Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

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Background. Antimicrobial-resistant infections are commonly encountered in US hospitals and result in significant morbidity and mortality. This guidance document provides recommendations for the treatment of infections caused by extended-spectrum β-lactamase–producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*).

Methods. A panel of 6 infectious diseases specialists with expertise in managing antimicrobial-resistant infections formulated common questions regarding the treatment of ESBL-E, CRE, and DTR-*P. aeruginosa* infections. Based on review of the published literature and clinical experience, the panel provide recommendations and associated rationale for each recommendation. Because of significant differences in the molecular epidemiology of resistance and the availability of specific anti-infective agents globally, this document focuses on treatment of antimicrobial-resistant infections in the United States.

Results. Approaches to empiric treatment selection, duration of therapy, and other management considerations are briefly discussed. The majority of guidance focuses on preferred and alternative treatment recommendations for antimicrobial-resistant infections, assuming that the causative organism has been identified and antibiotic susceptibility testing results are known. Treatment recommendations apply to both adults and children.

Conclusions. The field of antimicrobial resistance is dynamic and rapidly evolving, and the treatment of antimicrobial-resistant infections will continue to challenge clinicians. This guidance document is current as of 17 September 2020. Updates to this guidance document will occur periodically as new data emerge. Furthermore, the panel will expand recommendations to include other problematic gram-negative pathogens in future versions. The most current version of the guidance including the date of publication can be found at www.idsociety.org/practice-guideline/amr-guidance/.

The rise in antimicrobial resistance (AMR) continues to be a global crisis [1, 2]. Collectively, antimicrobial-resistant pathogens cause more than 2.8 million infections and more than 35 000 deaths annually in the United States, according to the 2019 Centers for Disease Control and Prevention (CDC) Antibiotic Resistant Threats Report [2]. Although there has been an increase in the availability of novel antibiotics to combat resistant infections in recent years [3], resistance to a number of these agents has been observed [4]. Three groups of antimicrobial-resistant gram-negative bacteria pose particular therapeutic challenges: extended-spectrum β-lactamase–producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa)* [5]. The CDC has designated these pathogens as urgent or serious threats [2]. They are encountered in US hospitals of all sizes and cause a wide range of serious infections that carry significant morbidity and mortality. Treatment options against ESBL-E, CRE, and DTR-*P. aeruginosa* infections remain limited despite approval

Received 23 September 2020; editorial decision 23 September 2020; published online 27 October 2020.

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Clinical Infectious Diseases® 2021;72(7):1109–16
DOI: 10.1093/cid/ciab295

of new antibiotics. There is often uncertainty about the precise role(s) of new agents in clinical practice [6–8].

The Infectious Diseases Society of America (IDSA) identified the development and dissemination of clinical practice guidelines and guidance documents for clinicians as a top initiative in its 2019 Strategic Plan [9]. 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. As an alternative and complement to comprehensive clinical practice guidelines, IDSA endorsed the development of more narrowly focused guidance documents for the treatment of specific infectious processes. Guidance documents address specific clinical questions for difficult-to-manage infections that are not covered by present guidelines. The documents are prepared by a small team of experts based on a comprehensive (but not necessarily systematic) review of the literature. Additionally, such guidance documents do not include a formal grading of the evidence, unlike IDSA guidelines that use the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework. This guidance document is current as of 17 September 2020. Updates to this document will occur periodically as new data emerge. Future iterations will also address other resistant pathogens. The most current version of the guidance including the date of publication can be found at www.idsociety.org/practice-guideline/amr-guidance/.

The overarching goal of this document is to assist clinicians, including those with and without infectious diseases expertise, in selecting antibiotic therapy for infections caused by ESBL-E, CRE, and DTR-*P. aeruginosa*. Although brief descriptions of notable clinical trials, resistance mechanisms, and susceptibility testing methods are included, this guidance is not meant to provide a comprehensive review of these topics. This document is framed as answers to a series of clinical questions, each of which can stand on its own. Because of significant differences in the molecular epidemiology of resistance and availability of specific anti-infectives globally, this document focuses on treatment recommendations for antimicrobial-resistant infections in the United States.

