70.
344. 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(3): 268-81.
345. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. *Clin Infect Dis* **2018**; 67(12): 1803-14.
346. Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. *Clin Microbiol Rev* **2009**; 22(4): 582-610.
347. Wolter DJ, Lister PD. Mechanisms of beta-lactam resistance among *Pseudomonas aeruginosa*. *Curr Pharm Des* **2013**; 19(2): 209-22.
348. 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(5): e0018922.
349. 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*. 2022 (accepted for publication).
350. 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(9).
351. 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(7).

352. 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(3): 277-97.
353. 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(12): 2533-41.
354. Gajdacs M. Carbapenem-Resistant but Cephalosporin-Susceptible *Pseudomonas aeruginosa* in Urinary Tract Infections: Opportunity for Colistin Sparing. *Antibiotics (Basel)* **2020**; 9(4).
355. 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**: AAC0120421.
356. Khalili Y, Yekani M, Goli HR, Memar MY. Characterization of carbapenem-resistant but cephalosporin-susceptible *Pseudomonas aeruginosa*. *Acta Microbiol Immunol Hung* **2019**; 66(4): 529-40.
357. 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(1): 57-62.
358. 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(3): 268-70.
359. 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(1).
360. 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.
361. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet* **2015**; 385(9981): 1949-56.
362. Walkty A, Adam H, Baxter M, et al. In vitro activity of plazomicin against 5,015 gram-negative and gram-positive clinical isolates obtained from patients in canadian hospitals as part of the CANWARD study, 2011-2012. *Antimicrob Agents Chemother* **2014**; 58(5): 2554-63.
363. Athans V, Neuner EA, Hassouna H, et al. Meropenem-Vaborbactam as Salvage Therapy for Ceftazidime-Avibactam-Resistant *Klebsiella pneumoniae* Bacteremia and Abscess in a Liver Transplant Recipient. *Antimicrob Agents Chemother* **2019**; 63(1).
364. Castanheira M, Duncan LR, Mendes RE, Sader HS, Shortridge D. Activity of Ceftolozane-Tazobactam against *Pseudomonas aeruginosa* and Enterobacteriaceae Isolates Collected from Respiratory Tract Specimens of Hospitalized Patients in the United States during 2013 to 2015. *Antimicrob Agents Chemother* **2018**; 62(3).

365. Sader HS, Castanheira M, Shortridge D, Mendes RE, Flamm RK. Antimicrobial Activity of Ceftazidime-Avibactam Tested against Multidrug-Resistant Enterobacteriaceae and *Pseudomonas aeruginosa* Isolates from U.S. Medical Centers, 2013 to 2016. *Antimicrob Agents Chemother* **2017**; 61(11).
366. Carvalhaes CG, Castanheira M, Sader HS, Flamm RK, Shortridge D. Antimicrobial activity of ceftolozane-tazobactam tested against gram-negative contemporary (2015-2017) isolates from hospitalized patients with pneumonia in US medical centers. *Diagn Microbiol Infect Dis* **2019**; 94(1): 93-102.
367. 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(2): 158-63.
368. Fraile-Ribot PA, Zamorano L, Orellana R, et al. Activity of Imipenem-Relebactam against a Large Collection of *Pseudomonas aeruginosa* Clinical Isolates and Isogenic beta-Lactam-Resistant Mutants. *Antimicrob Agents Chemother* **2020**; 64(2).
369. 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(3): 114833.
370. 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(12).
371. Sader HS, Flamm RK, Dale GE, Rhomberg PR, Castanheira M. Murepavadin activity tested against contemporary (2016-17) clinical isolates of XDR *Pseudomonas aeruginosa*. *J Antimicrob Chemother* **2018**; 73(9): 2400-4.
372. 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(5): 563-77.
373. 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(2): 181-9.
374. 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(6): 627-37.
375. 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.
376. 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(7).
377. Pfaller MA, Bassetti M, Duncan LR, Castanheira M. Ceftolozane/tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* causing urinary tract and intraabdominal infections in Europe: report from an antimicrobial surveillance programme (2012-15). *J Antimicrob Chemother* **2017**; 72(5): 1386-95.
378. 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(11): 3053-9.
379. 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(3): 342-9.
380. 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(3): 1684-92.
381. 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(6): 3656-9.
382. 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(3).
383. 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(4).
384. 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(3): 261-5.
385. 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(7): 4355-60.
386. 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(4): 473-8.

387. 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(4): 2537-41.
388. 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 United States medical centers (2011-2014). *Diagn Microbiol Infect Dis* **2015**; 83(4): 389-94.
389. 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(1): 53-9.
390. 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(7): ofab320.
391. 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(4): 115421.
392. 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(8): 2071-8.
393. 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(3): 274-81.
394. 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**.
395. Lob SH, Hackel MA, Kazmierczak KM, et al. In vitro 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(2): 171-6.
396. 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(1): 105841.
397. 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.

398. 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(2): 212-5.
399. 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(8): 2284-8.
400. 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.
401. 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: 12-9.
402. 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(7).
403. 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(7): 1872-9.
404. 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(6).
405. 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.
406. 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(2): 304-10.
407. 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.
408. Almagour 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.
409. 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(5): 1965-80.
410. 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(10): 1081-8.

411. 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(5).
412. Kollef MH, Novacek M, Kivistik U, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* **2019**; 19(12): 1299-311.
413. Torres A, Zhong N, Pacht J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis* **2018**; 18(3): 285-95.
414. Mazuski JE, Gasink LB, Armstrong J, et al. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. *Clin Infect Dis* **2016**; 62(11): 1380-9.
415. 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. *Antimicrobial Agents & Chemotherapy* **2014**; 58(9): 5350-7.
416. Lucasti C, Vasile L, Sandesc D, et al. Phase 2, Dose-Ranging Study of Relebactam with Imipenem-Cilastatin in Subjects with Complicated Intra-abdominal Infection. *Antimicrob Agents Chemother* **2016**; 60(10): 6234-43.
417. 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**.
418. 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-clAI). *Clin Infect Dis* **2015**; 60(10): 1462-71.
419. 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(3): dlab126.
420. 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.
421. 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(5): 2261-75.
422. 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(11): 6844-50.

423. Jaruratanasirikul S, Sriwiriyan 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(4): 1337-9.
424. 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(9): 2519-23.
425. Rolston KVI, Gerges B, Shelburne S, Aitken SL, Raad I, Prince RA. Activity of Cefiderocol and Comparators against Isolates from Cancer Patients. *Antimicrob Agents Chemother* **2020**; 64(5).
426. Falagas ME, Skolidis 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(6): 1704-8.
427. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against Carbapenem-Nonsusceptible and Multidrug-Resistant Isolates of Gram-Negative Bacilli Collected Worldwide in 2014 to 2016. *Antimicrob Agents Chemother* **2018**; 62(2).
428. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against a Recent Collection of Clinically Relevant Gram-Negative Bacilli from North America and Europe, Including Carbapenem-Nonsusceptible Isolates (SIDERO-WT-2014 Study). *Antimicrob Agents Chemother* **2017**; 61(9).
429. 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(4): e0172422.
430. 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* **2020**.
431. 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(6): 989-96.
432. 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(8): 4743-9.
433. 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(2): 1067-78.
434. Mushtaq S, Sadouki Z, Vickers A, Livermore DM, Woodford N. In Vitro Activity of Cefiderocol, a Siderophore Cephalosporin, against Multidrug-Resistant Gram-Negative Bacteria. *Antimicrob Agents Chemother* **2020**; 64(12).

