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INVITED REVIEW

Defining the Role of Novel β-Lactam Agents That Target Carbapenem-Resistant Gram-Negative Organisms

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With the current carbapenem-resistant organism crisis, conventional approaches to optimizing pharmacokinetic-pharmacodynamic parameters are frequently inadequate, and traditional salvage agents (eg, colistin, tigecycline, etc) confer high toxicity and/or have low efficacy. However, several β-lactam agents with activity against carbapenem-resistant organisms were approved recently by the US Food and Drug Administration, and more are anticipated to be approved in the near future. The primary goal of this review is to assist infectious disease practitioners with preferentially selecting 1 agent over another when treating patients infected with a carbapenem-resistant organism. However, resistance to some of these antibiotics has already developed. Antibiotic stewardship programs can ensure that they are reserved for situations in which other options are lacking and are paramount for the survival of these agents.

Keywords. aztreonam-avibactam; cefiderocol; ceftazidime-avibactam; ceftolozane-tazobactam; imipenem-cilastatin–relebactam; meropenem-vaborbactam.

Carbapenem-resistant Gram-negative organisms continue to pose a serious clinical threat, and few treatment options are available [1]. However, a number of β-lactam antibiotics with activity against these organisms are currently in or recently completed phase III studies in the United States. As clinical trials in adults continue, studies investigating dosage and infusion strategies for optimizing pharmacokinetics and pharmacodynamics in children are being explored or have begun for all of these agents.

In this article, we provide a brief overview of mechanisms of carbapenem resistance followed by a discussion of recently approved β-lactam agents (ie, ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam) and agents that, at the time this review was prepared, have not yet obtained US Food and Drug Administration (FDA) approval (eg, aztreonam-avibactam, cefiderocol, and imipenem-cilastatin–relebactam [referenced herein as imipenem-relebactam]) along with their role in the treatment of infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. The primary goal of this review is to assist infectious disease practitioners in preferentially selecting 1 agent over another when treating patients infected with a carbapenem-resistant organism. Information on pharmacokinetics and pharmacodynamics will generally not be addressed. Because ongoing studies are being conducted for all of these agents, particularly those not yet approved by the FDA, we anticipate that our understanding of the role of these antibiotics will continue to evolve over the next several months to years.

OVERVIEW OF MECHANISMS OF CARBAPENEM RESISTANCE

Carbapenem resistance occurs as a consequence of a number of heterogenous mechanisms [2]. Carbapenemase enzymes, which hydrolyze the β-lactam ring of carbapenem antibiotics, are common to *Enterobacteriaceae* and *A baumannii*. Carbapenemase producers account for slightly less than 50% of CRE strains in the United States; approximately 95% of carbapenemases are *Klebsiella pneumoniae* carbapenemases (KPCs), and the remainder belong to the New Delhi metallo-β-lactamases (NDMs) or oxacillinase-48-like (OXA-48-like) carbapenemase group [3, 4]. KPCs and OXA-48-like carbapenemases are serine carbapenemases, and NDMs, along with Verona integron-encoded metallo-β-lactamases (VIMs) and imipenemases (IMPs), are common metallo-β-lactamase (MBL) carbapenemases, named as such because they require the presence of zinc at their active site to function [5]. The remainder of carbapenem resistance in *Enterobacteriaceae* is generally caused by the production of extended-spectrum β-lactamases (ESBLs) and/or AmpC β-lactamases (AmpCs), in combination with reduced porin expression (eg, Ompk35 mutation, Ompk36 mutation, etc) [6] or overexpression of efflux pumps (eg, the AcrAB–TolC efflux pump) [7].

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The mechanisms of carbapenem resistance in glucose-nonfermenting organisms differ according to the organism. Carbapenem-resistant *P aeruginosa* strains generally evolve because of an interplay of multiple complex mechanisms, including mutations in OprD porins, hyperproduction of AmpCs, upregulation of efflux pumps, and mutations in penicillin-binding proteins [8]. Carbapenemases are an infrequent mechanism behind carbapenem-resistant *P aeruginosa* in the United States [8] and are found more commonly in other regions of the world such as Europe, Asia, and Latin America; VIM carbapenemases are responsible for approximately 11% of carbapenem-resistant *P aeruginosa* infections in Europe [9], 12% of overall *P aeruginosa* infections (regardless of carbapenem susceptibility) from Asia [10], and up to 19% of carbapenem-resistant infections in Latin America [11]. Carbapenem resistance in *A baumannii* strains in both the United States and abroad is generally the result of the production of class D carbapenemases, with OXA-23-like, OXA-40-like, OXA-58-like, and OXA-143-like carbapenemases commonly implicated [8]. *S maltophilia* has a chromosomally mediated MBL, L1 β-lactamase, that renders this organism intrinsically resistant to carbapenems [12]. A number of phenotypic and genotypic tests are available to clinical microbiology laboratories for identifying carbapenemase production by Gram-negative organisms and the specific carbapenemase(s) produced [13, 14]. Because the newer β-lactams exhibit unique profiles in their activity against some carbapenemases but not others, we believe that the role of the clinical microbiology laboratory in identifying both the presence of a carbapenemase as well as the specific carbapenemase gene is becoming increasingly important for guiding effective treatment decisions.

