

Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections

Yohei Doi^{1,2}

¹Center for Innovative Antimicrobial Therapy, Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pennsylvania; and ²Departments of Microbiology and Infectious Diseases, Fujita Health University School of Medicine, Aichi, Japan

Antimicrobial resistance has become one of the greatest threats to public health, with rising resistance to carbapenems being a particular concern due to the lack of effective and safe alternative treatment options. Carbapenem-resistant gram-negative bacteria of clinical relevance include the Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and more recently, *Stenotrophomonas maltophilia*. Colistin and tigecycline have been used as first-line agents for the treatment of infections caused by these pathogens; however, there are uncertainties regarding their efficacy even when used in combination with other agents. More recently, several new agents with activity against certain carbapenem-resistant pathogens have been approved for clinical use or are reaching late-stage clinical development. They include ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, plazomicin, eravacycline, and cefiderocol. In addition, fosfomycin has been redeveloped in a new intravenous formulation. Data regarding the clinical efficacy of these new agents specific to infections caused by carbapenem-resistant pathogens are slowly emerging and appear to generally favor newer agents over previous best available therapy. As more treatment options become widely available for carbapenem-resistant gram-negative infections, the role of antimicrobial stewardship will become crucial in ensuring appropriate and rationale use of these new agents.

Keywords. antimicrobial stewardship; carbapenemase; multidrug resistance; rapid diagnostics.

As the antimicrobial resistance crisis worsens, carbapenem resistance in gram-negative pathogens poses a special clinical challenge, as carbapenems have long been considered the most active and potent agents against multidrug-resistant (MDR) gram-negative pathogens. Indeed, on the global priority list of antibiotic-resistant bacteria published by the World Health Organization in 2017, 3 of the 4 pathogens designated as being of critical priority for research and development of new antibiotics are carbapenem-resistant pathogens, including carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii* [1]. The key elements that define the threat of carbapenem-resistant gram-negative pathogens include (i) increasing incidence of these pathogens worldwide since the turn of the century [2]; (ii) lack of safe and efficacious agents for treatment once the efficacy of carbapenems is lost due to resistance [3]; and (iii) high mortality rates associated with carbapenem-resistant gram-negative infections [4].

Clinical development of new antimicrobial agents had lagged in the 1990s, but increasing recognition of the clinical challenges

posed by carbapenem-resistant gram-negative bacteria has spurred renewed interests in developing new treatment modalities to treat such infections. These efforts are finally bringing novel antimicrobial agents with activity against carbapenem-resistant gram-negative pathogens into clinical practice. This review is intended to provide an overview of the current state of therapy for carbapenem-resistant gram-negative infections, the newer agents that have or are expected to become available, and how these new treatments may fit into clinical practice through sound antimicrobial stewardship.

CARBAPENEM-RESISTANT GRAM-NEGATIVE PATHOGENS: A CRITICAL PUBLIC HEALTH THREAT

Among the large group of gram-negative bacteria, a limited number are capable of causing illness in humans in the context of carbapenem resistance. The types of the mechanisms causing carbapenem resistance (eg, carbapenemase production, porin mutation, or efflux pump upregulation) are described in detail in the article by Nordmann and Poirel [5]. The key organisms to consider include the order Enterobacteriales (which includes the family Enterobacteriaceae), *P. aeruginosa*, *A. baumannii*, and *Stenotrophomonas maltophilia*.

Enterobacteriales

Historically, the order Enterobacteriales was highly susceptible to carbapenems, with the exception of the family Morganellaceae (*Proteus* species, *Morganella* species, and *Providencia* species),

Correspondence: Y. Doi, University of Pittsburgh School of Medicine, S829 Scaife Hall, 3550 Terrace St, Pittsburgh, PA 15261 (yod4@pitt.edu).

Clinical Infectious Diseases® 2019;69(S7):S565–75

© The Author(s) 2019. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
DOI: 10.1093/cid/ciz830

which are intrinsically nonsusceptible to imipenem. Acquired carbapenem resistance among the more commonly encountered species in the family Enterobacteriaceae, such as *Klebsiella pneumoniae* and *Escherichia coli*, emerged sporadically over the 1990s with the production of metallo- β -lactamases (MBLs; eg, imipenemase metallo- β -lactamase [IMP] and Verona integron-encoded metallo- β -lactamase [VIM] groups) [6, 7]. However, resistance was only recognized as a major public health concern in the early 2000s when CRE emerged and then spread in healthcare facilities in the mid-Atlantic states of the United States (US) [8]. This new epidemic was initiated by *K. pneumoniae* that produced carbapenemases (KPC)—a group of β -lactamases with the ability to hydrolyze carbapenems [9]. Within a decade, KPC-producing, carbapenem-resistant bacteria had spread to most of the rest of the US, Israel, and southern European countries (especially Greece and Italy) and, more recently, to the South American continent and China [10]. Just over 10% of *K. pneumoniae* that cause healthcare-associated infections in US hospitals are currently carbapenem-resistant [11], and much of this is due to KPC-producing organisms [12]. This was followed by the emergence of *K. pneumoniae* producing oxacillinase (OXA)-48 carbapenemases in Turkey [13], as well as *E. coli* producing New Delhi metallo- β -lactamase (NDM) MBLs in India [14]. Enterobacteriaceae producing OXA-48 and NDM carbapenemases have now been identified worldwide, and the situation with the latter in the Indian subcontinent appears to be particularly worrisome [15]. It is important to consider the specific groups of carbapenemases underlying carbapenem resistance, as each novel agent has been developed with a unique spectrum of activity against Enterobacteriaceae producing various carbapenemases.

Pseudomonas aeruginosa

Pseudomonas aeruginosa was the first species in which acquired carbapenem resistance emerged after the introduction of the first carbapenem, imipenem, in the mid-1980s; resistance was due to changes in porin expression, which rendered the outer bacterial membrane impermeable to imipenem [16]. Although meropenem is less prone to this resistance mechanism, *P. aeruginosa* can become resistant to meropenem by upregulation of efflux pumps [17]. In the US, 10%–20% of *P. aeruginosa* clinical isolates identified in healthcare settings are resistant to at least 1 carbapenem [18, 19]. Globally, carbapenem resistance due to production of MBLs (in particular the VIM group) appears to be common in *P. aeruginosa* [20], which has implications when considering treatment options, as most β -lactamase inhibitors (BLIs) are unable to inhibit their activity. MBLs are considered uncommon in *P. aeruginosa* in the US, but outbreaks by VIM-producing *P. aeruginosa* have been reported [21].

Acinetobacter baumannii

Acinetobacter baumannii had been considered an opportunistic pathogen of questionable clinical significance until the

1980s, but this view changed in the 1990s when MDR and often carbapenem-resistant *A. baumannii* strains started to cause infections (eg, ventilator-associated pneumonia [VAP]) in intensive care units in Europe, which then soon spread to hospitals worldwide [22]. These carbapenem-resistant strains were found to belong to several clonal groups (CG), especially CG1 and CG2, and produced acquired carbapenemases that were highly specific to *A. baumannii*. The most common *A. baumannii* carbapenemase is OXA-23, particularly in the US [23], whereas OXA-40 and OXA-58 carbapenemases are also distributed globally, albeit at lower frequencies than OXA-23. Unlike *P. aeruginosa*, noncarbapenemase-mediated mechanisms appear to play a lesser role in carbapenem resistance of *A. baumannii* [24].

Stenotrophomonas maltophilia

Stenotrophomonas maltophilia differs from the carbapenem-resistant pathogens discussed above in that it naturally produces inducible L1 MBL and is therefore intrinsically resistant to carbapenems as a species [25]. *Stenotrophomonas maltophilia* is an environmental species that can cause opportunistic respiratory tract and bloodstream infections in susceptible hosts, including those with cystic fibrosis, malignancy, and immunosuppressive conditions. Although the species used to be susceptible to several other agents (eg, ceftazidime, ticarcillin-clavulanate, trimethoprim-sulfamethoxazole, fluoroquinolones, and tetracyclines), susceptibility rates to these agents are declining [26].

APPROACH TO THERAPY OF CARBAPENEM-RESISTANT GRAM-NEGATIVE INFECTIONS

General Considerations

Selecting an antimicrobial regimen for carbapenem-resistant gram-negative infections is almost always challenging, though the degree of difficulty varies depending on the specific clinical scenario. In particular, tissue penetration and local free antibiotic concentration at the site of infection are important factors to consider in the selection of the most appropriate antibiotic therapy. Host variables, renal function in particular, may also have an impact on the decision-making process. Furthermore, the overall susceptibility profiles of the pathogens to noncarbapenem agents must be considered.