435. 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(8).
436. 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: 510-2.
437. 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.
438. 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(10): 6248-55.
439. 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(3): 658-63.
440. 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(12).
441. 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(1): 269-71.
442. 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(6): 774-80.
443. 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(6): 3091-9.
444. 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(11): 2191-200.
445. 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**.
446. 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(1): 110-20.
447. 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**.
448. Tamma PD, Beisken S, Bergman Y, et al. Modifiable Risk Factors for the Emergence of Ceftolozane-Tazobactam Resistance. *Clin Infect Dis* **2020**.

449. 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(5).
450. 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(6): 1650-8.
451. 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(4): 710-4.
452. 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(4): 957-68.
453. 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-e4.
454. 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(7): ofab311.
455. Kwa A, Kasiakou SK, Tam VH, Falagas ME. Polymyxin B: similarities to and differences from colistin (polymyxin E). *Expert Rev Anti Infect Ther* **2007**; 5(5): 811-21.
456. Akajagbor DS, Wilson SL, Shere-Wolfe KD, Dakum P, Charurat ME, Gilliam BL. Higher incidence of acute kidney injury with intravenous colistimethate sodium compared with polymyxin B in critically ill patients at a tertiary care medical center. *Clin Infect Dis* **2013**; 57(9): 1300-3.
457. Phe K, Lee Y, McDanel PM, et al. In vitro assessment and multicenter cohort study of comparative nephrotoxicity rates associated with colistimethate versus polymyxin B therapy. *Antimicrob Agents Chemother* **2014**; 58(5): 2740-6.
458. Tuon FF, Rigatto MH, Lopes CK, Kamei LK, Rocha JL, Zavascki AP. Risk factors for acute kidney injury in patients treated with polymyxin B or colistin methanesulfonate sodium. *Int J Antimicrob Agents* **2014**; 43(4): 349-52.
459. Rigatto MH, Oliveira MS, Perdigao-Neto LV, et al. Multicenter Prospective Cohort Study of Renal Failure in Patients Treated with Colistin versus Polymyxin B. *Antimicrob Agents Chemother* **2016**; 60(4): 2443-9.
460. Oliveira MS, Prado GV, Costa SF, Grinbaum RS, Levin AS. Polymyxin B and colistimethate are comparable as to efficacy and renal toxicity. *Diagn Microbiol Infect Dis* **2009**; 65(4): 431-4.
461. Lu Q, Luo R, Bodin L, et al. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Anesthesiology* **2012**; 117(6): 1335-47.
462. Kwa AL, Loh C, Low JG, Kurup A, Tam VH. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Clin Infect Dis* **2005**; 41(5): 754-7.

463. Falagas ME, Siempos, II, Rafailidis PI, Korbila IP, Ioannidou E, Michalopoulos A. Inhaled colistin as monotherapy for multidrug-resistant gram (-) nosocomial pneumonia: a case series. *Respir Med* **2009**; 103(5): 707-13.
464. Choi HK, Kim YK, Kim HY, Uh Y. Inhaled colistin for treatment of pneumonia due to colistin-only-susceptible *Acinetobacter baumannii*. *Yonsei Med J* **2014**; 55(1): 118-25.
465. Hsieh TC, Chen FL, Ou TY, Jean SS, Lee WS. Role of aerosolized colistin methanesulfonate therapy for extensively-drug-resistant *Acinetobacter baumannii* complex pneumonia and airway colonization. *J Microbiol Immunol Infect* **2016**; 49(4): 523-30.
466. Kang CH, Tsai CM, Wu TH, et al. Colistin inhalation monotherapy for ventilator-associated pneumonia of *Acinetobacter baumannii* in prematurity. *Pediatr Pulmonol* **2014**; 49(4): 381-8.
467. Chen YM, Fang WF, Kao HC, et al. Influencing factors of successful eradication of multidrug-resistant *Acinetobacter baumannii* in the respiratory tract with aerosolized colistin. *Biomed J* **2014**; 37(5): 314-20.
468. Jean SS, Hsieh TC, Lee WS, Hsueh PR, Hsu CW, Lam C. Treatment outcomes of patients with non-bacteremic pneumonia caused by extensively drug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex isolates: Is there any benefit of adding tigecycline to aerosolized colistimethate sodium? *Medicine (Baltimore)* **2018**; 97(39): e12278.
469. Tumbarello M, De Pascale G, Treccarichi EM, et al. Effect of aerosolized colistin as adjunctive treatment on the outcomes of microbiologically documented ventilator-associated pneumonia caused by colistin-only susceptible gram-negative bacteria. *Chest* **2013**; 144(6): 1768-75.
470. Kofteridis DP, Alexopoulou C, Valachis A, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. *Clin Infect Dis* **2010**; 51(11): 1238-44.
471. Korkmaz Ekren P, Toreyin N, Sayiner A, Bacakoglu F, Colistin Study G. The Role of Aerolized Colistin in the Treatment of Hospital-Acquired Pneumonia: Experience of Multicenter From Turkey. *Crit Care Med* **2016**; 44(5): e304.
472. 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.
473. Abdellatif S, Trifi A, Daly F, Mahjoub K, Nasri R, Ben Lakhal S. Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial. *Ann Intensive Care* **2016**; 6(1): 26.
474. Kim YK, Lee JH, Lee HK, et al. Efficacy of nebulized colistin-based therapy without concurrent intravenous colistin for ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. *J Thorac Dis* **2017**; 9(3): 555-67.
475. Michalopoulos A, Fotakis D, Virtzili S, et al. Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: a prospective study. *Respir Med* **2008**; 102(3): 407-12.
476. Kalin G, Alp E, Coskun R, Demiraslan H, Gundogan K, Doganay M. Use of high-dose IV and aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter*