AZTREONAM-AVIBACTAM

Spectrum of Activity

Aztreonam is known for its ability to withstand hydrolysis by MBL carbapenemases. Aztreonam, however, is generally susceptible to hydrolysis by serine β-lactamases, including ESBLs, AmpCs, KPCs, and OXA-48-like carbapenemases, which is concerning because plasmids that contain MBL genes generally also harbor genes that encode several of these other β-lactamases [5]. Avibactam is a β-lactamase inhibitor that is not susceptible to hydrolysis by ESBLs, AmpCs, KPCs, or OXA-48-like carbapenemases and therefore overcomes the shortcomings of aztreonam [15, 16]. Together, the combination of aztreonam and avibactam provides broad coverage against a wide range of β-lactamase–producing *Enterobacteriaceae* (Figure 1). More specifically, in a large surveillance study that included clinical isolates from both the United States and abroad, the minimum inhibitory concentrations required to inhibit the growth of 90% of organisms (MIC_{90}) for aztreonam-avibactam against KPC producers (n = 102), MBL producers (n = 59), and OXA-48-like producers (n = 57) were ≤0.50 μg/mL for all of these carbapenemase-producing *Enterobacteriaceae* [17]. A separate international collection of isolates yielded similar results [18]. MBL producers can be particularly challenging to treat given the limited number of agents with activity against them. Aztreonam-avibactam has

Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Aztreonam-avibactam						
Cefiderocol						
Ceftazidime-avibactam[1]						
Ceftolozane-tazobactam[1]						
Eravacycline[1,2]						
Fosfomycin (intravenous)						
Imipenem-relebactam[3]						
Meropenem-vaborbactam[1]						
Plazomicin[1,4]						
Polymyxin B[1,5] or Colistin[1,5]						
Tigecycline[1,2]						

Figure 1. Select antibiotics with activity against carbapenem-resistant organisms. Green, susceptibility anticipated to be >80%; yellow, susceptibility anticipated to be 30% to 80%; red, intrinsic resistance or susceptibility anticipated to be <30%. [1], US Food and Drug Administration–approved agent; [2], synthetic tetracycline derivative; [3], imipenem-cilastatin–relebactam; [4], synthetic aminoglycoside; [5], polymyxin class. Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase.

been found to be 8- to 32-fold more potent than meropenem against MBL-producing *Enterobacteriaceae* [9]. Furthermore, in vitro data have suggested that aztreonam-avibactam is also effective against isolates that simultaneously produce both serine and MBL carbapenemases [19].

The activity of aztreonam-avibactam against *P aeruginosa* is less reliable [9, 18]. In a collection of 11 842 international clinical isolates of *P aeruginosa*, the MIC_{90} of aztreonam-avibactam was 32 μg/mL regardless of whether the organisms were or were not producing MBLs [9]. The poor activity of aztreonam-avibactam against *P aeruginosa* highlights the multiple complex resistance mechanisms likely to be concurrently present in this organism. Because MBL production is intrinsic to *S maltophilia*, aztreonam-avibactam will generally provide coverage against this organism [20]. In contrast, the addition of avibactam to aztreonam is unlikely to restore susceptibility to aztreonam-resistant *A baumannii* [18].

Clinical Data

A phase II prospective nonrandomized study in which 36 hospitalized adults with complicated intra-abdominal infections (cIAIs) treated with aztreonam-avibactam was recently completed (ClinicalTrials.gov identifier NCT02655419); the results are still pending. Because the main objective of this study was to understand the safety and tolerability of aztreonam-avibactam, targeted enrollment of patients infected with CRE was not undertaken. A phase III randomized controlled trial (RCT) is currently enrolling adults with a serious Gram-negative infection, including those with cIAIs, hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP); these participants are being randomly assigned to receive aztreonam-avibactam with or without metronidazole or meropenem with or without colistin (ClinicalTrials.gov identifier NCT03329092). A subgroup analysis to evaluate patients infected with CRE is planned. An additional phase III RCT will focus specifically on serious infections caused by MBL-producing organisms and compare aztreonam-avibactam versus best available therapy (ClinicalTrials.gov identifier NCT03580044).