Even when carbapenem resistance is confirmed in a pathogen, some noncarbapenem agents (other than colistin, tigecycline, and minocycline) may be active against these pathogens. Among noncarbapenem agents, gentamicin is active against some CRE strains, and some observations suggest that gentamicin-containing regimens may be more efficacious than other combination regimens for sepsis due to CRE [27]. Ampicillin-sulbactam has been used successfully to treat invasive infections caused by *A. baumannii* strains [28], with sulbactam being the active component of this combination

against some carbapenem-resistant strains [29]. Of note, only a small proportion of the carbapenem-resistant *P. aeruginosa* strains are susceptible to noncarbapenem agents such as cefepime, ciprofloxacin, and amikacin [30]. The majority of *S. maltophilia* strains are susceptible to trimethoprim-sulfamethoxazole, and only some strains are susceptible to minocycline, ticarcillin-clavulanate, or fluoroquinolones [31]. Although clinical evidence is limited, fluoroquinolones may be as efficacious as trimethoprim-sulfamethoxazole in the treatment of *S. maltophilia* infections [32, 33]. However, the susceptibility patterns are not predictable for most carbapenem-resistant gram-negative bacteria, and therefore selection of any of these older agents must be guided by clear antibiotic-specific susceptibility testing results reported by the microbiologists. More recently, ceftazidime-avibactam and meropenem-vaborbactam for CRE and ceftolozane-tazobactam for carbapenem-resistant *P. aeruginosa* infections have become important treatment options in countries where these agents have become available for clinical use. Furthermore, several other new agents are reaching late-stage clinical development (Table 1).

Polymyxins (Colistin and Polymyxin B)

Colistin (or polymyxin E) is a mixture of cyclic polypeptide antibiotics with activity against most species in the order Enterobacteriales (except for *Serratia marcescens* and *Proteus*, *Providencia*, *Morganella*, and *Hafnia* species), *P. aeruginosa*, *A. baumannii*, and some *S. maltophilia* strains [34]. While prominent toxicity (both nephrotoxicity and neurotoxicity) has limited the clinical use of colistin, its broad-spectrum activity

against carbapenem-resistant pathogens has led to its widespread use for the treatment of infections caused by such pathogens. Although few head-to-head studies have been conducted, clinical observations suggest a less than optimal outcome of patients who received colistin monotherapy for these infections [35]. In addition, colistin is administered as an inactive prodrug—colistin methanesulfonate—which results in a prolonged period of low plasma concentrations of the active drug and theoretically increases the risk of resistance development [34]. Polymyxin B, the other approved agent in the polymyxin class of antibiotics, is not formulated as a prodrug, which mitigates the concerns related to a delayed increase in its plasma concentration, but less is known about its pharmacokinetic, efficacy, and safety profiles. Because of these concerns, the standard practice over the past decade has been to use colistin or polymyxin B in combination with at least 1 other agent of a different class when its use is warranted.

Tigecycline and Minocycline

Tigecycline is a glycylicycline agent that was designed to resist key tetracycline resistance mechanisms (ribosome protection and active efflux) and as a result has broad-spectrum activity against both gram-positive and gram-negative pathogens, with notable exceptions of *P. aeruginosa*, *Proteus* species, and *Providencia* species [36]. Among carbapenem-resistant gram-negative pathogens, tigecycline is active against the majority of CRE, *A. baumannii*, and *S. maltophilia* strains. Despite its in vitro activity against these problematic pathogens, data regarding clinically efficacy have been mixed, with an excess

Table 1. Activity and Indications of New Agents Against Carbapenem-resistant Gram-negative Pathogens

Agent	Activity						Indications (Including Expected)	Pathogen-directed Trial (Including Expected)
	Enterobacteriaceae			<i>P. aeruginosa</i>	<i>A. baumannii</i>	<i>S. maltophilia</i>		
	Class A Carbapenemase (eg, KPC)	Class B Carbapenemase (eg, NDM)	Class D Carbapenemase (eg, OXA-48)					
Ceftazidime-avibactam	Yes	No	Yes	Yes	No	No	cUTI/AP, cIAI, HABP/VABP	No
Ceftolozane-tazobactam	No	No	No	Yes	No	No	cUTI/AP, cIAI, NP	No
Meropenem-vaborbactam	Yes	No	No	No ^a	No	No	cUTI/AP	Yes
Imipenem-cilastatin-relebactam	Yes	No	No	Yes	No	No	cUTI/AP, cIAI, HABP/VABP	Yes
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	cUTI/AP, HABP/VABP	Yes
Plazomicin	Yes	Variable ^b	Yes	Variable	No	No	cUTI/AP	Yes
Eravacycline	Yes	Yes	Yes	No	Yes	Yes	cIAI	No
Fosfomycin	Yes	Yes	Yes	Variable	No	No	cUTI/AP	No

Abbreviations: *A. baumannii*, *Acinetobacter baumannii*; AP, acute pyelonephritis; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; NP, nosocomial pneumonia; OXA, oxacillinase; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. maltophilia*, *Stenotrophomonas maltophilia*; VABP, ventilator-associated bacterial pneumonia.

^aNot active beyond the activity of meropenem alone.

^bFrequently inactive against strains that produce NDM-type metallo-β-lactamases.

mortality risk shown in comparative clinical trials [37]. Double-dose tigecycline has been adopted by some clinicians for severe infections such as VAP, but clinical data are limited and many patients cannot tolerate the gastrointestinal side effects [38]. As with colistin, tigecycline is mostly used in combination regimens when treating carbapenem-resistant gram-negative infections to overcome the above pitfalls. In addition, tigecycline is generally not recommended for bacteremia because of its bacteriostatic activity and low steady-state concentrations in serum at current dosing recommendation [36, 39].

Minocycline, an old derivative of tetracycline, has been “rediscovered” as an agent with in vitro activity against most carbapenem-resistant *A. baumannii* strains [40]. It is not as active against CRE as tigecycline and has no activity against *P. aeruginosa*. Clinical data regarding its efficacy against carbapenem-resistant *A. baumannii* infections are currently limited to case series [41].

Ceftazidime-avibactam

Avibactam is a diazabicyclooctane BLI that was approved in combination with ceftazidime for the treatment of complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs) in 2015, and subsequently for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) in 2018 [42]. Avibactam binds reversibly to class A β -lactamases including KPC carbapenemases, class C β -lactamases, and certain oxacillinases (ie, OXA-48 carbapenemases), but it does not inhibit MBLs such as NDM carbapenemases [42]. Avibactam is renally excreted, and its pharmacokinetics are similar to those of ceftazidime, allowing for coformulation [43]. Ceftazidime-avibactam is highly active against KPC-producing CRE, and has become the first-line therapy for these infections in many hospitals. However, ceftazidime-avibactam-resistant KPC-producing *K. pneumoniae* may emerge upon treatment with this agent in as many as 10% of patients as a result of mutations in the *bla*_{KPC} gene [44]. These variant KPC β -lactamases are no longer able to hydrolyze carbapenems efficiently, and as a result these ceftazidime-avibactam-resistant *K. pneumoniae* strains are typically susceptible to carbapenems [45]. However, clinical significance of this observation is unclear, since subsequent exposure to carbapenems can restore resistance to them [46]. The majority of carbapenem-resistant *P. aeruginosa* strains are susceptible to ceftazidime-avibactam [47]. Nonetheless, susceptibility of *P. aeruginosa* strains to ceftazidime-avibactam depends on the coexistence of various resistance mechanisms affecting porin channel function, efflux pump expression, and/or β -lactamase enzyme expression [48–50]. Ceftazidime-avibactam is not active against *A. baumannii* or *S. maltophilia*.

