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SUPPLEMENT ARTICLE

Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections

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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),

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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 glycylcycline 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

	Activity							
	Enterobacteriaceae							
Agent	Class A Carbapenemase (eg, KPC)	Class B Carbapenemase (eg, NDM)	Class D Carbapenemase (eg, OXA-48)	*P. aeruginosa*	*A. baumannii*	*S. maltophilia*	Indications (Including Expected)	Pathogen-directed Trial (Including Expected)
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.

[a]Not active beyond the activity of meropenem alone.

[b]Frequently 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) (%*f*T > 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 mMITT 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, HABP, 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 (*f*AUC/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 μg/mL for meropenem-nonsusceptible isolates of Enterobacteriaceae, 0.5–1 μg/mL for meropenem-nonsusceptible isolates of *P. aeruginosa*, 1 μg/mL for meropenem-nonsusceptible *A. baumannii*, and 0.25–0.5 μg/mL for isolates of *S. maltophilia* [97]. As cefiderocol is a β-lactam agent, the pharmacodynamic parameter predictive of efficacy is %*f*T > 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 *f*AUC/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.

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