Potential Role

Overall, familiarity with both aztreonam and avibactam in children and adults makes aztreonam-avibactam an attractive treatment option. Furthermore, it can be administered safely to patients with CRE infections and severe penicillin allergies, when the use of other β-lactams should be avoided. In vitro data have suggested that aztreonam-avibactam has reliable activity against carbapenemase-producing *Enterobacteriaceae* and is indifferent to the type of carbapenemase produced (Figure 1). Furthermore, this agent is anticipated to provide coverage against *S maltophilia*, when first-line agents such as trimethoprim-sulfamethoxazole or ceftazidime are not active or when drug allergies preclude their use.

CEFIDEROCOL

Mechanism of Action

The innate immune system minimizes available free iron in response to bacterial infections ("nutritional immunity"), because iron is an essential cation for bacterial growth [21]. Most iron is bound to hemoglobin, myoglobin, or iron-binding proteins [21]. In response to reduced host availability of iron, bacteria upregulate the production of siderophores, which are high-affinity iron-chelating compounds that scavenge for available free iron [21].

Cefiderocol is an injectable siderophore cephalosporin. It binds to iron via a catechol moiety, using a "Trojan horse" approach to gain entry into bacteria by capitalizing on available active iron-transport systems [21, 22]. Once across the outer membrane, cefiderocol dissociates from the iron molecule and binds to penicillin-binding proteins, which disrupts cell-wall synthesis [22]. This unique mechanism of cell entry ensures transport into bacterial cells even in the presence of porin channel loss and overexpression of efflux pumps [22]. Furthermore, the structure of cefiderocol ensures that it is highly stable against hydrolysis from both serine carbapenemases and MBLs [23]. Experimental data have suggested that a deficiency of the iron transporter PiuA in *P aeruginosa* or CirA and Fiu in *Escherichia coli* causes a 16-fold increase in cefiderocol MICs, indicating that these iron transporters contribute to the permeation of cefiderocol across the outer membrane [24].

Spectrum of Activity

Cefiderocol confers activity against a broad range of highly drug-resistant Gram-negative organisms (Figure 1). In iron-depleted cation-adjusted Mueller–Hinton broth preparations, the antibacterial activity of cefiderocol remained favorable against 753 clinical isolates of multidrug-resistant Gram-negative organisms, including both serine carbapenemase and MBL-producing *Enterobacteriaceae*, *P aeruginosa*, and *A baumannii* [25]. Only colistin and tigecycline had comparable activity against many of these isolates (recognizing tigecycline's notable gap of pseudomonal coverage). However, cefiderocol has a more appealing pharmacokinetic-pharmacodynamic profile over either of these agents. In addition, cefiderocol has potent in vitro activity against *S maltophilia* and members of the *Burkholderia cepacia* complex [24, 26].

Clinical Data

In a multicenter double-blind RCT that included 371 adults with complicated urinary tract infections (cUTIs), cefiderocol met the noninferiority composite clinical and microbiological end points when compared with imipenem-cilastatin; 73% and 55% of patients in the cefiderocol and imipenem-cilastatin groups, respectively, achieved this end point (ClinicalTrials.gov identifier NCT02321800) [27]. Patients infected with a

carbapenem-resistant organism represented less than 3% of the study population. Emergence of resistance to cefiderocol was not investigated. Phase III studies evaluating the role of cefiderocol, administered as an extended 3-hour infusion are current underway; one compared with best available therapy for the treatment of carbapenem-resistant pathogens from a variety of sources, and another compared with meropenem for nosocomial pneumonia (ClinicalTrials.gov identifiers NCT02714595 and NCT03032380).

Although cefiderocol seems to be an exciting addition to the antibiotic armamentarium, it is important to proceed with caution, because unknowns remain in the use of siderophore antibiotics. The experience with MB-1, a siderophore monobactam conjugate, serves as a cautionary tale [28]. In vitro data against a cohort of *P aeruginosa* isolates seemed promising. However, in a neutropenic mouse thigh model, variable efficacy of MB-1 against *P aeruginosa* isolates was observed, and the correlation between in vitro MB-1 MICs and the corresponding level of MB-1 efficacy in vivo was limited [28]. Investigators hypothesized that increases in endogenously produced *P aeruginosa* siderophores downregulated other siderophore receptors, including those used by MB-1 [28]. It is fortunate that cefiderocol differs from MB-1 structurally, and potent activity of cefiderocol has been observed in a murine neutropenic thigh model [29].