METHODOLOGY

This IDSA guidance document was developed by a panel of 6 actively practicing infectious diseases specialists with clinical and research expertise in the treatment of resistant bacterial infections. Through a series of web-based meetings, the panel developed several commonly encountered treatment questions and corresponding answers for each pathogen group. They reached consensus on the recommendations for each question based on extensive review of the published literature, coupled with clinical experience. Answers include a brief discussion of the rationale that supports the recommendations. For each pathogen group, a table is provided with preferred and alternative treatment recommendations, after antimicrobial susceptibility data are known. Treatment recommendations apply to both adult and pediatric populations. Suggested antibiotic dosing for adult patients with antimicrobial-resistant infections, assuming normal renal and hepatic function, is provided in Table 1.

GENERAL MANAGEMENT RECOMMENDATIONS

Preferred and alternative treatment recommendations in this guidance document assume that the causative organism has been identified and in vitro activity of antibiotics has been demonstrated. The panel did not consider the cost of agents. Assuming 2 antibiotics are equally effective and safe, cost, convenience, and local formulary availability are important considerations in selecting a specific agent. The panel recommends that infectious diseases specialists be involved in the management of patients with antimicrobial-resistant infections, if feasible.

Empiric Therapy

Empiric treatment recommendations are not provided in this guidance document since a given host at risk for infection by 1 of the pathogen groups is usually at risk of infection by other antimicrobial-resistant pathogens. Empiric treatment decisions should be guided by local susceptibility patterns for the most likely pathogens. When determining empiric treatment for a given patient, clinicians should consider previous organisms and associated antibiotic susceptibility data in the past 6 months and antibiotic exposures in the past 30 days (eg, if a treatment course of piperacillin-tazobactam was recently completed, consider empiric coverage with a gram-negative agent from a different class that offers a comparable spectrum of activity, such as meropenem). Empiric decisions should be refined based on the severity of the patient's illness, whether the patient is immunocompromised, and the likely source of the infection (eg, presumed ventilator-associated pneumonia typically warrants broader empiric coverage than presumed cystitis).

Duration of Therapy

Recommendations on durations of therapy are not provided, but clinicians are advised that prolonged treatment courses are not necessary against infections by antimicrobial-resistant pathogens per se, compared with infections caused by the same bacterial species with a more susceptible phenotype. After antibiotic susceptibility results are available, it may become apparent that inactive antibiotic therapy was initiated empirically. This may impact the duration of therapy. For example, cystitis is typically a mild infection. If an antibiotic not active against the causative organism was administered empirically for 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 [11]. However, for all other

Table 1. Suggested Dosing of Antibiotics for the Treatment of Extended-spectrum β-Lactamase–Producing Enterobacterales, Carbapenem-resistant Enterobacterales, and *Pseudomonas aeruginosa* With Difficult-to-Treat Resistance Infections