- baumannii ventilator-associated pneumonia: do we really need this treatment? *J Infect Chemother* **2012**; 18(6): 872-7.
477. 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.
478. Lin CC, Liu TC, Kuo CF, Liu CP, Lee CM. Aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* pneumonia: experience in a tertiary care hospital in northern Taiwan. *J Microbiol Immunol Infect* **2010**; 43(4): 323-31.
479. Doshi NM, Cook CH, Mount KL, et al. Adjunctive aerosolized colistin for multi-drug resistant gram-negative pneumonia in the critically ill: a retrospective study. *BMC Anesthesiol* **2013**; 13(1): 45.
480. Mastoraki A, Douka E, Kriaras I, Stravopodis G, Manoli H, Geroulanos S. *Pseudomonas aeruginosa* susceptible only to colistin in intensive care unit patients. *Surg Infect (Larchmt)* **2008**; 9(2): 153-60.
481. Berlana D, Llop JM, Fort E, Badia MB, Jodar R. Use of colistin in the treatment of multiple-drug-resistant gram-negative infections. *Am J Health Syst Pharm* **2005**; 62(1): 39-47.
482. Korbila IP, Michalopoulos A, Rafailidis PI, Nikita D, Samonis G, Falagas ME. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. *Clin Microbiol Infect* **2010**; 16(8): 1230-6.
483. Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. *Crit Care* **2005**; 9(1): R53-9.
484. Ganapathy H, Pal SK, Teare L, Dziewulski P. Use of colistin in treating multi-resistant Gram-negative organisms in a specialised burns unit. *Burns* **2010**; 36(4): 522-7.
485. Falagas ME, Kasiakou SK, Kofteridis DP, Roditakis G, Samonis G. Effectiveness and nephrotoxicity of intravenous colistin for treatment of patients with infections due to polymyxin-only-susceptible (POS) gram-negative bacteria. *Eur J Clin Microbiol Infect Dis* **2006**; 25(9): 596-9.
486. Kuo SC, Lee YT, Yang SP, et al. Eradication of multidrug-resistant *Acinetobacter baumannii* from the respiratory tract with inhaled colistin methanesulfonate: a matched case-control study. *Clin Microbiol Infect* **2012**; 18(9): 870-6.
487. Motaouakkil S, Charra B, Hachimi A, et al. Colistin and rifampicin in the treatment of nosocomial infections from multiresistant *Acinetobacter baumannii*. *J Infect* **2006**; 53(4): 274-8.
488. 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.
489. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwina N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of

- ventilator-associated pneumonia caused by Gram-negative bacteria. *J Antimicrob Chemother* **2010**; 65(12): 2645-9.
490. Kollef MH, Ricard JD, Roux D, et al. A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia: IASIS Trial. *Chest* **2017**; 151(6): 1239-46.
491. Niederman MS, Alder J, Bassetti M, et al. Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial. *Lancet Infect Dis* **2020**; 20(3): 330-40.
492. 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(1): 6969.
493. Boisson M, Jacobs M, Gregoire N, et al. Comparison of intrapulmonary and systemic pharmacokinetics of colistin methanesulfonate (CMS) and colistin after aerosol delivery and intravenous administration of CMS in critically ill patients. *Antimicrob Agents Chemother* **2014**; 58(12): 7331-9.
494. Rouby JJ, Bouhemad B, Monsel A, et al. Aerosolized antibiotics for ventilator-associated pneumonia: lessons from experimental studies. *Anesthesiology* **2012**; 117(6): 1364-80.
495. Wenzler E, Fraidenburg DR, Scardina T, Danziger LH. Inhaled Antibiotics for Gram-Negative Respiratory Infections. *Clin Microbiol Rev* **2016**; 29(3): 581-632.
496. Biagi M, Butler D, Tan X, Qasmieh S, Wenzler E. A Breath of Fresh Air in the Fog of Antimicrobial Resistance: Inhaled Polymyxins for Gram-Negative Pneumonia. *Antibiotics (Basel)* **2019**; 8(1).
497. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* **2016**; 63(5): e61-e111.
498. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). *Pharmacotherapy* **2019**; 39(1): 10-39.
499. Rello J, Sole-Lleonart C, Rouby JJ, et al. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. *Clin Microbiol Infect* **2017**; 23(9): 629-39.
500. Maselli DJ, Keyt H, Restrepo MI. Inhaled Antibiotic Therapy in Chronic Respiratory Diseases. *Int J Mol Sci* **2017**; 18(5).
501. 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.

502. Butler DA, Biagi M, Tan X, Qasmieh S, Bulman ZP, Wenzler E. Multidrug Resistant *Acinetobacter baumannii*: Resistance by Any Other Name Would Still be Hard to Treat. *Curr Infect Dis Rep* **2019**; 21(12): 46.
503. Vijayakumar S, Biswas I, Veeraraghavan B. Accurate identification of clinically important *Acinetobacter* spp.: an update. *Future Sci OA* **2019**; 5(6): FSO395.
504. Turton JF, Ward ME, Woodford N, et al. The role of ISAb₁ in expression of OXA carbapenemase genes in *Acinetobacter baumannii*. *FEMS Microbiol Lett* **2006**; 258(1): 72-7.
505. Penwell WF, Shapiro AB, Giacobbe RA, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2015**; 59(3): 1680-9.
506. McLeod SM, Shapiro AB, Moussa SH, et al. Frequency and Mechanism of Spontaneous Resistance to Sulbactam Combined with the Novel beta-Lactamase Inhibitor ETX2514 in Clinical Isolates of *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2018**; 62(2): e01576-17.
507. Krizova L, Poirel L, Nordmann P, Nemeč A. TEM-1 beta-lactamase as a source of resistance to sulbactam in clinical strains of *Acinetobacter baumannii*. *J Antimicrob Chemother* **2013**; 68(12): 2786-91.
508. Nemeč 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.
509. Bonomo RA, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. *Clin Infect Dis* **2006**; 43 Suppl 2: S49-56.
510. Castanheira M, Deshpande LM, Woosley LN, Serio AW, Krause KM, Flamm RK. Activity of plazomicin compared with other aminoglycosides against isolates from European and adjacent countries, including Enterobacteriaceae molecularly characterized for aminoglycoside-modifying enzymes and other resistance mechanisms. *J Antimicrob Chemother* **2018**; 73(12): 3346-54.
511. Kaye KS, University of Michigan. Trial for the Treatment of Extensively Drug-Resistant Gram-negative Bacilli. Available at: <https://clinicaltrials.gov/ct2/show/NCT01597973>. Accessed 14 August 2021.
512. Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis* **2018**; 18(4): 391-400.
513. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomicin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. *Antimicrob Agents Chemother* **2014**; 58(9): 5598-601.
514. Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. *Clin Infect Dis* **2013**; 57(3): 349-58.

515. Aydemir H, Akduman D, Piskin N, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Epidemiol Infect* **2013**; 141(6): 1214-22.
516. Makris D, Petinaki E, Tsolaki V, et al. Colistin versus Colistin Combined with Ampicillin-Sulbactam for Multiresistant *Acinetobacter baumannii* Ventilator-associated Pneumonia Treatment: An Open-label Prospective Study. *Indian J Crit Care Med* **2018**; 22(2): 67-77.
517. 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.
518. Lenhard JR, Smith NM, Bulman ZP, et al. High-Dose Ampicillin-Sulbactam Combinations Combat Polymyxin-Resistant *Acinetobacter baumannii* in a Hollow-Fiber Infection Model. *Antimicrob Agents Chemother* **2017**; 61(3): e01268-16.
519. Beganovic M, Daffinee KE, Luther MK, LaPlante KL. Minocycline Alone and in Combination with Polymyxin B, Meropenem, and Sulbactam against Carbapenem-Susceptible and -Resistant *Acinetobacter baumannii* in an In Vitro Pharmacodynamic Model. *Antimicrob Agents Chemother* **2021**; 65(3).
520. Abdul-Mutakabbir JC, Yim J, Nguyen L, et al. In Vitro Synergy of Colistin in Combination with Meropenem or Tigecycline against Carbapenem-Resistant *Acinetobacter baumannii*. *Antibiotics (Basel)* **2021**; 10(7).
521. Rodriguez-Hernandez MJ, Cuberos L, Pichardo C, et al. Sulbactam efficacy in experimental models caused by susceptible and intermediate *Acinetobacter baumannii* strains. *J Antimicrob Chemother* **2001**; 47(4): 479-82.
522. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant *Acinetobacter baumannii*. *Scand J Infect Dis* **2007**; 39(1): 38-43.
523. 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(1): 11-6.
524. 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.
525. Jung SY, Lee SH, Lee SY, et al. Antimicrobials for the treatment of drug-resistant *Acinetobacter baumannii* pneumonia in critically ill patients: a systemic review and Bayesian network meta-analysis. *Crit Care* **2017**; 21(1): 319.
526. 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(4): 221-3.
527. 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(3): 692-7.

528. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *J Infect* **2008**; 56(6): 432-6.
529. Yilmaz GR, Guven T, Guner R, et al. Colistin alone or combined with sulbactam or carbapenem against *A. baumannii* in ventilator-associated pneumonia. *J Infect Dev Ctries* **2015**; 9(5): 476-85.
530. Trial for the Treatment of Extensively Drug-Resistant Gram-negative Bacilli. 2021. <https://clinicaltrials.gov/ct2/show/NCT01597973>. Accessed December 31, 2022.
531. Ku NS, Lee SH, Lim YS, et al. In vivo efficacy of combination of colistin with fosfomycin or minocycline in a mouse model of multidrug-resistant *Acinetobacter baumannii* pneumonia. *Sci Rep* **2019**; 9(1): 17127.
532. Yang YS, Lee Y, Tseng KC, et al. In Vivo and In Vitro Efficacy of Minocycline-Based Combination Therapy for Minocycline-Resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2016**; 60(7): 4047-54.
533. Bowers DR, Cao H, Zhou J, et al. Assessment of minocycline and polymyxin B combination against *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2015**; 59(5): 2720-5.
534. Montero A, Ariza J, Corbella X, et al. Antibiotic combinations for serious infections caused by carbapenem-resistant *Acinetobacter baumannii* in a mouse pneumonia model. *J Antimicrob Chemother* **2004**; 54(6): 1085-91.
535. Bernabeu-Wittel M, Pichardo C, Garcia-Curiel A, et al. Pharmacokinetic/pharmacodynamic assessment of the in-vivo efficacy of imipenem alone or in combination with amikacin for the treatment of experimental multiresistant *Acinetobacter baumannii* pneumonia. *Clin Microbiol Infect* **2005**; 11(4): 319-25.
536. Joly-Guillou ML, Wolff M, Farinotti R, Bryskier A, Carbon C. In vivo activity of levofloxacin alone or in combination with imipenem or amikacin in a mouse model of *Acinetobacter baumannii* pneumonia. *J Antimicrob Chemother* **2000**; 46(5): 827-30.
537. Zusman O, Avni T, Leibovici L, et al. Systematic review and meta-analysis of in vitro synergy of polymyxins and carbapenems. *Antimicrob Agents Chemother* **2013**; 57(10): 5104-11.
538. 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.
539. Lenhard JR, Nation RL, Tsuji BT. Synergistic combinations of polymyxins. *Int J Antimicrob Agents* **2016**; 48(6): 607-13.
540. Falagas ME, Rafailidis PI, Ioannidou E, et al. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients. *Int J Antimicrob Agents* **2010**; 35(2): 194-9.
541. Ye JJ, Lin HS, Kuo AJ, et al. The clinical implication and prognostic predictors of tigecycline treatment for pneumonia involving multidrug-resistant *Acinetobacter baumannii*. *J Infect* **2011**; 63(5): 351-61.

542. Tseng YC, Wang JT, Wu FL, Chen YC, Chie WC, Chang SC. Prognosis of adult patients with bacteremia caused by extensively resistant *Acinetobacter baumannii*. *Diagn Microbiol Infect Dis* **2007**; 59(2): 181-90.
543. Hernandez-Torres A, Garcia-Vazquez E, Gomez J, Canteras M, Ruiz J, Yague G. Multidrug and carbapenem-resistant *Acinetobacter baumannii* infections: Factors associated with mortality. *Med Clin (Barc)* **2012**; 138(15): 650-5.
544. Poulakou G, Kontopidou FV, Paramythiotou E, et al. Tigecycline in the treatment of infections from multi-drug resistant gram-negative pathogens. *J Infect* **2009**; 58(4): 273-84.
545. Kalin G, Alp E, Akin A, Coskun R, Doganay M. Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Infection* **2014**; 42(1): 37-42.
546. Liang CA, Lin YC, Lu PL, Chen HC, Chang HL, Sheu CC. Antibiotic strategies and clinical outcomes in critically ill patients with pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. *Clin Microbiol Infect* **2018**; 24(8): 908 e1- e7.
547. Kim WY, Moon JY, Huh JW, et al. Comparable Efficacy of Tigecycline versus Colistin Therapy for Multidrug-Resistant and Extensively Drug-Resistant *Acinetobacter baumannii* Pneumonia in Critically Ill Patients. *PLoS One* **2016**; 11(3): e0150642.
548. Tasbakan MS, Pullukcu H, Sipahi OR, Tasbakan MI, Aydemir S, Bacakoglu F. Is tigecyclin a good choice in the treatment of multidrug-resistant *Acinetobacter baumannii* pneumonia? *J Chemother* **2011**; 23(6): 345-9.
549. Shields RK, Clancy CJ, Gillis LM, et al. Epidemiology, clinical characteristics and outcomes of extensively drug-resistant *Acinetobacter baumannii* infections among solid organ transplant recipients. *PLoS One* **2012**; 7(12): e52349.
550. Kuo LC, Lai CC, Liao CH, et al. Multidrug-resistant *Acinetobacter baumannii* bacteraemia: clinical features, antimicrobial therapy and outcome. *Clin Microbiol Infect* **2007**; 13(2): 196-8.
551. Simsek F, Gedik H, Yildirmak MT, et al. Colistin against colistin-only-susceptible *Acinetobacter baumannii*-related infections: Monotherapy or combination therapy? *Indian J Med Microbiol* **2012**; 30(4): 448-52.
552. Lim SK, Lee SO, Choi SH, et al. The outcomes of using colistin for treating multidrug resistant *Acinetobacter* species bloodstream infections. *J Korean Med Sci* **2011**; 26(3): 325-31.
553. 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.
554. 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(8): 1311-22.
555. 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(6): 630-4.