Potential Role

Cefiderocol circumvents common resistance mechanisms. Moreover, cross-resistance to cefiderocol is anticipated to be low because of its unique mechanism of action. For patients at high risk of infection from extremely drug-resistant organisms, this agent offers broad empiric Gram-negative coverage. All other agents discussed in this review fail to provide comprehensive coverage against CRE (regardless of the specific mechanism of resistance), carbapenem-resistant *P aeruginosa*, carbapenem-resistant *A baumannii*, and *S maltophilia*. The fact that clinical experience with siderophore antibiotics is still in its nascency is an important concern. The adverse event profile will not be well understood until more clinical data are available.

CEFTAZIDIME-AVIBACTAM

Spectrum of Activity

Avibactam is a synthetic β-lactamase inhibitor that binds reversibly to β-lactamases [30] and, unlike older inhibitors (eg, tazobactam, sulbactam, clavulanate), has activity against carbapenemases. Various in vitro studies have found the activity of ceftazidime-avibactam against KPC-producing organisms to consistently be well over 95% [31–34]. However, resistance has been observed in KPC-2– and KPC-3–producing isolates and is generally caused by decreased porin expression [35–44]. Perhaps of even greater concern is that resistance has emerged during exposure to ceftazidime-avibactam therapy, most frequently because of an amino acid substitution within or proximal to the omega loop of the KPC enzyme [40, 43, 45–47]. Study results have suggested that the emergence of resistance during ceftazidime-avibactam therapy occurs approximately 10% of the time [43, 46]. Interestingly, some of the mutations that confer resistance to ceftazidime-avibactam can reduce the carbapenemase activity of KPC-3, resulting in lower carbapenem MICs and restoring the susceptibility of these isolates to carbapenems [43, 46, 48]. However, this restored carbapenem activity is generally not sustainable [49].

Avibactam is able to reinstate the activity of ceftazidime against isolates that produce OXA-48-like enzymes [15, 50] (Figure 1). Although OXA-48-like enzymes only weakly hydrolyze ceftazidime, they generally exist in an environment in which multiple other β-lactamases are present. Ceftazidime-avibactam also provides enhanced activity against carbapenem-resistant *P aeruginosa*. In various studies, ceftazidime-avibactam was active against 67% to 88% of meropenem-nonsusceptible *P aeruginosa* isolates [33, 51]. The addition of avibactam to ceftazidime does not improve its activity against carbapenem-resistant *A baumannii* or *S maltophilia*. However, when ceftazidime-avibactam is used in combination with aztreonam, an inhibitor of MBLs, activity against *S maltophilia* can be restored [20, 52].

Clinical Data

Ceftazidime-avibactam received approval from the FDA in February 2015 for the treatment of cUTIs and for the treatment of cIAIs when used in combination with metronidazole [53] (Table 1). A phase I study to evaluate pharmacokinetics, safety, and tolerability of ceftazidime-avibactam in healthy 3-month to <18-year-olds [54] and a phase II study comparing ceftazidime-avibactam with metronidazole versus meropenem in children with cIAIs in the same age range informed the dosing recommendations outlined in Table 1 (ClinicalTrials.gov identifiers NCT01893346 and NCT02475733).

Phase II clinical trials in adults consisted of a study that compared ceftazidime-avibactam and imipenem-cilastatin for cUTIs [55] and a study that compared ceftazidime-avibactam (with metronidazole) to meropenem for cIAIs [56]. Both studies met the predetermined clinical and microbiological noninferiority end points. Phase III trials in adults include a study that compared ceftazidime-avibactam to doripenem for the treatment of cUTIs [57] and a study that compared ceftazidime-avibactam (with metronidazole) to meropenem for cIAIs [58]; again, both studies met the clinical and microbiological noninferiority end points. CRE infections were not evaluated for any of the aforementioned phase II or III studies. A subsequent phase III study compared ceftazidime-avibactam versus best available therapy for patients with cUTIs or cIAIs caused by a ceftazidime-resistant *Enterobacteriaceae* or *P aeruginosa* in a randomized open-label trial [59]; 97% of those in the best-available-therapy group received a carbapenem. Clinical outcomes

Table 1. Dosing Under Evaluation for Novel β-Lactam Agents That Target Carbapenem-Resistant Gram-Negative Organisms