Several phase 3 studies have been completed and reported. The cUTI study (RECAPTURE; Ceftazidime-Avibactam Compared With Doripenem Followed by Oral Therapy for

Hospitalized Adults With Complicated Urinary Tract Infections [UTIs]) enrolled and randomized 1033 patients to receive ceftazidime-avibactam or doripenem [51]. Among the 810 patients in the microbiological modified intent-to-treat (mMITT) population, the noninferiority criterion (both US Food and Drug Administration [FDA] and European Medicines Agency margins [–10% and –12.5%, respectively]) was met for the coprimary endpoints of symptomatic resolution at day 5 (70.2% vs 66.2%) and the composite symptomatic resolution/microbiological eradication at test of cure (TOC) (71.2% vs 64.5%). The cIAI study enrolled and randomized 1066 patients to receive ceftazidime-avibactam plus metronidazole or meropenem [52]. Clinical cure rates among the 823 patients in the mMITT population at TOC were 81.6% and 85.1%, respectively, fulfilling the –10% noninferiority criteria. It should be noted that the majority of the patients had appendicitis and low Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and therefore were not as ill as those who would require ceftazidime-avibactam for treatment in clinical practice. The third phase 3 study (REPRISE) was an open-label, pathogen-directed trial involving 333 patients with cUTI or cIAI due to ceftazidime-resistant Enterobacteriaceae or *P. aeruginosa* strains who were randomized to receive ceftazidime-avibactam or best available therapy [53]. The clinical cure rates at TOC were comparable at 91% in both groups in this study. Finally, in the double-blind, noninferiority phase 3 trial of HABP/VABP (REPROVE; A Study Comparing Ceftazidime-Avibactam Versus Meropenem in Hospitalized Adults With Nosocomial Pneumonia), 879 patients were randomly assigned to ceftazidime-avibactam or meropenem [54]. Predominant gram-negative baseline pathogens in the mMITT population were *K. pneumoniae* (37%) and *P. aeruginosa* (30%), and 28% were ceftazidime-nonsusceptible. In the clinical modified intent-to-treat (MITT) population, 68.8% in the ceftazidime-avibactam group were clinically cured, compared with 73.0% in the meropenem group, meeting the prespecified –12.5% noninferiority criteria.

Although randomized trials specifically targeting carbapenem-resistant gram-negative infections have not been conducted, treatment of CRE infections with ceftazidime-avibactam has been associated with higher rates of clinical success and survival compared with colistin or aminoglycoside-containing regimens [55].

Ceftolozane-tazobactam

Ceftolozane is a new 3'-aminopyrazolium cephalosporin with robust activity against *P. aeruginosa* [56]. It is stable by itself against multiple resistance mechanisms including overexpression of AmpC, a chromosomal cephalosporinase (β -lactamase) [56]. The combination with tazobactam further improves its antipseudomonal activity and also imparts activity against strains producing extended-spectrum β -lactamases (ESBLs) (but not any carbapenemases). Ceftolozane-tazobactam is active against 67%–89% of carbapenem-nonsusceptible

P. aeruginosa strains [57, 58] but is not active against CRE, *A. baumannii*, or *S. maltophilia*. As a β -lactam–BLI combination, its efficacy is best correlated with time above the minimum inhibitory concentration (MIC) ($\%fT > MIC$) [59].

Phase 3 studies have been completed for cUTI (ASPECT-cUTI; Study Comparing the Safety and Efficacy of Intravenous CXA-201 and Intravenous Levofloxacin in Complicated Urinary Tract Infection, Including Pyelonephritis) and cIAI (ASPECT-cIAI; Study Comparing the Safety and Efficacy of Intravenous CXA-201 and Intravenous Meropenem in Complicated Intraabdominal Infections). ASPECT-cUTI enrolled 1083 patients with cUTI or acute pyelonephritis (AP; 82% of patients), mostly caused by *E. coli*, to receive ceftolozane-tazobactam or levofloxacin [60]. The composite cure rates at TOC were 76.9% and 68.4%, respectively, in the mMITT population in favor of ceftolozane-tazobactam. ASPECT-cIAI enrolled 993 patients with cIAI, frequently polymicrobial, to receive ceftolozane-tazobactam plus metronidazole or meropenem [61]. The clinical cure rates at TOC in the mITT population were 83% and 87.3%, respectively. Both studies met the predefined noninferiority margin. The combination was generally well tolerated. Another noninferiority phase 3 study of nosocomial pneumonia (ASPECT-NP; Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia [MK-7625A-008] [ASPECT-NP]) has been completed and demonstrated comparable rates in day 28 all-cause mortality and in clinical cure rate at the TOC visit between ceftolozane-tazobactam and meropenem (ClinicalTrials.gov identifier NCT02070757) [62].

Clinical data on patients infected with carbapenem-resistant *P. aeruginosa* are limited. In a series of 21 patients with infections due to MDR *P. aeruginosa*, most of which were carbapenem-resistant and caused pneumonia, 71% (15/21) had clinical success and 30-day all-cause mortality was 10% (2/21), suggesting a potential role of this combination in this patient population [63]. However, resistance emerged in 3 of the 21 patients, indicating the need for monitoring of susceptibility in the event of persistently positive cultures.

Meropenem-vaborbactam

Vaborbactam is the first boronic acid BLI, a group that is known to reversibly and competitively inhibit serine- β -lactamases; vaborbactam is the first agent to be approved for clinical use. It inhibits class A β -lactamases, including KPC carbapenemases, but not class B MBLs such as NDM and VIM carbapenemases or class D β -lactamases [64]. Vaborbactam also inhibits class A ESBLs and class C AmpC β -lactamases, but these activities are considered ancillary because meropenem, which is partnered with vaborbactam, is highly stable against these β -lactamases. As such, the primary role of vaborbactam is inhibition of KPC carbapenemases. Vaborbactam has been developed in combination with meropenem, which has pharmacokinetics consistent with those of vaborbactam [65].

Two phase 3 studies of meropenem-vaborbactam have been completed. TANGO-I (Efficacy/Safety of Meropenem-Vaborbactam Compared to Piperacillin-Tazobactam in Adults With cUTI and AP) randomized 550 patients with cUTI/AP to receive meropenem-vaborbactam or piperacillin-tazobactam [66]. In the study, patients could be switched to oral levofloxacin after receiving 15 or more doses of intravenous therapy if they met prespecified criteria to complete 10 days of total treatment. The primary endpoint of composite clinical and microbiological cure in the mMITT population was achieved in 98.4% of the meropenem-vaborbactam group and in 94.0% of the piperacillin-tazobactam group at the end of therapy, meeting the prespecified –15% noninferiority margin. TANGO-II (Efficacy, Safety, Tolerability of Vabomere Compared to Best Available Therapy in Treating Serious Infections in Adults) was a pathogen-directed study in which 72 patients with cUTI, HABP/VABP, cIAI, or bacteremia suspected or confirmed ($n = 47$) to be due to CRE were randomized to receive meropenem-vaborbactam or best available therapy [67]. Randomization for this trial was stopped early when the interim analysis indicated statistically significant differences in the efficacy at TOC favoring meropenem-vaborbactam. Meropenem-vaborbactam appears to be well tolerated. Real-world clinical experience on the use of meropenem-vaborbactam is not yet available.

Plazomicin

Aminoglycosides exert bactericidal activity against gram-negative bacteria by inhibiting protein synthesis by the 30S ribosome. However, resistance is common, primarily due to production of various aminoglycoside-modifying enzymes, with efflux playing a lesser role in general [68]. Plazomicin is a synthetic derivative of sisomicin with hydroxyl-aminobutyric acid at position 1 and 2-hydroxyethyl group at position 6' [69]. These changes in the structure allow plazomicin to resist modification by all aminoglycoside-modifying enzymes, with the exception of AAC(2')-I, which is produced by *Providencia stuartii*. Plazomicin is broadly active against the family Enterobacteriaceae, including strains that are resistant to existing aminoglycosides (amikacin, gentamicin, tobramycin) [70]; however, it is not active against many of the strains producing NDM carbapenemases because of frequent coproduction of 16S ribosomal RNA (rRNA) methyltransferases that protect the aminoglycoside binding site of 16S rRNA and consequently confer high-level resistance to amikacin, gentamicin, tobramycin, and plazomicin [71]. Plazomicin activity toward *P. aeruginosa* and *A. baumannii* is overall comparable to existing aminoglycosides and is not predictable [70, 72]. Although beyond the scope of this review, plazomicin is also highly active against *Staphylococcus aureus* and coagulase-negative staphylococci, including methicillin-resistant strains [70]. As an aminoglycoside, the efficacy of plazomicin is predicted by the peak plasma concentration over the MIC of the pathogen (fC_{max}/MIC); plazomicin is

administered once daily as a 30-minute intravenous infusion, although dosing frequency needs to be adjusted for patients with severe renal impairment [73].