556. Lopez-Cortes LE, Cisneros JM, Fernandez-Cuenca F, et al. Monotherapy versus combination therapy for sepsis due to multidrug-resistant *Acinetobacter baumannii*: analysis of a multicentre prospective cohort. *J Antimicrob Chemother* **2014**; 69(11): 3119-26.
557. Dickstein Y, Lellouche J, Ben Dalak Amar M, et al. Treatment Outcomes of Colistin- and Carbapenem-resistant *Acinetobacter baumannii* Infections: An Exploratory Subgroup Analysis of a Randomized Clinical Trial. *Clin Infect Dis* **2019**; 69(5): 769-76.
558. Petrosillo N, Giannella M, Antonelli M, et al. Clinical experience of colistin-glycopeptide combination in critically ill patients infected with Gram-negative bacteria. *Antimicrob Agents Chemother* **2014**; 58(2): 851-8.
559. Freire MP, de Oliveira Garcia D, Garcia CP, et al. Bloodstream infection caused by extensively drug-resistant *Acinetobacter baumannii* in cancer patients: high mortality associated with delayed treatment rather than with the degree of neutropenia. *Clin Microbiol Infect* **2016**; 22(4): 352-8.
560. Kaye KS, Marchaim D, Thamlikitkul V, et al. Colistin monotherapy versus combination therapy for carbapenem-resistant organisms. *NEJM Evidence*. 2022 (accepted for publication).
561. 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(9): 901-11.
562. Noguchi JK, Gill MA. Sulbactam: a beta-lactamase inhibitor. *Clin Pharm* **1988**; 7(1): 37-51.
563. Jaruratanasirikul S, Wongpoowarak W, Aeinlang N, Jullangkoon M. Pharmacodynamics modeling to optimize dosage regimens of sulbactam. *Antimicrob Agents Chemother* **2013**; 57(7): 3441-4.
564. Reddy T, Chopra T, Marchaim D, et al. Trends in antimicrobial resistance of *Acinetobacter baumannii* isolates from a metropolitan Detroit health system. *Antimicrob Agents Chemother* **2010**; 54(5): 2235-8.
565. 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.
566. Study to Evaluate the Efficacy and Safety of Intravenous Sulbactam-ETX2514 in the Treatment of Patients With Infections Caused by *Acinetobacter Baumannii-calcoaceticus* Complex (ATTACK).
ClinicalTrials.gov Identifier: NCT03894046. Accessed January 10th, 2023.
567. 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.
568. 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(9): e0078122.
569. 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(4).

570. Sagan O, Yakubsevitch R, Yanev K, et al. Pharmacokinetics and Tolerability of Intravenous Sulbactam-Durlobactam with Imipenem-Cilastatin in Hospitalized Adults with Complicated Urinary Tract Infections, Including Acute Pyelonephritis. *Antimicrob Agents Chemother* **2020**; 64(3).
571. Seifert H, Muller C, Stefanik D, Higgins PG, Miller A, Kresken M. In vitro activity of sulbactam/durlobactam against global isolates of carbapenem-resistant *Acinetobacter baumannii*. *J Antimicrob Chemother* **2020**; 75(9): 2616-21.
572. Qureshi ZA, Hittle LE, O'Hara JA, et al. Colistin-resistant *Acinetobacter baumannii*: beyond carbapenem resistance. *Clin Infect Dis* **2015**; 60(9): 1295-303.
573. Nation RL, Rigatto MHP, Falci DR, Zavascki AP. Polymyxin Acute Kidney Injury: Dosing and Other Strategies to Reduce Toxicity. *Antibiotics (Basel)* **2019**; 8(1): 24.
574. Cheah SE, Wang J, Nguyen VT, Turnidge JD, Li J, Nation RL. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in mouse thigh and lung infection models: smaller response in lung infection. *J Antimicrob Chemother* **2015**; 70(12): 3291-7.
575. Landersdorfer CB, Wang J, Wirth V, et al. Pharmacokinetics/pharmacodynamics of systemically administered polymyxin B against *Klebsiella pneumoniae* in mouse thigh and lung infection models. *J Antimicrob Chemother* **2018**; 73(2): 462-8.
576. Montero A, Ariza J, Corbella X, et al. Efficacy of colistin versus beta-lactams, aminoglycosides, and rifampin as monotherapy in a mouse model of pneumonia caused by multiresistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2002**; 46(6): 1946-52.
577. Rojas LJ, Salim M, Cober E, et al. Colistin Resistance in Carbapenem-Resistant *Klebsiella pneumoniae*: Laboratory Detection and Impact on Mortality. *Clin Infect Dis* **2017**; 64(6): 711-8.
578. Marchaim D, Chopra T, Pogue JM, et al. Outbreak of colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae* in metropolitan Detroit, Michigan. *Antimicrob Agents Chemother* **2011**; 55(2): 593-9.
579. Lesho E, Yoon EJ, McGann P, et al. Emergence of colistin-resistance in extremely drug-resistant *Acinetobacter baumannii* containing a novel *pmrCAB* operon during colistin therapy of wound infections. *J Infect Dis* **2013**; 208(7): 1142-51.
580. Lopez-Rojas R, McConnell MJ, Jimenez-Mejias ME, Dominguez-Herrera J, Fernandez-Cuenca F, Pachon J. Colistin resistance in a clinical *Acinetobacter baumannii* strain appearing after colistin treatment: effect on virulence and bacterial fitness. *Antimicrob Agents Chemother* **2013**; 57(9): 4587-9.
581. Fluit AC, Florijn A, Verhoef J, Milatovic D. Presence of tetracycline resistance determinants and susceptibility to tigecycline and minocycline. *Antimicrob Agents Chemother* **2005**; 49(4): 1636-8.
582. Petersen PJ, Jacobus NV, Weiss WJ, Sum PE, Testa RT. In vitro and in vivo antibacterial activities of a novel glycylicycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936). *Antimicrob Agents Chemother* **1999**; 43(4): 738-44.

583. Montana S, Vilacoba E, Traglia GM, et al. Genetic Variability of AdeRS Two-Component System Associated with Tigecycline Resistance in XDR-Acinetobacter baumannii Isolates. *Curr Microbiol* **2015**; 71(1): 76-82.
584. 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.
585. Allen JC. Minocycline. *Ann Intern Med* **1976**; 85(4): 482-7.
586. Flamm RK, Castanheira M, Streit JM, Jones RN. Minocycline activity tested against Acinetobacter baumannii complex, Stenotrophomonas maltophilia, and Burkholderia cepacia species complex isolates from a global surveillance program (2013). *Diagn Microbiol Infect Dis* **2016**; 85(3): 352-5.
587. Flamm RK, Shortridge D, Castanheira M, Sader HS, Pfaller MA. In Vitro Activity of Minocycline against U.S. Isolates of Acinetobacter baumannii-Acinetobacter calcoaceticus Species Complex, Stenotrophomonas maltophilia, and Burkholderia cepacia Complex: Results from the SENTRY Antimicrobial Surveillance Program, 2014 to 2018. *Antimicrob Agents Chemother* **2019**; 63(11): e01154-19.
588. 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.
589. Chan JD, Graves JA, Dellit TH. Antimicrobial treatment and clinical outcomes of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. *J Intensive Care Med* **2010**; 25(6): 343-8.
590. 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.
591. Wood GC, Hanes SD, Boucher BA, Croce MA, Fabian TC. Tetracyclines for treating multidrug-resistant Acinetobacter baumannii ventilator-associated pneumonia. *Intensive Care Med* **2003**; 29(11): 2072-6.
592. Livermore DM, Mushtaq S, Warner M, Woodford N. In Vitro Activity of Eravacycline against Carbapenem-Resistant Enterobacteriaceae and Acinetobacter baumannii. *Antimicrob Agents Chemother* **2016**; 60(6): 3840-4.
593. Lee YT, Wang YC, Kuo SC, et al. Multicenter Study of Clinical Features of Breakthrough Acinetobacter Bacteremia during Carbapenem Therapy. *Antimicrob Agents Chemother* **2017**; 61(9): e00931-17.
594. Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis* **2010**; 68(2): 140-51.
595. Qvist N, Warren B, Leister-Tebbe H, et al. Efficacy of tigecycline versus ceftriaxone plus metronidazole for the treatment of complicated intra-abdominal infections: results from a randomized, controlled trial. *Surg Infect (Larchmt)* **2012**; 13(2): 102-9.
596. Towfigh S, Pasternak J, Poirier A, Leister H, Babinchak T. A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections. *Clin Microbiol Infect* **2010**; 16(8): 1274-81.