Novel β-Lactam	Dose (Assuming Normal Renal Function)		Data Informing Dosing
	Adult	Pediatric[a]	
Aztreonam-avibactam	Aztreonam 6500 mg with avibactam 2167 mg (loading dose, extended loading dose and maintenance dose) by IV infusion on day 1, followed by a total daily dose of aztreonam 6000 mg with avibactam 2000 mg	TBD	Adult dosing informed by an ongoing phase III study (ClinicalTrials.gov identifier NCT03329092) for the treatment of serious infections, including those caused by a metallo-β-lactamase producing bacterium; dosing here differs from that in a completed phase II study that evaluated aztreonam-avibactam for generally susceptible IAI (ClinicalTrials.gov identifier NCT02655419)
Cefiderocol	Cefiderocol 2000 mg IV q8h infused over 3 hours	TBD	Adult dosing informed by an ongoing phase III study (ClinicalTrials.gov identifier NCT02714595) of carbapenem-resistant infections, which is the same dose used in an ongoing phase III pneumonia study (ClinicalTrials.gov identifier NCT03032380). A completed phase II UTI study used the same adult dosing shown in column 2 but as 1-hour infusions (ClinicalTrials.gov identifier NCT02321800).
Ceftazidime-avibactam	Ceftazidime 2000 mg with avibactam 500 mg IV q8h infused over 2 hours	3 months to <6 months: ceftazidime 40 mg/kg per dose with avibactam 10 mg/kg per dose IV q8h infused over 2 hours; 6 months to <18 years of age: ceftazidime 50 mg/kg per dose with avibactam 12.5 mg/kg per dose IV q8h infused over 2 hours	Adult dosing is the FDA-approved dose; pediatric dosing informed by a completed phase I study (ClinicalTrials.gov identifier NCT01893346) and completed phase II IAI study (ClinicalTrials.gov identifier NCT02475733) of children aged 3 months to <18 years
Ceftolozane-tazobactam	UTI and IAI: ceftolozane 1000 mg with tazobactam 500 mg IV q8h; pneumonia: ceftolozane 2000 mg with tazobactam 1000 mg IV q8h	>32 weeks gestational age and >/=7 days postnatal age to <18 years old, for UTI and IAI: ceftolozane 20 mg/kg per dose with tazobactam 10 mg/kg per dose IV q8h; for pneumonia: ceftolozane 40 mg/kg per dose with tazobactam 20 mg/kg per dose IV q8h	Adult dosing for UTI and IAI is the FDA-approved dose; adult pneumonia dosing here was informed by a completed phase III pneumonia study in adults (ClinicalTrials.gov identifier NCT02070757); because epithelial lining fluid concentrations of ceftolozane are approximately 50% of serum concentrations, dosages were doubled in the pneumonia study; pediatric dosing for ceftolozane-tazobactam to treat pneumonia was extrapolated from the adult data; pediatric UTI and IAI dosing here is being investigated in an ongoing pediatric phase II UTI study (ClinicalTrials.gov identifier NCT03230838) and ongoing pediatric phase II IAI study (ClinicalTrials.gov identifier NCT03217136)
Imipenem-cilastatin–relebactam	Imipenem 500 mg with cilastatin 500 mg with relebactam 250 mg IV q6h	1 month to <18 years old: imipenem 15 mg/kg per dose with cilastatin 15 mg/kg per dose with relebactam 7.5 mg/kg per dose IV q6h	Adult dosing informed by a completed phase III study of carbapenem-resistant infections in adults (ClinicalTrials.gov identifier NCT02452047); pediatric dosing is being investigated in an ongoing phase I study (ClinicalTrials.gov identifier NCT03230916). Based on experience with dosing imipenem-cilastatin in infants and children, these doses can be considered for infants 1 month of age and older until additional data become available.
Meropenem-vaborbactam	Meropenem 2000 mg with vaborbactam 2000 mg IV q8h, infused over 3 hours	1 month to <18 years old: meropenem 40 mg/kg per dose with vaborbactam 40 mg/kg per dose IV q8h, infused over 3 hours	Adult dosing is the FDA-approved dose; pediatric dosing is being investigated in an ongoing phase I study (ClinicalTrials.gov identifier NCT02687906). Based on experience with dosing meropenem in infants and children, these doses can be considered for infants 1 month of age and older until additional data become available.

Abbreviations: FDA, US Food and Drug Administration; IAI, intra-abdominal infection; IV, intravenous; q6h, every 6 hours; q8h, every 8 hours; TBD, to be determined; UTI, urinary tract infection.
[a]Pediatric dose should not exceed the adult dose for the specified indication.

in the treatment groups were similar [59]. Finally another phase III study found ceftazidime-avibactam to be noninferior to meropenem for the treatment of adults with HAP or VAP [60].

Postmarketing surveillance from observational studies that include patients with infections caused by carbapenem-resistant organisms is becoming increasingly available. These studies are a welcome addition to the literature because they investigate the performance of ceftazidime-avibactam in clinical scenarios in which the agent is likely to be prescribed. Shields et al [61] evaluated the outcomes of patients with KPC-producing bloodstream infections and compared ceftazidime-avibactam (n = 13), carbapenems plus aminoglycosides (n = 25), carbapenems plus colistin (n = 30), and a variety of other combinations (n = 41). Patients who received ceftazidime-avibactam had significantly better clinical outcomes and survival compared to patients who received any of the other regimens. Moreover, the risk of acute kidney injury was lower with ceftazidime-avibactam than with other combinations. A separate observational study that compared 137 patients receiving either ceftazidime-avibactam or colistin-based regimens for CRE infections from a variety of sources found ceftazidime-avibactam to be superior to colistin for the 30-day all-cause mortality outcome [62].