Agent	Adult Dosage, Assuming Normal Renal and Liver Function
Amikacin	Cystitis: 15 mg/kg/dose[a] IV once
	All other infections: 20 mg/kg/dose[a] IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation
Amoxicillin-clavulanate	Cystitis: 875 mg (amoxicillin component) PO every 12 hours
Cefiderocol	2 g IV every 8 hours, infused over 3 hours
Ceftazidime-avibactam	2.5 g IV every 8 hours, infused over 3 hours
Ceftazidime-avibactam and aztreonam (infused together)	Ceftazidime-avibactam: 2.5 g IV every 8 hours, infused over 3 hours
	plus
	Aztreonam: 2 g IV every 8 hours, infused over 3 hours
Ceftolozane-tazobactam	Cystitis: 1.5 g IV every 8 hours, infused over 1 hour
	All other infections: 3 g IV every 8 hours, infused over 3 hours
Ciprofloxacin	400 mg IV every 8 hours or 750 mg PO every 12 hours
Colistin	Refer to international consensus guidelines on polymyxins[10]
Eravacycline	1 mg/kg/dose IV every 12 hours
Ertapenem	1 g IV every 24 hours, infused over 30 minutes
Fosfomycin	Cystitis: 3 g PO × 1 dose
Gentamicin	Cystitis: 5 mg/kg/dose[a] IV once
	All other infections: 7 mg/kg/dose[a] IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation
Imipenem-cilastatin	Cystitis (standard infusion): 500 mg IV every 6 hours, infused over 30 minutes
	All other infections (extended-infusion): 500 mg IV every 6 hours, infused over 3 hours
Imipenem-cilastatin-relebactam	1.25 g IV every 6 hours, infused over 30 minutes
Levofloxacin	750 mg IV/PO every 24 hours
Meropenem	Cystitis (standard infusion): 1 g IV every 8 hours
	All other infections (extended-infusion): 2 g IV every 8 hours, infused over 3 hours
Meropenem-vaborbactam	4 g IV every 8 hours, infused over 3 hours
Nitrofurantoin	Cystitis: macrocrystal/monohydrate (Macrobid®)100 mg PO every 12 hours
	Cystitis: Oral suspension: 50 mg every 6 hours
Plazomicin	Cystitis: 15 mg/kg[a] IV × 1 dose
	All other infections: 15 mg/kg[a] IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation
Polymyxin B	Refer to international consensus guidelines on polymyxins[10]
Tigecycline	Uncomplicated intra-abdominal infections (standard dose): 100 mg IV × 1 dose, then 50 mg IV every 12 hours
	Complicated intra-abdominal infections (high dose): 200 mg IV × 1 dose, then 100 mg IV every 12 hours
Tobramycin	Cystitis: 7 mg/kg/dose[a] IV × 1 dose
	All other infections: 7 mg/kg/dose[a] IV × 1 dose; subsequent doses and dosing interval based on pharmacokinetic evaluation
Trimethoprim-sulfamethoxazole	Cystitis: 160 mg (trimethoprim component) IV/PO every 12 hours
	Other infections: 8–10 mg/kg/day (trimethoprim component) IV/PO divided every 8–12 hours; maximum dose 320 mg PO every 8 hours

Abbreviations: IV, intravenous; PO, by mouth.
[a]Recommend using adjusted body weight for patients >120% of ideal body weight for aminoglycoside dosing.

infections included in this document, if antibiotic susceptibility data 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.

EXTENDED-SPECTRUM β-LACTAMASE–PRODUCING ENTEROBACTERALES

The incidence of ESBL-E infections in the United States increased by 53% from 2012 through 2017, in large part due to increased community-acquired infections [12]. 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

(eg, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin). However, organisms that carry ESBL genes often carry 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* [13, 14]. CTX-M enzymes, particularly CTX-M-15, are the most common ESBLs in the United States [14]. ESBLs other than CTX-M with unique hydrolyzing abilities have been identified, including variants of narrow-spectrum TEM and SHV β-lactamases with amino acid substitutions [15–17]. Routine EBSL testing is not performed by most clinical microbiology laboratories [18, 19]. Rather, nonsusceptibility to ceftriaxone (ie, ceftriaxone minimum inhibitory concentrations [MICs] ≥2 μg/mL), is often used as a proxy for ESBL production [19]. For this guidance document, ESBL-E refers to presumed or confirmed ESBL-producing *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*. Table 2 outlines preferred and alternative treatment recommendations for ESBL-E infections. Treatment recommendations for ESBL-E infections assume in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 1: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by ESBL-E?

Recommendation: Nitrofurantoin and trimethoprim-sulfamethoxazole are preferred treatment options for uncomplicated cystitis caused by ESBL-E.

Question 2: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections (cUTIs) caused by ESBL-E?

Recommendation: Ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole are preferred treatment options for pyelonephritis and cUTIs caused by ESBL-E.

Question 3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by ESBL-E?

Recommendation: A carbapenem is preferred for the treatment of infections outside of the urinary tract caused by ESBL-E.

Question 4: Is there a role for piperacillin-tazobactam in the treatment of infections caused by ESBL-E when in vitro susceptibility to piperacillin-tazobactam is demonstrated?