597. Fanning WL, Gump DW. Distressing side-effects of minocycline hydrochloride. *Arch Intern Med* **1976**; 136(7): 761-2.
598. Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible *Acinetobacter baumannii*. *Int J Antimicrob Agents* **2018**; 51(1): 62-4.
599. Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Quale J. Activity of eravacycline against Enterobacteriaceae and *Acinetobacter baumannii*, including multidrug-resistant isolates, from New York City. *Antimicrob Agents Chemother* **2015**; 59(3): 1802-5.
600. 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(5): e0047922.
601. 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(12): 1299-307.
602. 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(4): 1715-23.
603. Nakamura R, Ito-Horiyama T, Takemura M, et al. In Vivo Pharmacodynamic Study of Cefiderocol, a Novel Parenteral Siderophore Cephalosporin, in Murine Thigh and Lung Infection Models. *Antimicrob Agents Chemother* **2019**; 63(9): e02031-18.
604. Ito A, Kohira N, Bouchillon SK, et al. In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria. *J Antimicrob Chemother* **2016**; 71(3): 670-7.
605. 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(1).
606. Stracquadiano S, Bonomo C, Marino A, et al. *Acinetobacter baumannii* and Cefiderocol, between Cidality and Adaptability. *Microbiol Spectr* **2022**; 10(5): e0234722.
607. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* **2021**; 21(2): 213-25.
608. 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(5): e0214221.
609. Lesho E, Wortmann G, Moran K, Craft D. Fatal *Acinetobacter baumannii* infection with discordant carbapenem susceptibility. *Clin Infect Dis* **2005**; 41(5): 758-9.
610. Jones RN, Sader HS, Fritsche TR, Rhomberg PR. Carbapenem susceptibility discords among *Acinetobacter* isolates. *Clin Infect Dis* **2006**; 42(1): 158.
611. Esterly JS, Qi C, Malczynski M, Scheetz MH. Predictability of doripenem susceptibility in *Acinetobacter baumannii* isolates based on other carbapenem susceptibilities and bla OXA gene status. *Pharmacotherapy* **2010**; 30(4): 354-60.
612. Wehrli W. Rifampin: mechanisms of action and resistance. *Rev Infect Dis* **1983**; 5 Suppl 3: S407-11.

613. Luna B, Trebosc V, Lee B, et al. A nutrient-limited screen unmasks rifabutin hyperactivity for extensively drug-resistant *Acinetobacter baumannii*. *Nat Microbiol* **2020**; 5(9): 1134-43.
614. Cheng J, Yan J, Reyna Z, et al. Synergistic Rifabutin and Colistin Reduce Emergence of Resistance When Treating *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2021**; 65(4): e02204-20.
615. Trebosc V, Schellhorn B, Schill J, et al. In vitro activity of rifabutin against 293 contemporary carbapenem-resistant *Acinetobacter baumannii* clinical isolates and characterization of rifabutin mode of action and resistance mechanisms. *J Antimicrob Chemother* **2020**; 75(12): 3552-62.
616. Phillips MC, Wald-Dickler N, Loomis K, Luna BM, Spellberg B. Pharmacology, Dosing, and Side Effects of Rifabutin as a Possible Therapy for Antibiotic-Resistant *Acinetobacter* Infections. *Open Forum Infect Dis* **2020**; 7(11): ofaa460.
617. Rothstein DM. Rifamycins, Alone and in Combination. *Cold Spring Harb Perspect Med* **2016**; 6(7).
618. Mojica MF, Humphries R, Lipuma JJ, et al. Clinical challenges treating *Stenotrophomonas maltophilia* infections: an update. *JAC Antimicrob Resist* **2022**; 4(3): dlac040.
619. Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. *Clin Microbiol Rev* **2012**; 25(1): 2-41.
620. Groschel MI, Meehan CJ, Barilar I, et al. The phylogenetic landscape and nosocomial spread of the multidrug-resistant opportunist *Stenotrophomonas maltophilia*. *Nat Commun* **2020**; 11(1): 2044.
621. Mojica MF, Rutter JD, Taracila M, et al. Population Structure, Molecular Epidemiology, and beta-Lactamase Diversity among *Stenotrophomonas maltophilia* Isolates in the United States. *mBio* **2019**; 10(4): e00405-19.
622. Isom CM, Fort B, Anderson GG. Evaluating Metabolic Pathways and Biofilm Formation in *Stenotrophomonas maltophilia*. *J Bacteriol* **2022**; 204(1): e0039821.
623. Paez JI, Costa SF. Risk factors associated with mortality of infections caused by *Stenotrophomonas maltophilia*: a systematic review. *J Hosp Infect* **2008**; 70(2): 101-8.
624. Osawa K, Shigemura K, Kitagawa K, Tokimatsu I, Fujisawa M. Risk factors for death from *Stenotrophomonas maltophilia* bacteremia. *J Infect Chemother* **2018**; 24(8): 632-6.
625. Falagas ME, Kastoris AC, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Dimopoulos G. Attributable mortality of *Stenotrophomonas maltophilia* infections: a systematic review of the literature. *Future Microbiol* **2009**; 4(9): 1103-9.
626. Jeon YD, Jeong WY, Kim MH, et al. Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia. *Medicine (Baltimore)* **2016**; 95(31): e4375.
627. Araoka H, Baba M, Yoneyama A. Risk factors for mortality among patients with *Stenotrophomonas maltophilia* bacteremia in Tokyo, Japan, 1996-2009. *Eur J Clin Microbiol Infect Dis* **2010**; 29(5): 605-8.
628. 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.

629. Karaba SM, Goodman KE, Amoah J, Cosgrove SE, Tamma PD. StenoSCORE: Predicting *Stenotrophomonas maltophilia* Bloodstream Infections in the Hematologic Malignancy Population. *Antimicrob Agents Chemother* **2021**; 65(8): e0079321.
630. Micozzi A, Venditti M, Monaco M, et al. Bacteremia due to *Stenotrophomonas maltophilia* in patients with hematologic malignancies. *Clin Infect Dis* **2000**; 31(3): 705-11.
631. Widmer AF, Kern WV, Roth JA, et al. Early versus late onset bloodstream infection during neutropenia after high-dose chemotherapy for hematologic malignancy. *Infection* **2019**; 47(5): 837-45.
632. Safdar A, Rolston KV. *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin Infect Dis* **2007**; 45(12): 1602-9.
633. Kim SH, Cha MK, Kang CI, et al. Pathogenic significance of hemorrhagic pneumonia in hematologic malignancy patients with *Stenotrophomonas maltophilia* bacteremia: clinical and microbiological analysis. *Eur J Clin Microbiol Infect Dis* **2019**; 38(2): 285-95.
634. Tada K, Kurosawa S, Hiramoto N, et al. *Stenotrophomonas maltophilia* infection in hematopoietic SCT recipients: high mortality due to pulmonary hemorrhage. *Bone Marrow Transplant* **2013**; 48(1): 74-9.
635. Araoka H, Fujii T, Izutsu K, et al. Rapidly progressive fatal hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in hematologic malignancy. *Transpl Infect Dis* **2012**; 14(4): 355-63.
636. 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(4): R74.
637. Okazaki A, Avison MB. Aph(3')-IIc, an aminoglycoside resistance determinant from *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother* **2007**; 51(1): 359-60.
638. 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(3): 483-9.
639. Alonso A, Martinez JL. Cloning and characterization of SmeDEF, a novel multidrug efflux pump from *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother* **2000**; 44(11): 3079-86.
640. 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.
641. Sanchez MB, Martinez JL. The efflux pump SmeDEF contributes to trimethoprim-sulfamethoxazole resistance in *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother* **2015**; 59(7): 4347-8.
642. Barnhill AE, Brewer MT, Carlson SA. Adverse effects of antimicrobials via predictable or idiosyncratic inhibition of host mitochondrial components. *Antimicrob Agents Chemother* **2012**; 56(8): 4046-51.
643. 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.