Potential Role

Ceftazidime-avibactam remains an excellent choice for treating infections caused by non–MBL-producing CRE. However, while the availability of aztreonam-avibactam is pending, ceftazidime-avibactam can be used in combination with aztreonam to treat infections caused by an MBL-producing organism. While ceftolozane-tazobactam remains the primary consideration out of existing commercially available agents for carbapenem-resistant *P aeruginosa* infections, it is reasonable to test ceftazidime-avibactam against such organisms. In 1 cohort of patients, most of whom had carbapenem-resistant *P aeruginosa* infections, 62% of the isolates were susceptible to ceftazidime-avibactam, whereas 73% were susceptible to ceftolozane-tazobactam [63]. Among

ceftolozane-tazobactam–resistant isolates, 9% were susceptible to ceftazidime-avibactam, whereas 36% of the ceftazidime-avibactam–resistant isolates were susceptible to ceftolozane-tazobactam [63]. The biggest concern with ceftazidime-avibactam is the reports of emergence of resistance in KPC-producing organisms that seem remarkably consistent across preclinical and postmarketing studies, which raises concerns about the continued effectiveness of this agent once it is prescribed with increasing frequency.

CEFTOLOZANE-TAZOBACTAM

Spectrum of Activity

Ceftolozane-tazobactam has the most potent antipseudomonal activity compared with other commercially available β-lactam–β-lactamase inhibitor combinations. Farrell et al [64] evaluated ceftolozane-tazobactam activity against 1019 *P aeruginosa* isolates from the United States and Europe. Ceftolozane-tazobactam was active against 78% of the carbapenem-resistant *P aeruginosa* isolates. Activity of ceftolozane-tazobactam against *P aeruginosa* strains varies between the United States and Europe, partly because of the higher prevalence of VIM-producing *P aeruginosa* strains in Europe. Activities were 93% and 57%, respectively, against US and European extensively drug-resistant *P aeruginosa* isolates. In an evaluation of 720 meropenem-nonsusceptible *P aeruginosa* isolates from European hospitals, 58% were susceptible to ceftolozane-tazobactam [65]. In a separate cohort of 42 US carbapenem-resistant *P aeruginosa* isolates, ceftolozane-tazobactam remained active against 95% of isolates; whereas, ceftazidime-avibactam remained active against 71% of the same isolates [66].

The activity of ceftolozane-tazobactam against *P aeruginosa* isolates from patients with cystic fibrosis, which frequently display a mucoid phenotype, is less reliable. Although some investigations have reported activity against a high percentage of *P aeruginosa* isolates recovered from the lungs of patients with cystic fibrosis [67, 68], when specifically evaluated against extensively drug-resistant *P aeruginosa* isolates from patients with cystic fibrosis, ceftolozane-tazobactam was active against 30% to 54% of isolates [69, 70]. Ceftolozane-tazobactam susceptibility of *S maltophilia* isolates from patients with cystic fibrosis has been reported to range from 0% to 85%, using the *P aeruginosa* breakpoint [67, 69, 71] (Figure 1). Ceftolozane-tazobactam has limited to no activity against CRE, MBL-producing *P aeruginosa*, or carbapenem-resistant *A baumannii* [72]. The emergence of resistance in *P aeruginosa* during ceftolozane-tazobactam therapy has been reported. In 1 study, 14% of adults with multidrug-resistant *P aeruginosa* infection experienced emergence of ceftolozane-tazobactam resistance during therapy [73], attributed mainly to de novo mutations that affect AmpC expression.

Clinical Data

Ceftolozane-tazobactam was approved in December 2014 by the FDA for the treatment of cUTIs and cIAIs in patients aged ≥18 years [74]. Phase II RCTs are currently underway to investigate the safety and efficacy of ceftolozane-tazobactam versus meropenem in children with cUTIs (ClinicalTrials.gov identifier NCT03230838) and (in combination with metronidazole) cIAIs (ClinicalTrials.gov identifier NCT03217136).

Available phase II and III clinical trial data indicate that ceftolozane-tazobactam is safe and effective compared to commonly prescribed agents for both cUTIs [75, 76] and cIAIs [77, 78]. These studies were unable to provide data on its role for the treatment of carbapenem-resistant organisms. A phase III clinical study of ceftolozane-tazobactam versus meropenem for adult patients with VAP was recently completed, and preliminary reports [79] indicate that ceftolozane-tazobactam met the pre-specified non-inferiority clinical end points of mortality and clinical cure (ClinicalTrials.gov identifier NCT02070757).