Two phase 3 trials have been completed for plazomicin. The first one enrolled 609 adult patients with cUTI including AP to receive plazomicin or meropenem allowing for stepdown to oral levofloxacin in both arms (A Study of Plazomicin Compared With Meropenem for the Treatment of Complicated Urinary Tract Infection [cUTI] Including Acute Pyelonephritis [AP] [EPIC] study) [74]. In this study, the composite clinical and microbiological cure rates of the mITT population were 88.0% and 91.4% at day 5, and 81.7% and 70.1% at TOC for plazomicin and meropenem, meeting the prespecified –15% noninferiority criterion. Increase in serum creatinine was reported in 7.0% and 4.0% of patients in the plazomicin and meropenem groups, respectively. The second clinical trial was a pathogen-directed trial aimed specifically at CRE infections (A Study of Plazomicin Compared With Colistin in Patients With Infection Due to Carbapenem-Resistant Enterobacteriaceae [CRE] [CARE] study) [75]. In this study, patients with bloodstream infection, HABB, or VABP due to CRE were enrolled and randomized to a plazomicin-based combination regimen or a colistin-based regimen. The second agents were meropenem or tigecycline and were selected by the investigator. Among the 39 evaluable patients, rates of day 28 all-cause mortality or significant disease-related complications were 23.5% for plazomicin and 50.0% for colistin, while the rates of day 28 all-cause mortality were 11.8% for plazomicin and 40.0% colistin, with the survival benefit especially pronounced for those with bloodstream infection (day 28 all-cause mortality: 7.1% for plazomicin and 40.0% for colistin) [75]. The incidence of serum creatinine increases was 16.7% in the plazomicin group and 50.0% in the colistin group [75]. Although superiority of plazomicin-containing regimens over colistin-containing regimens was not demonstrated in the CARE study due to underenrollment, the data support the role of plazomicin-based combination therapy as an alternative to colistin-based combination therapy. The CARE study is also significant in that it provided data on the efficacy of colistin-based regimens for the treatment of CRE infections in the context of a prospective, randomized trial. Plazomicin was approved for the treatment of cUTI in the US in 2018 [73]. Real-life clinical use of plazomicin in the treatment of infections caused by carbapenem-resistant gram-negative bacteria will add to the existing body of evidence on its efficacy and safety profile.

Eravacycline

Eravacycline is a synthetic tetracycline with a fluorine atom at C-7 and a pyrrolidinoacetamido group at the C-9 position in the tetracycline D-ring [76]. Similarly to other tetracyclines, eravacycline inhibits protein synthesis by binding to the 30S ribosomal subunit of bacteria, and as with tigecycline, its activity is not affected by ribosome protection proteins such as TetM, which compromises activity of other tetracyclines. However,

eravacycline is less prone to efflux similar to the other tetracyclines [77]. Eravacycline has activity against gram-negative pathogens including CRE, carbapenem-resistant strains of *A. baumannii* and *S. maltophilia*, but not those of *P. aeruginosa* [78]. It is also active against gram-positive pathogens (including methicillin-resistant *S. aureus* and vancomycin-resistant enterococci) and many of the clinically relevant anaerobic species [79]. Eravacycline is administered as an intravenous infusion and its pharmacodynamic driver of efficacy is free drug area under the curve divided over MIC of the pathogen ($fAUC/MIC$) [80].

The initial clinical development program for eravacycline included 2 phase 3 studies (cIAI and cUTI/AP), which have been completed and reported. In the IGNITE 1 (Efficacy and Safety Study of Eravacycline Compared With Ertapenem in Complicated Intra-abdominal Infections) study, 541 patients with cIAI were enrolled, with 270 patients randomized to receive eravacycline and 271 patients to receive ertapenem [81]. For the mITT population, the clinical cure rates at the TOC visit were 86.8% in the eravacycline group and 87.6% in the ertapenem group, meeting the prespecified –10% noninferiority criterion. Both study drugs were well tolerated overall, but nausea (8.1%) and phlebitis (3.0%) occurred more commonly in the eravacycline group. IGNITE 2 (Efficacy and Safety Study of Eravacycline Compared With Levofloxacin in Complicated Urinary Tract Infections; NCT01978938) was a phase 3 study of cUTI/AP in which 908 patients were enrolled and randomized to receive eravacycline or levofloxacin intravenously for at least 3 days, with an option to a stepdown to oral formulation of the same drugs to complete the 7-day treatment period. The primary outcome was the composite clinical and microbiological outcome at the TOC visit in the mITT population using a –10% noninferiority margin, which eravacycline did not meet (NCT01978938). In response, the manufacturer initiated an intravenous-only cUTI/AP study (Efficacy and Safety Study of Eravacycline Compared With Ertapenem in Participants With Complicated Urinary Tract Infections [IGNITE 3]; NCT03032510) and a second cIAI study (Efficacy and Safety Study of Eravacycline Compared With Meropenem in Complicated Intra-abdominal Infections [IGNITE 4]; NCT02784704). In IGNITE 4, 500 patients were randomized to eravacycline or meropenem. The clinical cure rates in the mITT population were 90.8% and 91.2%, respectively, meeting the prespecified –10% noninferiority criterion [82]. However, for IGNITE 3, which enrolled and randomized 1205 patients to receive intravenous eravacycline or ertapenem for a minimum of 5 days followed by optional oral regimens, the combined clinical and microbiological success rates for eravacycline and ertapenem in the mITT population were 84.8% and 94.8% at the end of intravenous therapy, and 68.5% and 74.9% at TOC, respectively, both missing the prespecified noninferiority margin of –10% (unpublished data). Based on these results, the new drug application for cIAI was approved in 2018 by the FDA [83].

Imipenem-Cilastatin-Relebactam

Relebactam is a new BLI with a diazabicyclooctane core, similar to avibactam [84]. It inhibits class A β -lactamases including KPC carbapenemases and class C β -lactamases, but not class B or class D β -lactamases [85]. Its presence substantially restores the activity of imipenem-cilastatin against the majority of KPC-producing CRE strains and carbapenem-resistant strains of *P. aeruginosa*, but not those of *A. baumannii* or *S. maltophilia* [85, 86].

Two phase 2 studies have been conducted to demonstrate the efficacy and safety of imipenem-cilastatin-relebactam. The first study enrolled and randomized 302 adult patients with cUTI/AP to receive imipenem-cilastatin with or without relebactam at 2 different doses, with stepdown to oral ciprofloxacin allowed [87]. The rates of favorable microbiological response at the end of therapy in the microbiologically evaluable (ME) population were comparable and ranged between 95.5% and 98.7%. The second study enrolled and randomized 351 patients with cIAI to receive similar dose-ranging regimens [88]. Favorable clinical response at the end of therapy in the ME population was documented in 95.2%–98.8% of the patients. The relebactam-containing regimens were as well tolerated as the imipenem-cilastatin-only regimen in these 2 studies. A small, pathogen-directed, phase 3 trial (Efficacy and Safety of Imipenem+Cilastatin/Relebactam [MK-7655A] Versus Colistimethate Sodium+Imipenem+Cilastatin in Imipenem-Resistant Bacterial Infection [MK-7655A-013] [RESTORE-IMI 1]) randomizing patients with VABP, HABP, cIAI, or cUTI due to imipenem-resistant gram-negative bacteria to imipenem-cilastatin-relebactam or imipenem-cilastatin and colistin has been completed. In the study, 31 of 47 randomized and treated patients met the mMITT criteria [89, 90]. Favorable overall response was comparable for imipenem-cilastatin-relebactam (71.4%) and imipenem-cilastatin plus colistin (70.0%) in the mMITT population. Favorable clinical response at day 28 was higher for imipenem-cilastatin-relebactam (71.4%) compared with imipenem-cilastatin plus colistin (40.0%), and 28-day all-cause mortality was lower for imipenem-cilastatin-relebactam (9.5%) than imipenem-cilastatin plus colistin (30.0%), respectively. Fewer patients who received imipenem-cilastatin-relebactam had a drug-related adverse event compared with imipenem-cilastatin plus colistin (16.1% vs 31.3%), including treatment-emergent nephrotoxicity (10% vs 56%). Another phase 3 trial (Imipenem/Relebactam/Cilastatin Versus Piperacillin/Tazobactam for Treatment of Participants With Bacterial Pneumonia [MK-7655A-014] [RESTORE-IMI 2]) randomizing VABP and HABP patients to imipenem-cilastatin-relebactam and piperacillin-tazobactam has been completed (NCT02493764).