Recommendation: Piperacillin-tazobactam should be avoided for the treatment of infections caused by ESBL-E, even if susceptibility to piperacillin-tazobactam is demonstrated. If piperacillin-tazobactam is initiated as empiric therapy for cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary.

Question 5: Is there a role for cefepime in the treatment of infections caused by ESBL-E when in vitro susceptibility to cefepime is demonstrated?

Recommendation: Cefepime should be avoided for the treatment of infections caused by ESBL-E, even if susceptibility to cefepime is demonstrated. If cefepime is initiated as empiric therapy for cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary.

Question 6: What are preferred antibiotics in the treatment of infections caused by *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* not susceptible to ceftriaxone if confirmatory phenotypic ESBL testing is negative?

Recommendation: Antibiotic treatment selection can be based on susceptibility testing results if a locally validated ESBL phenotypic test does not indicate ESBL production.

Table 2. Recommended Antibiotic Treatment Options for Presumed or Confirmed Extended-spectrum β-Lactamase–Producing Enterobacterales, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Nitrofurantoin, trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate, single-dose aminoglycosides, fosfomycin (*Escherichia coli* only) Ciprofloxacin, levofloxacin, ertapenem, meropenem, imipenem-cilastatin
Pyelonephritis or complicated urinary tract infection[a]	Ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole	
Infections outside of the urinary tract	Meropenem, imipenem-cilastatin, ertapenem Oral step-down therapy to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole should be considered[b]	

[a]A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[b]Oral step-down therapy can be considered after susceptibility to the oral agent is demonstrated, patients are afebrile and hemodynamically stable, appropriate source control is achieved, and there are no issues with intestinal absorption.

Question 7: What is the preferred antibiotic for the treatment of bloodstream infections caused by ceftriaxone nonsusceptible *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*, if a $bla_{\text{CTX-M}}$ gene is not detected using a molecular platform that includes this target?

Recommendation: Carbapenem therapy is preferred if a $bla_{\text{CTX-M}}$ gene is not detected in *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* isolates that are not susceptible to ceftriaxone since the absence of a $bla_{\text{CTX-M}}$ gene does not exclude the presence of other ESBL genes.

CARBAPENEM-RESISTANT ENTEROBACTERALES

CRE account for more than 13 000 nosocomial infections and contribute to more than 1000 deaths annually in the United States [2]. The CDC defines CRE as members of the Enterobacterales order resistant to at least 1 carbapenem antibiotic or producing a carbapenemase enzyme [2]. A CRE isolate may be resistant to some carbapenems (eg, ertapenem) but not others (eg, meropenem). CRE comprise a heterogenous group of pathogens with multiple potential mechanisms of resistance, broadly divided into those that are carbapenemase-producing and those that are not carbapenemase-producing. Carbapenemase-producing isolates account for approximately half of all CRE infections in the United States [44–46]. The most common carbapenemases in the United States are *Klebsiella pneumoniae* carbapenemases (KPCs), which can be produced by any Enterobacterales. 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 oxacillinase (eg, OXA-48–like) carbapenemases [47, 48]. Knowledge of whether a CRE clinical isolate is carbapenemase-producing and, if it is, the specific carbapenemase produced are important in guiding treatment decisions.

Phenotypic tests such as the modified carbapenem inactivation method and the Carba NP test can differentiate carbapenemase and non-carbapenemase–producing CRE [49]. Molecular testing can identify specific carbapenemase families (eg, differentiating a KPC from an OXA-48–like carbapenemase). There are several molecular platforms used in US clinical microbiology laboratories to identify carbapenemase genes (eg, Verigene Gram-Negative Blood Culture Test, GenMark ePlex Blood Culture Identification Gram-negative Panel, BioFire FilmArray Blood Culture Identification Panels). Carbapenemase phenotypic and/or genotypic testing are not performed by all clinical microbiology laboratories. Table 3 outlines preferred and alternative treatment recommendations for CRE infections. Treatment recommendations for CRE infections assume in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 1: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by CRE?

Recommendation: Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside are preferred treatment options for uncomplicated cystitis caused by CRE. Standard infusion meropenem is a preferred treatment option for cystitis caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative.