Potential Role

Ceftolozane-tazobactam is a reasonable consideration for patients infected with carbapenem-resistant *P aeruginosa*, with greater activity observed for isolates from patients without cystic fibrosis, compared to patients with cystic fibrosis. The fact that a significant proportion of *P aeruginosa* isolates resistant to all other antipseudomonal β-lactams exhibit elevated ceftolozane-tazobactam MIC values is concerning, particularly as little progress in the development of new anti-infectives targeting *P aeruginosa* has been made.

IMIPENEM-CILASTATIN–RELEBACTAM

Spectrum of Activity

Relebactam is a novel β-lactamase inhibitor that is structurally related to avibactam [80, 81]. Similar to avibactam, it provides potent activity against KPC producers [82, 83]. In a collection of clinical isolates from New York City, imipenem was active against 9% of 111 KPC-producing *K pneumoniae* isolates, whereas imipenem-relebactam was active against 97% of these isolates [82]. Imipenem-relebactam does not have activity against MBL carbapenemases, regardless of whether they are produced by *Enterobacteriaceae* or *P aeruginosa* [84]. Available data indicate that its activity against OXA-48-like carbapenemases is poor, and more in vitro testing to evaluate its specific role against OXA-48-like carbapenemases is needed [84]. Given the similarities between avibactam and relebactam, the limited to no restoration of activity against OXA-48-like producers is intriguing. In an evaluation of 27 imipenem-nonsusceptible *K pneumoniae* isolates, imipenem-relebactam restored activity against 74% of the isolates [85]. The 7 isolates to which both imipenem and imipenem-relebactam were inactive produced either VIM-type, OXA-48-like, or the class A GES-type carbapenemases [85].

In addition to activity against KPCs, imipenem-relebactam has excellent activity against carbapenem-resistant *P aeruginosa*

[82, 83, 86, 87]. The enhanced activity of imipenem-relebactam compared to that of imipenem is largely a result of the ability of relebactam to inhibit the imipenem-hydrolyzing AmpC enzymes commonly produced by this species [84]. Moreover, imipenem is a poor substrate for efflux pumps common to *P aeruginosa*, which makes it an attractive option for conjugating to relebactam [84]. In the previously described cohort of New York City isolates, imipenem-relebactam was active against 92% of imipenem-resistant *P aeruginosa* isolates [82]. In a separate investigation, relebactam restored imipenem susceptibility for 81% of 251 imipenem-nonsusceptible *P aeruginosa* isolates [85]. It is notable that imipenem-relebactam does not seem to have enhanced activity against *A baumannii* isolates that are resistant to imipenem [82, 85] and does not have activity against *S maltophilia* [82, 84].

Clinical Data

A phase I study is currently underway to investigate the pharmacokinetics, safety, and tolerability of single doses of imipenem-relebactam for children less than 18 years of age with confirmed or suspected Gram-negative infections (ClinicalTrials.gov identifier NCT03230916) (Table 1). Phase II studies evaluated the performance of imipenem-relebactam versus that of imipenem against cUTIs (ClinicalTrials.gov identifier NCT01505634) [88] and, separately, cIAIs (ClinicalTrials.gov identifier NCT01506271) [89] in adults. Both studies included predominantly imipenem-susceptible isolates, and outcomes were similar between the comparators. The phase II cIAI study included 34 patients with imipenem-resistant infections, all of whom had favorable outcomes [89]. A phase III study compared imipenem-relebactam versus imipenem in combination with colistin for HAP/VAP, cIAIs, and cUTIs caused by imipenem-resistant organisms (ClinicalTrials.gov identifier NCT02452047). Preliminary results demonstrated 28-day clinical responses of 71% and 40% in the imipenem-relebactam and imipenem-colistin arms, respectively, and all-cause mortality of 10% in the imipenem-relebactam group and 30% in the imipenem-colistin group [90]. A phase III study is enrolling patients with HAP and VAP comparing imipenem-relebactam versus piperacillin-tazobactam (ClinicalTrials.gov identifier NCT02493764).

Potential Role

Our long-standing experience with β-lactams in general, and imipenem specifically, makes imipenem-relebactam an appealing option. KPC-producing and carbapenem-resistant *P aeruginosa* strains—particularly carbapenem-resistant *P aeruginosa*—pose the most likely threat among Gram-negative pathogens for hospitals of all sizes in the United States [91], and imipenem-relebactam restores activity against both of them. This spectrum of activity is an attractive feature of imipenem-relebactam compared to those of other β-lactam–β-lactamase inhibitor combinations that are currently available on the US market (Figure 1).