POSSIBLE TREATMENT OPTIONS IN THE NEAR FUTURE

Cefiderocol

Cefiderocol is a novel siderophore cephalosporin in which the catechol side chain forms a chelated complex with ferric

iron [91]. This mechanism enables cefiderocol to actively cross the outer membrane of gram-negative bacteria into the periplasmic space using a receptor-mediated bacterial iron transport system, as described in more detail by Sato and Yamawaki [92, 93]. In addition, cefiderocol is stable against hydrolysis by a variety of β -lactamases, including class A (eg, KPC, ESBL), class B (eg, NDM, VIM, IMP, L1), class C (AmpC), and class D (eg, OXA-48 of Enterobacteriaceae and OXA-23, OXA-24 of *A. baumannii*) [91, 94, 95]. As a result, cefiderocol is active against gram-negative bacteria ranging from Enterobacteriaceae to *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*, including carbapenem-resistant strains [91, 96]. In a large surveillance study of gram-negative bacteria isolated from patients at North American and European hospitals (SIDERO-WT-2014), cefiderocol was highly active across all gram-negative species [97]. Specifically, the minimum inhibitory concentrations inhibiting growth of 90% of tested isolates (MIC_{90} s) were 1–4 μ g/mL for meropenem-nonsusceptible isolates of Enterobacteriaceae, 0.5–1 μ g/mL for meropenem-nonsusceptible isolates of *P. aeruginosa*, 1 μ g/mL for meropenem-nonsusceptible *A. baumannii*, and 0.25–0.5 μ g/mL for isolates of *S. maltophilia* [97]. As cefiderocol is a β -lactam agent, the pharmacodynamic parameter predictive of efficacy is $\%fT > MIC$ (the percentage of a dosing period that the unbound drug concentration exceeded the MIC) [98–100].

One phase 2 study has been completed and 2 international, randomized phase 3 studies are under way for cefiderocol. The phase 2 APEKS-cUTI study enrolled and randomized 452 patients to receive cefiderocol or imipenem-cilastatin. No oral stepdown was allowed in this study. The composite clinical and microbiological efficacy endpoint at TOC was met in 72.6% and 54.6% of the patients, respectively, meeting the prespecified –15% noninferiority criterion. Cefiderocol was well tolerated overall, with a lower serious adverse event rate compared with the imipenem-cilastatin group (5% and 8%, respectively) [101]. The CREDIBLE-CR (A MultiCenter, RandomizED, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-Resistant Gram-negative Pathogens) study is an ongoing pathogen-directed trial of carbapenem-resistant gram-negative infections in which patients with VAP, hospital-acquired pneumonia, healthcare-associated pneumonia, bloodstream infection, sepsis, or cUTI are randomized to receive cefiderocol or best available therapy (NCT02714595). Furthermore, the APEKS-NP (A Multicenter, Randomized, Double-blind, Parallel-group, Clinical Study of S-649266 Compared With Meropenem for the Treatment of Hospital-acquired Bacterial Pneumonia, Ventilator-associated Bacterial Pneumonia, or Healthcare-associated Bacterial Pneumonia Caused by Gram-negative Pathogens) study, an ongoing HABP/VABP study comparing cefiderocol with meropenem, is expected to have results in the near future (NCT03032380).

Fosfomycin

Fosfomycin is a phosphoenolpyruvate analog that exhibits bactericidal activity by inhibiting one of the first steps in peptidoglycan synthesis. It is active against a wide range of gram-negative pathogens, in particular *E. coli*, and has been used successfully as an oral formulation for the treatment of uncomplicated urinary tract infections for several decades [102]. Fosfomycin is active against the majority of CRE and carbapenem-resistant *P. aeruginosa* strains but not those of *A. baumannii* or *S. maltophilia* based on current susceptibility breakpoint for urinary tract isolates [102, 103]. Dose fractionation studies in murine thigh infection model demonstrated that the pharmacodynamic driver of fosfomycin most likely linked to its efficacy was $fAUC/MIC$ [104]. Of note, the currently widely used susceptibility testing methods (eg, automated testing by Sensititre, VITEK-2, Phoenix, and manual tests performed by Etest) have limitations in providing the fosfomycin MIC values accurately for *E. coli* and *K. pneumoniae* isolates [105, 106], and also when the pathogen produces KPC enzymes [105]. When compared with the standard agar dilution method, such tests performed with high very major error (ie, false susceptible) rates [106].

A phase 2/3 study of intravenous fosfomycin (ZEUS; Randomized, Double-Blind, Comparative Study to Evaluate the Safety and Efficacy of ZTI-01 vs Piperacillin/Tazobactam in the Treatment of cUTI/AP Infection in Hospitalized Adults; NCT02753946) has been completed. In this intravenous-only study, 465 patients with cUTI or AP were enrolled and randomized to receive fosfomycin or piperacillin-tazobactam. The study met the -15% noninferiority criterion, with overall success rates at TOC of 64.7% and 54.5%, respectively, in the mMITT population [107].

One major uncertainty about intravenous fosfomycin is whether monotherapy is efficacious in the treatment of systemic infections other than cUTI/AP, as carbapenem-resistant strains tend to have reduced susceptibility to fosfomycin [108]. In countries where intravenous fosfomycin is already available, it has mostly been used in combination with various other agents [109]. A potential, novel therapeutic strategy to avoid the issues related to resistance development during fosfomycin monotherapy, namely, its combination with ceftazidime-avibactam, has been proposed by Papp-Wallace et al for infections with high bacterial burden [110].

CONSIDERATIONS ON ANTIMICROBIAL STEWARDSHIP AND RAPID DIAGNOSTICS

As newer agents with activity against carbapenem-resistant organisms become available for clinical use, approaches to treatment selection and optimization become important considerations. Challenges that are unique to these agents from the antibiotic stewardship point of view relate to their rapid streamlined development, which resulted in fewer clinical trials being

conducted before regulatory approval. These challenges include (i) insufficient high-quality clinical data to guide their use in the target patient population; (ii) often delayed approval of susceptibility testing methods; (iii) complexity of their antibacterial spectra; and (iv) high acquisition costs.

First, the pivotal clinical trials supporting the approval of these agents are typically noninferiority trials that do not specifically target infections from carbapenem-resistant organisms. Although more pathogen-directed trials targeting carbapenem-resistant gram-negative infections are being conducted for agents seeking approval, these studies are not powered to allow for statistical inference of superiority of the study drugs over the comparators. Therefore, postmarketing clinical experience will likely play an important role in informing appropriate use of the new agents. Second, approval of clinical breakpoints and susceptibility testing methods may lag behind the approval of the new agents by a year or more. In such cases, patients could potentially be treated with a new agent that lacks in vitro activity, therefore risking treatment failure. It is encouraging to see that more efforts are now being made to address this issue, and it is hoped that susceptibility testing methods will be available at the time of product launch in the future. Third, beyond their shared activity against KPC-producing organisms, the spectrum of activity is nuanced, even within the same class. For example, ceftazidime-avibactam has activity against organisms producing OXA-48 carbapenemase, whereas meropenem-vaborbactam and imipenem-relebactam lack activity. Finally, the costs of the new agents will be considerably higher than those that have been on the market, and this will likely preclude their empiric use in most circumstances unless the likelihood of infection from a carbapenem-resistant pathogen is compellingly high and the clinical condition does not allow for any delay in appropriate therapy. The last 2 points in particular highlight the crucial role of antimicrobial stewardship led by infectious diseases pharmacists and physicians in promoting appropriate and rational use of the new agents against carbapenem-resistant gram-negative pathogens.