Question 2: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections (cUTIs) caused by CRE?

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis and cUTIs caused by CRE resistant to both ertapenem and meropenem. Extended-infusion meropenem is a preferred treatment option for pyelonephritis and cUTIs caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative.

Question 3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative?

Recommendation: Extended-infusion meropenem is the preferred treatment for infections outside of the urinary tract caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative.

Question 4: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem when carbapenemase testing results are either not available or negative?

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem when carbapenemase testing results are either not available or negative.

Question 5: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if carbapenemase production is present?

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for KPC-producing infections outside of the urinary tract. Ceftazidime-avibactam in combination with aztreonam or cefiderocol as monotherapy are preferred treatment options for NDM and other metallo-β-lactamase–producing CRE infections. Ceftazidime-avibactam is the preferred treatment for OXA-48-like–producing CRE infections.

Table 3. Recommended Antibiotic Treatment Options for Carbapenem-Resistant Enterobacterales, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol
	Meropenem[a] (standard infusion): only if ertapenem-resistant, meropenem-susceptible, AND carbapenemase testing results are either not available or negative	Colistin (when no alternative options are available)
Pyelonephritis or complicated urinary tract infection[b]	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol	Once-daily aminoglycosides
	Meropenem[a] (extended-infusion): only if ertapenem-resistant, meropenem-susceptible, AND carbapenemase testing results are either not available or negative	
Infections outside of the urinary tract Resistant to ertapenem, susceptible to meropenem, AND carbapenemase testing results are either not available or negative	Meropenem[a] (extended-infusion)	Ceftazidime-avibactam
Infections outside of the urinary tract	Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam	Cefiderocol
Resistant to ertapenem, resistant to meropenem, AND carbapenemase testing results are either not available or negative		Tigecycline, eravacycline (generally limited to intra-abdominal infections)
Klebsiella pneumoniae carbapenemases identified (or carbapenemase positive but identify of carbapenemase unknown[c])	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam	Cefiderocol
		Tigecycline, eravacycline (generally limited to intra-abdominal infections)
Metallo-β-lactamase (ie, NDM, VIM, IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam, cefiderocol	Tigecycline, eravacycline (generally limited to intra-abdominal infections)
OXA-48-like carbapenemase identified	Ceftazidime-avibactam	Cefiderocol
		Tigecycline, eravacycline (generally limited to intra-abdominal infections)

[a]The majority of infections caused by carbapenem-resistant Enterobacterales (CRE) resistant to ertapenem but susceptible to meropenem are caused by organisms that do not produce carbapenemases.

[b]A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[c]The vast majority of carbapenemase-producing Enterobacterales infections in the United States are due to bacteria that produce *Klebsiella pneumoniae* carbapenemases (KPC). If a disease-causing Enterobacterales is carbapenemase-producing but the specific carbapenemase enzyme is unknown, it is reasonable to treat as if the strain is a KPC producer. If a patient is infected with a CRE strain with an unknown carbapenemase status and the patient has recently traveled from an area where metallo-β-lactamases are endemic (eg, Middle East, South Asia, Mediterranean), treatment with ceftazidime-avibactam plus aztreonam or cefiderocol as monotherapy is recommended. Preferred treatment approaches for infections caused by metallo-β-lactamase producers also provide activity against KPC and OXA (oxacillinase)-48-like enzymes.

Question 6: What is the role of polymyxins for the treatment of infections caused by CRE?

Recommendation: Polymyxin B and colistin should be avoided for the treatment of infections caused by CRE. Colistin can be considered as a last resort for uncomplicated CRE cystitis.

Question 7: What is the role of combination antibiotic therapy for the treatment of infections caused by CRE?