MEROPENEM-VABORBACTAM

Spectrum of Activity

Meropenem-vaborbactam consists of an injectable synthetic carbapenem and a boronic acid β-lactamase inhibitor [92]. In a collection of 991 KPC-producing *Enterobacteriaceae* isolates, vaborbactam restored meropenem activity against 99% of the isolates [93]. In an evaluation of 133 KPC-producing clinical isolates between 2013 and 2014 from patients in New York City, meropenem-vaborbactam had activity against 99% of KPC-producing *K pneumoniae* isolates [94]. Meropenem-vaborbactam MICs remain elevated against MBL- or OXA-48-like–producing *Enterobacteriaceae*. In addition, this combination has lower activity against *Enterobacteriaceae* that exhibit decreased porin expression (Ompk35, Ompk36, Ompk37) [94–97] and/or elevated expression of the AcrAB–TolC efflux system [96, 97]. Resistance to meropenem-vaborbactam seems rare and less frequent than resistance to ceftazidime-avibactam, but this may change with increased clinical use [97–99]. On the basis of preliminary reports [93], cross-resistance between meropenem-vaborbactam and ceftazidime-avibactam is anticipated to occur for approximately 20% of isolates. Vaborbactam does not enhance the activity of meropenem against meropenem-resistant *P aeruginosa* or meropenem-resistant *A baumannii* [94, 100] (Table 1).

Clinical Data

A phase I study to evaluate single-dose pharmacokinetics, safety, and tolerability of meropenem-vaborbactam in children is currently underway (ClinicalTrials.gov identifier NCT02687906) (Table 1). Because of the completion of clinical trials for a similar agent (biapenem-RPX7009), evaluation of meropenem-vaborbactam proceeded directly to phase III studies in adults. In a phase III cUTI trial that included patients treated with meropenem-vaborbactam or piperacillin-tazobactam, clinical success rates were similar between the groups (ClinicalTrials.gov identifier NCT02166476) [101]. Meropenem-vaborbactam was subsequently approved by the FDA for the treatment of patients aged 18 years or older with cUTI caused by *Enterobacteriaceae* [102]. A subsequent phase III study evaluated meropenem-vaborbactam in 77 adults with cUTIs, cIAIs, HAP/VAP, or bacteremia caused by a CRE (ClinicalTrials.gov identifier NCT02168946) [103]. Better clinical outcomes were observed with meropenem-vaborbactam than with best available therapy; clinical cure at the end of therapy was achieved in 66% of patients in the meropenem-vaborbactam group and 33% in the best available therapy group, and 28-day mortality rates were 16% and 33% in the meropenem-vaborbactam and best available therapy arms,

respectively. Finally, results from a phase III study performed to compare meropenem-vaborbactam and piperacillin-tazobactam for patients with nosocomial pneumonia is under evaluation (ClinicalTrials.gov identifier NCT03006679).

Potential Role

Although meropenem-vaborbactam has excellent activity against KPC-producing isolates, its activity against other carbapenemase-producing *Enterobacteriaceae* is negligible. However, because resistance to ceftazidime-avibactam, the only other β-lactam–β-lactamase inhibitor combination currently available to treat KPC-producing *Enterobacteriaceae* infections, is emerging, meropenem-vaborbactam provides a valuable treatment option for organisms that produce KPCs. Head-to-head comparisons of clinical outcomes of meropenem-vaborbactam and ceftazidime-avibactam are not currently available. Although as of August 2018 approval is limited to adults, pediatric dosing for meropenem-vaborbactam is currently being studied (Table 1).

CONCLUSION

With the current crisis of carbapenem-resistant organisms, conventional approaches to optimizing pharmacokinetic-pharmacodynamic parameters such as extended-infusion carbapenem administration are frequently inadequate. Similarly, traditional salvage agents, including polymyxins and tigecycline, confer high toxicity and have low efficacy. However, several β-lactam agents with activity against carbapenem-resistant organisms were approved recently, and more are anticipated to be approved in the near future. Administration of the newer β-lactams as monotherapy versus combination therapy (ie, addition of aminoglycoside, polymyxin, etc) has not been evaluated rigorously. Phase III studies that have evaluated their use for the treatment of carbapenem-resistant infections (ClinicalTrials.gov identifiers NCT02452047 and NCT02168946) and observational studies published since FDA approval of ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam have overwhelmingly reported favorable outcomes when these agents are used as monotherapy [61, 62, 99, 104, 105]. The general consensus is that when a strain is susceptible, these agents can be used without the routine addition of a second agent, even for invasive infections. It is unfortunate that resistance to some of these newer agents is already being observed. Antibiotic stewardship programs are paramount to the survival of these agents, because they can ensure that these agents are reserved for situations in which other, more commonly used antibiotics are inactive.

Notes

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