644. 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.
645. Satlin MJ, Lewis JS, Weinstein MP, et al. Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing Position Statements on Polymyxin B and Colistin Clinical Breakpoints. *Clin Infect Dis* **2020**; 71(9): e523-e9.
646. Martinez-Servat S, Yero D, Huedo P, et al. Heterogeneous Colistin-Resistance Phenotypes Coexisting in *Stenotrophomonas maltophilia* Isolates Influence Colistin Susceptibility Testing. *Front Microbiol* **2018**; 9: 2871.
647. Moskowitz SM, Garber E, Chen Y, et al. Colistin susceptibility testing: evaluation of reliability for cystic fibrosis isolates of *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*. *J Antimicrob Chemother* **2010**; 65(7): 1416-23.
648. Zelenitsky SA, Iacovides H, Ariano RE, Harding GK. Antibiotic combinations significantly more active than monotherapy in an in vitro infection model of *Stenotrophomonas maltophilia*. *Diagn Microbiol Infect Dis* **2005**; 51(1): 39-43.
649. Yu VL, Felegie TP, Yee RB, Pasculle AW, Taylor FH. Synergistic interaction in vitro with use of three antibiotics simultaneously against *Pseudomonas maltophilia*. *J Infect Dis* **1980**; 142(4): 602-7.
650. Biagi M, Vialichka A, Jurkovic M, et al. Activity of Cefiderocol Alone and in Combination with Levofloxacin, Minocycline, Polymyxin B, or Trimethoprim-Sulfamethoxazole against Multidrug-Resistant *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother* **2020**; 64(9).
651. Wei C, Ni W, Cai X, Zhao J, Cui J. Evaluation of Trimethoprim/Sulfamethoxazole (SXT), Minocycline, Tigecycline, Moxifloxacin, and Ceftazidime Alone and in Combinations for SXT-Susceptible and SXT-Resistant *Stenotrophomonas maltophilia* by In Vitro Time-Kill Experiments. *PLoS One* **2016**; 11(3): e0152132.
652. Shah MD, Coe KE, El Boghdady Z, et al. Efficacy of combination therapy versus monotherapy in the treatment of *Stenotrophomonas maltophilia* pneumonia. *J Antimicrob Chemother* **2019**; 74(7): 2055-9.
653. 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.
654. Muder RR, Harris AP, Muller S, et al. Bacteremia due to *Stenotrophomonas* (*Xanthomonas*) *maltophilia*: a prospective, multicenter study of 91 episodes. *Clin Infect Dis* **1996**; 22(3): 508-12.
655. 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.
656. Cai B, Tillotson G, Benjumea D, Callahan P, Echols R. The Burden of Bloodstream Infections due to *Stenotrophomonas Maltophilia* in the United States: A Large, Retrospective Database Study. *Open Forum Infect Dis* **2020**; 7(5): ofaa141.
657. Al-Jasser AM. *Stenotrophomonas maltophilia* resistant to trimethoprim-sulfamethoxazole: an increasing problem. *Ann Clin Microbiol Antimicrob* **2006**; 5: 23.

658. 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(4): 559-65.
659. 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(2): ofab644.
660. Ko JH, Kang CI, Cornejo-Juarez P, et al. Fluoroquinolones versus trimethoprim-sulfamethoxazole for the treatment of *Stenotrophomonas maltophilia* infections: a systematic review and meta-analysis. *Clin Microbiol Infect* **2019**; 25(5): 546-54.
661. Nys C, Cherabuddi K, Venugopalan V, Klinker KP. Clinical and Microbiologic Outcomes in Patients with Monomicrobial *Stenotrophomonas maltophilia* Infections. *Antimicrob Agents Chemother* **2019**; 63(11): e00788-19.
662. Hand E, Davis H, Kim T, Duhon B. Monotherapy with minocycline or trimethoprim/sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *J Antimicrob Chemother* **2016**; 71(4): 1071-5.
663. Tekce YT, Erbay A, Cabadak H, Sen S. Tigecycline as a therapeutic option in *Stenotrophomonas maltophilia* infections. *J Chemother* **2012**; 24(3): 150-4.
664. Cho SY, Kang CI, Kim J, et al. Can levofloxacin be a useful alternative to trimethoprim-sulfamethoxazole for treating *Stenotrophomonas maltophilia* bacteremia? *Antimicrob Agents Chemother* **2014**; 58(1): 581-3.
665. 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.
666. Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *Antimicrob Agents Chemother* **2014**; 58(1): 176-82.
667. 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(11): 3187-93.
668. 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(3): e0216721.
669. 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.
670. Biagi M, Tan X, Wu T, et al. Activity of Potential Alternative Treatment Agents for *Stenotrophomonas maltophilia* Isolates Nonsusceptible to Levofloxacin and/or Trimethoprim-Sulfamethoxazole. *J Clin Microbiol* **2020**; 58(2).
671. Wei C, Ni W, Cai X, Cui J. A Monte Carlo pharmacokinetic/pharmacodynamic simulation to evaluate the efficacy of minocycline, tigecycline, moxifloxacin, and levofloxacin in the