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

PSEUDOMONAS AERUGINOSA WITH DIFFICULT-TO-TREAT RESISTANCE

The CDC reports that 32 600 cases of multidrug-resistant *P. aeruginosa* infection occurred in patients hospitalized in the United States in 2017, resulting in 2700 deaths [2]. Multidrug resistance is defined as nonsusceptibility to at least 1 antibiotic in at least 3 classes for which *P. aeruginosa* susceptibility is generally expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems. In 2018, the concept of "difficult-to-treat" resistance (DTR) was proposed [5]. In this guidance document, DTR is defined

Table 4. Recommended Antibiotic Treatment Options for Difficult-to-Treat *Pseudomonas aeruginosa*, Assuming In Vitro Susceptibility to Agents in Table

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol, or a single dose of an aminoglycoside	Colistin
Pyelonephritis or complicated urinary tract infection[a]	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol	Once-daily aminoglycosides
Infections outside of the urinary tract	Ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam	Cefiderocol Aminoglycoside monotherapy: limited to uncomplicated bloodstream infections with complete source control[b]

[a]A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[b]Uncomplicated bloodstream infections include a bloodstream infection that is due to a urinary source or a catheter-related bloodstream infection with removal of the infected vascular catheter.

as *P. aeruginosa* that exhibits nonsusceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin. Table 4 outlines preferred and alternative treatment recommendations for DTR-*P. aeruginosa* infections. Treatment recommendations for DTR-*P. aeruginosa* infections assume in vitro activity of preferred and alternative antibiotics has been demonstrated.

Question 1: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by DTR-*P. aeruginosa*?

Recommendation: Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, cefiderocol, or a single dose of an aminoglycoside are the preferred treatment options for uncomplicated cystitis caused by DTR-*P. aeruginosa*.

Question 2: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections (cUTI) caused by DTR-*P. aeruginosa*?

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

Question 3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*?

Recommendation: Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam as monotherapy are the preferred treatment options for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*.

Question 4: What is the role of combination antibiotic therapy for the treatment of infections caused by DTR-*P. aeruginosa*?

Recommendation: Combination antibiotic therapy is not routinely recommended for infections caused by DTR-*P. aeruginosa* if in vitro susceptibility to a first-line antibiotic (ie, ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam) has been confirmed.

Rationale: Although empiric combination antibiotic therapy (ie, the addition of an aminoglycoside or polymyxin to a β-lactam agent) to broaden the likelihood of at least 1 active therapeutic 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 [91]. Rather, the continued use of a second agent increases the likelihood of antibiotic-associated adverse events [91].

CONCLUSIONS

The field of AMR is dynamic and rapidly evolving, and the treatment of antimicrobial-resistant infections will continue to challenge clinicians. As newer antibiotics against resistant pathogens are incorporated into clinical practice, we are learning more about their effectiveness and propensity to develop resistance. This AMR Treatment Guidance will be updated through an iterative review process that will incorporate new evidence-based data. Furthermore, the panel will expand recommendations to include other problematic gram-negative pathogens in future versions of this guidance document.

Notes

Acknowledgments. The authors thank Helen Boucher, Vance Fowler, and Cynthia Sears for their guidance in the development of this document. They also thank Deanna Buehrle, Kathleen Chiotos, Jennifer Girotto, Erin McCreary, and Jason Pogue for their critical review of this document. Finally, they express their sincere gratitude to the Infectious Diseases Society of America for organizing the development of this Antimicrobial Resistance Treatment Guidance.

Potential conflicts of interest. P.D.T. reports no disclosures. S. J. A. served on the advisory panel for Merck; served on the advisory board for Paratek, Medicines Company, Zavante, Shionogi, Sempra, and Theravance; and receives research funding paid to his institution from Melinta and Merck. R. A. B. receives research funding paid to his institution from VenatoRx, Merck, Entasis, and Tetraphase. A. J. M. served as an advisor for Rempex; serves as a consultant/advisory panel member for Qpex Biopharma, Acceclerate Diagnostics, VenatoRX, and Antimicrobial Resistance Services. D. D. serves as an advisory panel member for Qpex Biopharma and served as an advisory board member for Shionogi,

Entasis, Merck, Roche, Allergan, and Achaogen. C. J. C. served on the advisory board for Merck, Qpex Biopharma, Astellas, Cidara, and Scynexis; serves as a consultant for Needham & Associates; and receives research funding paid to his institution from Astellas and Merck. 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.

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