Traditional culture-based susceptibility testing requires 48–72 hours from specimen collection to availability of results. However, it typically takes another 24 hours to test susceptibility of the new agents as they are not routinely tested, and additional tests are required in response to reports of carbapenem resistance. Ideally, rapid diagnostic tests can shorten this turnaround time and thus time to appropriate therapy. Several nucleic acid amplification testing platforms that contain probes or primers for carbapenemase genes are commercially available [111]. Some of these tests can be run directly from a positive blood culture bottle and can predict carbapenem resistance based on the genotype, for example, the presence of a KPC gene, as described earlier by Nordmann and Poirel [5]. However, these tests require dedicated instruments, and the cost of each test is relatively high, which precludes their universal use. Therefore, an

implementation strategy needs to be formulated at each institution based on local epidemiology and needs, a process that will benefit from inputs from the antimicrobial stewardship program. Rapid phenotypic tests for carbapenemase activity (eg, Carba NP test [bioMérieux, La Balme-les-Grottes, France], carbapenem-inactivation method) are less expensive alternatives to nucleic acid amplification tests and can be considered in certain circumstances [112, 113]. However, they do not differentiate classes of carbapenemases, information which is often needed in selecting appropriate β -lactam-BLI agents that have class-specific activity. Therefore, they would be most useful in settings where a specific carbapenemase is known to predominate. Thus, rapid diagnostic tests should be integrated into antimicrobial stewardship programs to obtain more accurate susceptibility testing results to impact therapeutic choices in a timely manner [111].

CONCLUSIONS

Carbapenem-resistant gram-negative pathogens have become a major healthcare burden in the 21st century, and treatment options had been limited to agents such as colistin and tigecycline in combination with other antibiotics. Fortunately, several new agents with activity against carbapenem-resistant pathogens have been approved or are in late-stage clinical development, which is encouraging. These newer agents will become important additions to the currently limited armamentarium and are expected to improve the outcome of patients affected by carbapenem-resistant pathogens. As each new agent comes with its own strengths and caveats, antimicrobial stewardship will play a crucial role in ensuring their optimal and rational use.

Notes

Acknowledgments. Editorial support was provided by Highfield (Oxford, United Kingdom), sponsored by Shionogi Inc (Florham Park, New Jersey).

Financial support. This review article is sponsored by Shionogi & Co, Ltd (Osaka, Japan), but the author did not receive any fee for his authorship.

Supplement sponsorship. This supplement is sponsored by Shionogi & Co., Ltd.

Potential conflicts of interest. The author has served as a consultant to Roche, Pfizer, Tetrphase, Recida, VenatoRx, and Fedora; has received speaking fees from Shionogi, Pfizer, MSD, and Astellas; and has received research funding from Accelerate Diagnostics, Pfizer, Astellas, MSD, BD, Shionogi, and Kanto Chemical. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017. Available at: https://www.who.int/medicines/publications/WHO-PPL-Short-Summary_25Feb-ET_NM_WHO.pdf?ua=1. Accessed 1 February 2019.
- van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. *Virulence* 2017; 8:460–9.
- Morrill HJ, Pogue JM, Kaye KS, LaPlante KL. Treatment options for carbapenem-resistant Enterobacteriaceae infections. *Open Forum Infect Dis* 2015; 2:ofv050.

- Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. *Emerg Infect Dis* 2014; 20:1170–5.
- Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in gram-negative bacteria. *Clin Infect Dis* 2019; 69(Suppl 7):521–8.
- Osano E, Arakawa Y, Wacharotayankun R, et al. Molecular characterization of an enterobacterial metallo-beta-lactamase found in a clinical isolate of *Serratia marcescens* that shows imipenem resistance. *Antimicrob Agents Chemother* 1994; 38:71–8.
- Lauretti L, Riccio ML, Mazzariol A, et al. Cloning and characterization of blaVIM, a new integron-borne metallo-beta-lactamase gene from a *Pseudomonas aeruginosa* clinical isolate. *Antimicrob Agents Chemother* 1999; 43:1584–90.
- Bratu S, Landman D, Haag R, et al. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. *Arch Intern Med* 2005; 165:1430–5.
- Bradford PA, Bratu S, Urban C, et al. Emergence of carbapenem-resistant *Klebsiella* species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 beta-lactamases in New York City. *Clin Infect Dis* 2004; 39:55–60.
- Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *Lancet Infect Dis* 2013; 13:785–96.
- Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. *Infect Control Hosp Epidemiol* 2016; 37:1288–301.
- Castanheira M, Farrell SE, Krause KM, Jones RN, Sader HS. Contemporary diversity of β -lactamases among Enterobacteriaceae in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent β -lactamase groups. *Antimicrob Agents Chemother* 2014; 58:833–8.
- Poirel L, Héritier C, Tolün V, Nordmann P. Emergence of oxacillinase-mediated resistance to imipenem in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2004; 48:15–22.
- Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother* 2009; 53:5046–54.
- Ranjan A, Shaik S, Mondal A, et al. Molecular epidemiology and genome dynamics of New Delhi metallo- β -lactamase-producing extraintestinal pathogenic *Escherichia coli* strains from India. *Antimicrob Agents Chemother* 2016; 60:6795–805.
- Quinn JP, Dudek EJ, DiVincenzo CA, Lucks DA, Lerner SA. Emergence of resistance to imipenem during therapy for *Pseudomonas aeruginosa* infections. *J Infect Dis* 1986; 154:289–94.
- Köhler T, Michea-Hamzehpour M, Epp SF, Pechere JC. Carbapenem activities against *Pseudomonas aeruginosa*: respective contributions of OprD and efflux systems. *Antimicrob Agents Chemother* 1999; 43:424–7.
- Huband MD, Castanheira M, Flamm RK, Farrell DJ, Jones RN, Sader HS. In vitro activity of ceftazidime-avibactam against contemporary *Pseudomonas aeruginosa* isolates from U.S. medical centers by census region, 2014. *Antimicrob Agents Chemother* 2016; 60:2537–41.
- Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of gram-negative organisms isolated from patients hospitalized with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009–2012. *Int J Antimicrob Agents* 2014; 43:328–34.
- Kazmierczak KM, Rabine S, Hackel M, et al. Multiyear, multinational survey of the incidence and global distribution of metallo- β -lactamase-producing Enterobacteriaceae and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2016; 60:1067–78.
- Lolans K, Queenan AM, Bush K, Sahud A, Quinn JP. First nosocomial outbreak of *Pseudomonas aeruginosa* producing an integron-borne metallo-beta-lactamase (VIM-2) in the United States. *Antimicrob Agents Chemother* 2005; 49:3538–40.
- Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. *Clin Microbiol Rev* 2008; 21:538–82.
- Adams-Haduch JM, Onuoha EO, Bogdanovich T, et al. Molecular epidemiology of carbapenem-nonsusceptible *Acinetobacter baumannii* in the United States. *J Clin Microbiol* 2011; 49:3849–54.
- Adams-Haduch JM, Paterson DL, Sidjabat HE, et al. Genetic basis of multidrug resistance in *Acinetobacter baumannii* clinical isolates at a tertiary medical center in Pennsylvania. *Antimicrob Agents Chemother* 2008; 52:3837–43.
- Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. *Clin Microbiol Rev* 2012; 25:2–41.
- 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.