- treatment of hospital-acquired pneumonia caused by *Stenotrophomonas maltophilia*. *Infect Dis (Lond)* **2015**; 47(12): 846-51.
672. Looney WJ, Narita M, Muhlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. *Lancet Infect Dis* **2009**; 9(5): 312-23.
673. Farrell DJ, Sader HS, Jones RN. Antimicrobial susceptibilities of a worldwide collection of *Stenotrophomonas maltophilia* isolates tested against tigecycline and agents commonly used for *S. maltophilia* infections. *Antimicrob Agents Chemother* **2010**; 54(6): 2735-7.
674. Burkhardt O, Rauch K, Kaever V, Hadem J, Kielstein JT, Welte T. Tigecycline possibly underdosed for the treatment of pneumonia: a pharmacokinetic viewpoint. *Int J Antimicrob Agents* **2009**; 34(1): 101-2.
675. Watanabe A, Anzai Y, Niitsuma K, Saito M, Yanase K, Nakamura M. Penetration of minocycline hydrochloride into lung tissue and sputum. *Chemotherapy* **2001**; 47(1): 1-9.
676. De Pascale G, Lisi L, Ciotti GMP, et al. Pharmacokinetics of high-dose tigecycline in critically ill patients with severe infections. *Ann Intensive Care* **2020**; 10(1): 94.
677. Crandon JL, Kim A, Nicolau DP. Comparison of tigecycline penetration into the epithelial lining fluid of infected and uninfected murine lungs. *J Antimicrob Chemother* **2009**; 64(4): 837-9.
678. Jacobson S, Junco Noa L, Wallace MR, Bowman MC. Clinical outcomes using minocycline for *Stenotrophomonas maltophilia* infections. *J Antimicrob Chemother* **2016**; 71(12): 3620.
679. 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(4): 2415-29.
680. Falagas ME, Vardakas KZ, Tsiveriotis KP, Triarides NA, Tansarli GS. Effectiveness and safety of high-dose tigecycline-containing regimens for the treatment of severe bacterial infections. *Int J Antimicrob Agents* **2014**; 44(1): 1-7.
681. Lodise TP, Van Wart S, Sund ZM, et al. Pharmacokinetic and Pharmacodynamic Profiling of Minocycline for Injection following a Single Infusion in Critically Ill Adults in a Phase IV Open-Label Multicenter Study (ACUMIN). *Antimicrob Agents Chemother* **2021**; 65(3).
682. Hsueh SC, Lee YJ, Huang YT, Liao CH, Tsuji M, Hsueh PR. In vitro activities of cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam and other comparative drugs against imipenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, all associated with bloodstream infections in Taiwan. *J Antimicrob Chemother* **2019**; 74(2): 380-6.
683. Yamano Y. In Vitro Activity of Cefiderocol Against a Broad Range of Clinically Important Gram-negative Bacteria. *Clin Infect Dis* **2019**; 69(Suppl 7): S544-S51.
684. Kawaguchi N, Katsube T, Echols R, Wajima T. Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses of Cefiderocol, a Parenteral Siderophore Cephalosporin, in Patients with Pneumonia, Bloodstream Infection/Sepsis, or Complicated Urinary Tract Infection. *Antimicrob Agents Chemother* **2021**; 65(3): e01437-20.
685. 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.
686. 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(4).
687. 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(10): e0061822.
688. Heil EL, Tamma PD. Cefiderocol: the Trojan horse has arrived but will Troy fall? *Lancet Infect Dis* **2021**; 21(2): 153-5.
689. 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(12): 2805-6.
690. 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(3): 106395.
691. 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(11): 2021-4.
692. Zhang L, Li XZ, Poole K. Multiple antibiotic resistance in *Stenotrophomonas maltophilia*: involvement of a multidrug efflux system. *Antimicrob Agents Chemother* **2000**; 44(2): 287-93.
693. 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.
694. Garcia-Leon G, Ruiz de Alegria Puig C, Garcia de la Fuente C, Martinez-Martinez L, Martinez JL, Sanchez MB. High-level quinolone resistance is associated with the overexpression of smeVWX in *Stenotrophomonas maltophilia* clinical isolates. *Clin Microbiol Infect* **2015**; 21(5): 464-7.
695. Hamdi AM, Fida M, Abu Saleh OM, Beam E. *Stenotrophomonas* Bacteremia Antibiotic Susceptibility and Prognostic Determinants: Mayo Clinic 10-Year Experience. *Open Forum Infect Dis* **2020**; 7(1): ofaa008.
696. Baek JH, Kim CO, Jeong SJ, et al. Clinical factors associated with acquisition of resistance to levofloxacin in *Stenotrophomonas maltophilia*. *Yonsei Med J* **2014**; 55(4): 987-93.
697. Grillon A, Schramm F, Kleinberg M, Jehl F. Comparative Activity of Ciprofloxacin, Levofloxacin and Moxifloxacin against *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* Assessed by Minimum Inhibitory Concentrations and Time-Kill Studies. *PLoS One* **2016**; 11(6): e0156690.
698. Ba BB, Feghali H, Arpin C, Saux MC, Quentin C. Activities of ciprofloxacin and moxifloxacin against *Stenotrophomonas maltophilia* and emergence of resistant mutants in an in vitro pharmacokinetic-pharmacodynamic model. *Antimicrob Agents Chemother* **2004**; 48(3): 946-53.

699. Bonfiglio G, Cascone C, Azzarelli C, Cafiso V, Marchetti F, Stefani S. Levofloxacin in vitro activity and time-kill evaluation of *Stenotrophomonas maltophilia* clinical isolates. *J Antimicrob Chemother* **2000**; 45(1): 115-7.
700. Giamarellos-Bourboulis EJ, Karnesis L, Galani I, Giamarellou H. In vitro killing effect of moxifloxacin on clinical isolates of *Stenotrophomonas maltophilia* resistant to trimethoprim-sulfamethoxazole. *Antimicrob Agents Chemother* **2002**; 46(12): 3997-9.
701. 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.
702. 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**.
703. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. *JAMA Intern Med* **2017**; 177(9): 1308-15.
704. Biagi M, Lamm D, Meyer K, et al. Activity of Aztreonam in Combination with Avibactam, Clavulanate, Relebactam, and Vaborbactam against Multidrug-Resistant *Stenotrophomonas maltophilia*. *Antimicrob Agents Chemother* **2020**; 64(12): e00297-20.
705. Mojica MF, Papp-Wallace KM, Taracila MA, et al. Avibactam Restores the Susceptibility of Clinical Isolates of *Stenotrophomonas maltophilia* to Aztreonam. *Antimicrob Agents Chemother* **2017**; 61(10): e00777-17.
706. Mojica MF, Ouellette CP, Leber A, et al. Successful Treatment of Bloodstream Infection Due to Metallo-beta-Lactamase-Producing *Stenotrophomonas maltophilia* in a Renal Transplant Patient. *Antimicrob Agents Chemother* **2016**; 60(9): 5130-4.
707. Lin Q, Zou H, Chen X, et al. Avibactam potentiated the activity of both ceftazidime and aztreonam against *S. maltophilia* clinical isolates in vitro. *BMC Microbiol* **2021**; 21(1): 60.
708. Sader HS, Duncan LR, Arends SJR, Carvalhaes CG, Castanheira M. Antimicrobial Activity of Aztreonam-Avibactam and Comparator Agents When Tested against a Large Collection of Contemporary *Stenotrophomonas maltophilia* Isolates from Medical Centers Worldwide. *Antimicrob Agents Chemother* **2020**; 64(11): e01433-20.
709. Emeraud C, Escaut L, Boucly A, et al. Aztreonam plus Clavulanate, Tazobactam, or Avibactam for Treatment of Infections Caused by Metallo-beta-Lactamase-Producing Gram-Negative Bacteria. *Antimicrob Agents Chemother* **2019**; 63(5): e00010-19.
710. 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.
711. Cowart MC, Ferguson CL. Optimization of Aztreonam in Combination With Ceftazidime/Avibactam in a Cystic Fibrosis Patient With Chronic *Stenotrophomonas maltophilia* Pneumonia Using Therapeutic Drug Monitoring: A Case Study. *Ther Drug Monit* **2021**; 43(2): 146-9.
712. 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(5): 889-94.