27. Gonzalez-Padilla M, Torre-Cisneros J, Rivera-Espinar F, et al. Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*. *J Antimicrob Chemother* **2015**; 70:905–13.
28. Qureshi ZA, Hittle LE, O'Hara JA, et al. Colistin-resistant *Acinetobacter baumannii*: beyond carbapenem resistance. *Clin Infect Dis* **2015**; 60:1295–303.
29. Penwell WF, Shapiro AB, Giacobbe RA, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* **2015**; 59:1680–9.
30. Falagas ME, Skandalis T, Vardakas KZ, Legakis NJ; Hellenic Cefiderocol Study Group. Activity of cefiderocol (S-649266) against carbapenem-resistant gram-negative bacteria collected from inpatients in Greek hospitals. *J Antimicrob Chemother* **2017**; 72:1704–8.
31. Wei C, Ni W, Cai X, Zhao J, Cui J. Evaluation of trimethoprim/sulfamethoxazole (SXT), minocycline, tigecycline, moxifloxacin, and ceftazidime alone and in combinations for SXT-susceptible and SXT-resistant *Stenotrophomonas maltophilia* by in vitro time-kill experiments. *PLoS One* **2016**; 11:e0152132.
32. Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. Monotherapy with fluorquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *Antimicrob Agents Chemother* **2014**; 58:176–82.
33. Cho SY, Kang CI, Kim J, et al. Can levofloxacin be a useful alternative to trimethoprim-sulfamethoxazole for treating *Stenotrophomonas maltophilia* bacteremia? *Antimicrob Agents Chemother* **2014**; 58:581–3.
34. Tran TB, Velkov T, Nation RL, et al. Pharmacokinetics/pharmacodynamics of colistin and polymyxin B: are we there yet? *Int J Antimicrob Agents* **2016**; 48:592–7.
35. Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. *J Antimicrob Chemother* **2017**; 72:29–39.
36. Stein GE, Babinchak T. Tigecycline: an update. *Diagn Microbiol Infect Dis* **2013**; 75:331–6.
37. McGovern PC, Wible M, El-Tahtawy A, Biswas P, Meyer RD. All-cause mortality imbalance in the tigecycline phase 3 and 4 clinical trials. *Int J Antimicrob Agents* **2013**; 41:463–7.
38. 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**; 44:1–7.
39. Geng TT, Xu X, Huang M. High-dose tigecycline for the treatment of nosocomial carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections: a retrospective cohort study. *Medicine (Baltimore)* **2018**; 97:e9961.
40. Goff DA, Kaye KS. Minocycline: an old drug for a new bug: multidrug-resistant *Acinetobacter baumannii*. *Clin Infect Dis* **2014**; 59(Suppl 6):S365–6.
41. 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.
42. Falcone M, Paterson D. Spotlight on ceftazidime/avibactam: a new option for MDR gram-negative infections. *J Antimicrob Chemother* **2016**; 71:2713–22.
43. Merdjan H, Rangaraju M, Tarral A. Safety and pharmacokinetics of single and multiple ascending doses of avibactam alone and in combination with ceftazidime in healthy male volunteers: results of two randomized, placebo-controlled studies. *Clin Drug Investig* **2015**; 35:307–17.
44. Shields RK, Potoski BA, Haidar G, et al. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. *Clin Infect Dis* **2016**; 63:1615–8.
45. Haidar G, Clancy CJ, Shields RK, Hao B, Cheng S, Nguyen MH. Mutations in blaKPC-3 that confer ceftazidime-avibactam resistance encode novel KPC-3 variants that function as extended-spectrum B-lactamases. *Antimicrob Agents Chemother* **2017**; 61:e02534–16.
46. Shields RK, Nguyen MH, Press EG, Chen L, Kreiswirth BN, Clancy CJ. Selection of meropenem resistance among ceftazidime-avibactam-resistant, meropenem-susceptible *Klebsiella pneumoniae* isolates with variant KPC-3 carbapenemases. *Antimicrob Agents Chemother* **2017**; 61:e00079–17.
47. Grupper M, Sutherland C, Nicolau DP. Multicenter evaluation of ceftazidime-avibactam and ceftolozane-tazobactam inhibitory activity against meropenem non-susceptible *P. aeruginosa* from blood, respiratory tract and wounds. *Antimicrob Agents Chemother* **2017**; 61:e00875–17.
48. Wi YM, Greenwood-Quaintance KE, Schuetz AN, et al. Activity of ceftolozane-tazobactam against carbapenem-resistant, non-carbapenemase-producing *Pseudomonas aeruginosa* and associated resistance mechanisms. *Antimicrob Agents Chemother* **2018**; 62:e01970–17.
49. Castanheira M, Doyle TB, Smoth CJ, Mendes RE, Sader HS. Combination of MexAB-OprM overexpression and mutations in efflux regulators, PBPs and chaperone proteins is responsible for ceftazidime/avibactam resistance in *Pseudomonas aeruginosa* clinical isolates from US hospitals [manuscript published online ahead of print 21 June 2019]. *J Antimicrob Chemother* **2019**. doi:10.1093/jac/dkz243.
50. Torrens G, Cabot G, Ocampo-Sosa AA, et al. Activity of ceftazidime-avibactam against clinical and isogenic laboratory *Pseudomonas aeruginosa* isolates expressing combinations of most relevant β -lactam resistance mechanisms. *Antimicrob Agents Chemother* **2016**; 60:6407–10.
51. Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. *Clin Infect Dis* **2016**; 63:754–62.
52. Mazuski JE, Gasink LB, Armstrong J, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. *Clin Infect Dis* **2016**; 62:1380–9.
53. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis* **2016**; 16:661–73.
54. Torres A, Zhong N, Pachel J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis* **2018**; 18:285–95.
55. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Antimicrob Agents Chemother* **2017**; 61:e00883–17.
56. Takeda S, Nakai T, Wakai Y, Ikeda F, Hatano K. In vitro and in vivo activities of a new cephalosporin, FR264205, against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* **2007**; 51:826–30.
57. 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**; 72:1386–95.
58. 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* **2017**; 61:e00465–7.
59. Craig WA, Andes DR. In vivo activities of ceftolozane, a new cephalosporin, with and without tazobactam against *Pseudomonas aeruginosa* and Enterobacteriaceae, including strains with extended-spectrum β -lactamases, in the thighs of neutropenic mice. *Antimicrob Agents Chemother* **2013**; 57:1577–82.
60. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet* **2015**; 385:1949–56.
61. Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). *Clin Infect Dis* **2015**; 60:1462–71.
62. Kollef M, Novacek M, Kivistik U, et al. ASPECT-NP: a randomized, double-blind, phase 3 trial comparing efficacy and safety of ceftolozane/tazobactam vs meropenem in patients with ventilated nosocomial pneumonia. Poster presented at: 29th European Congress of Clinical Microbiology and Infectious Diseases, Amsterdam, Netherlands, 13–16 April 2019. Poster 1917.
63. Haidar G, Philips NJ, Shields RK, et al. Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: clinical effectiveness and evolution of resistance. *Clin Infect Dis* **2017**; 65:110–20.
64. Livermore DM, Mushtaq S. Activity of biapenem (RPX2003) combined with the boronate β -lactamase inhibitor RPX7009 against carbapenem-resistant Enterobacteriaceae. *J Antimicrob Chemother* **2013**; 68:1825–31.
65. Griffith DC, Loutit JS, Morgan EE, Durso S, Dudley MN. Phase 1 study of the safety, tolerability, and pharmacokinetics of the β -lactamase inhibitor vaborbactam (RPX7009) in healthy adult subjects. *Antimicrob Agents Chemother* **2016**; 60:6326–32.
66. Kaye KS, Bhowmick T, Metallidis S, et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. *JAMA* **2018**; 319:788–99.
67. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II randomized clinical trial. *Infect Dis Ther* **2018**; 7:439–55.
68. Ramirez MS, Tolmasky ME. Aminoglycoside modifying enzymes. *Drug Resist Updat* **2010**; 13:151–71.

69. Aggen JB, Armstrong ES, Goldblum AA, et al. Synthesis and spectrum of the neoglycoside ACHN-490. *Antimicrob Agents Chemother* **2010**; 54:4636–42.
70. Walkty A, Adam H, Baxter M, et al. In vitro activity of plazomicin against 5,015 gram-negative and gram-positive clinical isolates obtained from patients in Canadian hospitals as part of the CANWARD study, 2011–2012. *Antimicrob Agents Chemother* **2014**; 58:2554–63.
71. Doi Y, Wachino JI, Arakawa Y. Aminoglycoside resistance: the emergence of acquired 16S ribosomal RNA methyltransferases. *Infect Dis Clin North Am* **2016**; 30:523–37.
72. Landman D, Kelly P, Bäcker M, et al. Antimicrobial activity of a novel aminoglycoside, ACHN-490, against *Acinetobacter baumannii* and *Pseudomonas aeruginosa* from New York City. *J Antimicrob Chemother* **2011**; 66:332–4.
73. Achaogen. Zemdri (plazomicin) injection, for intravenous use. Prescribing information. San Francisco, CA: Achaogen, **2018**.
74. Wagenlehner FME, Cloutier DJ, Komirenko AS, et al; EPIC Study Group. Once-daily plazomicin for complicated urinary tract infections. *N Engl J Med* **2019**; 380:729–40.
75. McKinnell JA, Dwyer JP, Talbot GH, et al; CARE Study Group. Plazomicin for infections caused by carbapenem-resistant Enterobacteriaceae. *N Engl J Med* **2019**; 380:791–3.
76. Xiao XY, Hunt DK, Zhou J, et al. Fluorocyclines. 1. 7-fluoro-9-pyrrolidinoacetamido-6-demethyl-6-deoxytetracycline: a potent, broad spectrum antibacterial agent. *J Med Chem* **2012**; 55:597–605.
77. Grossman TH, Starosta AL, Fyfe C, et al. Target- and resistance-based mechanistic studies with TP-434, a novel fluorocycline antibiotic. *Antimicrob Agents Chemother* **2012**; 56:2559–64.
78. Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Quale J. Activity of eravacycline against Enterobacteriaceae and *Acinetobacter baumannii*, including multidrug-resistant isolates, from New York City. *Antimicrob Agents Chemother* **2015**; 59:1802–5.
79. Sutcliffe JA, O'Brien W, Fyfe C, Grossman TH. Antibacterial activity of eravacycline (TP-434), a novel fluorocycline, against hospital and community pathogens. *Antimicrob Agents Chemother* **2013**; 57:5548–58.
80. Zhao M, Lepak AJ, Marchillo K, VanHecker J, Andes DR. In vivo pharmacodynamic target assessment of eravacycline against *Escherichia coli* in a murine thigh infection model. *Antimicrob Agents Chemother* **2017**; 61:e00250–17.
81. Solomkin J, Evans D, Slepavicius A, et al. Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the investigating gram-negative infections treated with eravacycline (IGNITE 1) trial: a randomized clinical trial. *JAMA Surg* **2017**; 152:224–32.
82. Efficacy and safety study of eravacycline compared with meropenem in complicated intra-abdominal infections (IGNITE4). Available at: <https://clinicaltrials.gov/ct2/show/NCT02784704>. Accessed 7 April 2019.
83. Tetrphase Pharmaceuticals. Xerava (eravacycline) injection, for intravenous use. Prescribing information. Watertown, MA: Tetrphase Pharmaceuticals, **2018**.
84. Mangion IK, Ruck RT, Rivera N, Huffman MA, Shevlin M. A concise synthesis of a β -lactamase inhibitor. *Org Lett* **2011**; 13:5480–3.
85. Livermore DM, Warner M, Mushtaq S. Activity of MK-7655 combined with imipenem against Enterobacteriaceae and *Pseudomonas aeruginosa*. *J Antimicrob Chemother* **2013**; 68:2286–90.
86. Lob SH, Hackel MA, Kazmierczak KM, et al. In vitro activity of imipenem-relebactam against gram-negative ESKAPE pathogens isolated by clinical laboratories in the United States in 2015 (results from the SMART global surveillance program). *Antimicrob Agents Chemother* **2017**; 61:e02209–16.
87. Sims M, Mariyanovski V, McLeroth P, et al. Prospective, randomized, double-blind, phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections. *J Antimicrob Chemother* **2017**; 72:2616–26.
88. Lucasti C, Vasile L, Sandesc D, et al. Phase 2, dose-ranging study of relebactam with imipenem-cilastatin in subjects with complicated intra-abdominal infection. *Antimicrob Agents Chemother* **2016**; 60:6234–43.
89. 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 versus colistin plus imipenem in patients with imipenem-non-susceptible bacterial infections [manuscript published online ahead of print 10 August 2019]. *Clin Infect Dis* **2019**. doi:10.1093/cid/ciz530.
90. Efficacy and safety of imipenem + cilastatin/relebactam (MK-7655A) versus colistimethate sodium + imipenem + cilastatin in imipenem-resistant bacterial infection (MK-7655A-013) (RESTORE-IMI 1). Available at: <https://clinicaltrials.gov/ct2/show/NCT02452047>. Accessed 7 April 2019.
91. Kohira N, West J, Ito A, et al. In vitro antimicrobial activity of a siderophore cephalosporin, S-649266, against Enterobacteriaceae clinical isolates, including carbapenem-resistant strains. *Antimicrob Agents Chemother* **2016**; 60:729–34.
92. Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and pharmacological profiles of a novel siderophore cephalosporin. *Clin Infect Dis* **2019**; 69(Suppl 7): 538–43.
93. Ito A, Nishikawa T, Matsumoto S, et al. Siderophore cephalosporin cefiderocol utilizes ferric iron transporter systems for antibacterial activity against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* **2016**; 60:7396–401.
94. Ito-Horiyama T, Ishii Y, Ito A, et al. Stability of novel siderophore cephalosporin S-649266 against clinically relevant carbapenemases. *Antimicrob Agents Chemother* **2016**; 60:4384–6.
95. Poirel L, Nordmann P. Carbapenem resistance in *Acinetobacter baumannii*: mechanisms and epidemiology. *Clin Microbiol Infect* **2006**; 12:826–36.
96. 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**; 71:670–7.
97. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlosky JA, Sahn 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 non-susceptible isolates: the SIDERO-WT-2014 study. *Antimicrob Agents Chemother* **2017**; 61:e00093–17.
98. Katsube T, Wajima T, Ishibashi T, Arjona Ferreira JC, Echols R. Pharmacokinetic/pharmacodynamic modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, for dose adjustment based on renal function. *Antimicrob Agents Chemother* **2016**; 61:e01381–16.
99. Nakamura R, Toba S, Ito A, Tsuji M, Yamano Y, Shimada J. S-649266, a novel siderophore cephalosporin: V. Pharmacodynamic assessment in murine thigh infection models. Poster presented at: 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington DC, 5–9 September 2014. Poster F-1559.
100. Monogue ML, Tsuji M, Yamano Y, Echols R, Nicolau DP. Efficacy of humanized exposures of cefiderocol (S-649266) against a diverse population of gram-negative bacteria in a murine thigh infection model. *Antimicrob Agents Chemother* **2017**; 61:e01022–17.
101. 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**; 18:1319–28.
102. Silver LL. Fosfomicin: mechanism and resistance. *Cold Spring Harb Perspect Med* **2017**; 7:a025262.
103. Keepers TR, Gomez M, Celeri C, Krause KM, Biek D, Critchley I. Fosfomicin and comparator activity against select Enterobacteriaceae, *Pseudomonas*, and *Enterococcus* urinary tract infection isolates from the United States in 2012. *Infect Dis Ther* **2017**; 6:233–43.
104. Lepak AJ, Zhao M, VanScoy B, et al. In vivo pharmacokinetics and pharmacodynamics of ZTI-01 (fosfomicin for injection) in the neutropenic murine thigh infection model against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* **2017**; 61:e00476–17.
105. Camarlinghi G, Parisio EM, Antonelli A, et al. Discrepancies in fosfomicin susceptibility testing of KPC-producing *Klebsiella pneumoniae* with various commercial methods. *Diagn Microbiol Infect Dis* **2019**; 93:74–6.
106. van den Bijllaardt W, Schijffelen MJ, Bosboom RW, et al. Susceptibility of ESBL *Escherichia coli* and *Klebsiella pneumoniae* to fosfomicin in the Netherlands and comparison of several testing methods including Etest, MIC test strip, Vitek2, Phoenix and disc diffusion. *J Antimicrob Chemother* **2018**; 73:2380–7.
107. Kaye KS, Rice LB, Dane A, et al. Fosfomicin for injection (ZTI-01) vs piperacillin-tazobactam (PIP-TAZ) for the treatment of complicated urinary tract infection (cUTI) including acute pyelonephritis (AP): ZEUS, a phase 2/3 randomized trial [manuscript published online ahead of print 6 March 2019]. *Clin Infect Dis* **2019**. doi:10.1093/cid/ciz181.
108. Vardakas KZ, Legakis NJ, Triarides N, Falagas ME. Susceptibility of contemporary isolates to fosfomicin: a systematic review of the literature. *Int J Antimicrob Agents* **2016**; 47:269–85.
109. Grabein B, Graninger W, Rodríguez Baño J, Dinh A, Liesenfeld DB. Intravenous fosfomicin—back to the future. Systematic review and meta-analysis of the clinical literature. *Clin Microbiol Infect* **2017**; 23:363–72.
110. Papp-Wallace KM, Zeiser ET, Becka SA, et al. Ceftazidime-avibactam in combination with fosfomicin: a novel therapeutic strategy against multidrug-resistant *Pseudomonas aeruginosa* [manuscript published online ahead of print 17 May 2019]. *J Infect Dis* **2019**. doi:10.1093/infdis/jiz149.
111. Banerjee R, Humphries R. Clinical and laboratory considerations for the rapid detection of carbapenem-resistant Enterobacteriaceae. *Virulence* **2017**; 8:427–39.
112. van der Zwaluw K, de Haan A, Pluister GN, Bootsma HJ, de Neeling AJ, Schouls LM. The carbapenem inactivation method (CIM), a simple and low-cost alternative for the Carba NP test to assess phenotypic carbapenemase activity in gram-negative rods. *PLoS One* **2015**; 10:e0123690.
113. Nordmann P, Poirel L, Dortet L. Rapid detection of carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis* **2012**; 18:1503–7.