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ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ieds20

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To cite this article: Matteo Bassetti, Antonio Falletta, Giovanni Cenderello, Daniele R. Giacobbe & Antonio Vena (2022) Safety evaluation of current therapies for high-risk severely ill patients with carbapenem-resistant infections, Expert Opinion on Drug Safety, 21:4, 487-498, DOI: 10.1080/14740338.2022.1990262

To link to this article: https://doi.org/10.1080/14740338.2022.1990262

EXPERT OPINION ON DRUG SAFETY
2022, VOL. 21, NO. 4, 487–498
https://doi.org/10.1080/14740338.2022.1990262

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REVIEW

Safety evaluation of current therapies for high-risk severely ill patients with carbapenem-resistant infections

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ABSTRACT

Introduction: Infections due to carbapenem-resistant Gram-negative bacteria (CR-GNB) are increasingly frequent events, which are associated with a high mortality rate. Traditionally, combination regimens including high doses of "old antibiotics" such as polymyxins, tigecycline, and aminoglycosides have been used to treat these infections, but they were often associated with low efficacy and high excess of side effects and toxicity, especially nephrotoxicity. Along with the development of new compounds, the last decade has seen substantial improvements in the management of CR infections.

Areas covered: In this review, we aimed to discuss the safety characteristics and tolerability of different new options for treatment of CR infections.

Expert opinion: The availability of new drugs showing a potent *in vitro* activity against CR-GNB represents a unique opportunity to face the threat of resistance, while potentially reducing toxicity. A thorough understanding of the safety profile from clinical trials may guide the use of these new drugs in critically ill patients at high risk for the development of adverse events. Future data coming from real-life studies for drugs targeting CR infections are crucial to confirm the safety profile observed in pivotal trials.

ARTICLE HISTORY
Received 15 May 2021
Accepted 4 October 2021

KEYWORDS
Carbapenem-resistant infections; carbapenemases; drug toxicity; acute kidney injury; new antibiotics

1. Introduction

During the last decade, serious infections due to carbapenem-resistant (CR) Gram-negative bacteria (GNB) have posed a special clinical challenge [1], owing to the lack of safe and efficacious therapeutic options [2] and their high attributable mortality rates [3–5]. For a long time, treatment of CR-infections has been limited to polymyxins, tigecycline, or aminoglycosides [6–8], but these therapies were often associated with low efficacy (due to resistance, unfavorable pharmacokinetics, and pharmacodynamic profiles) and high excess of side effects and non-negligible toxicity.

Precious additions to the antibiotic armamentarium have recently allow us to renew the availability of antibiotics for treating CR-GNB [7,8] (Table 1). Thanks to the ability of these drugs in increasing the cure rates, with a better safety profile compared to colistin or to aminoglycosides, we are now observing an epochal revolution in the treatment of CR infections [9–12]. In addition, these new drugs finally allow us to personalize the management of serious CR infections with more therapeutic choice depending on clinical needs [13,14]. For these reasons, the knowledge of potential toxicities related to the use of these new compounds appears to be of great importance, especially considering that patients with severe infections due to CR-GNB are often critically ill, present multiple comorbidities, and receive concomitant medications with potential interactions [15,16].

This review is intended to provide an overview of the safety and tolerability profile of the newer agents available for treatment of carbapenem-resistant infections. We will mainly focus on drugs currently approved by US Food and Drug administration (FDA) and European medicine agency (EMA).

2. Ceftazidime-avibactam

Avibactam is a new β-lactamase inhibitor belonging to the diazabicyclooctane family (DBOs). Avibactam inhibits class A β-lactamases, including extended spectrum β-lactamases (ESBL) and *Klebsiella pneumoniae* carbapenemase (KPCs), class C β-lactamases (AmpC), and some class D β-lactamases (e.g. OXA-48 carbapenemase), but not class B β-lactamases (e.g. NDM carbapenemase). Its presence substantially restores the activity of ceftazidime against the majority of KPC-producing CR-*Enterobacterales* (CRE) strains and carbapenem-resistant strains of *P. aeruginosa* (excluding metallo β-lactamase producers), but not those of *A. baumannii* [17,18].

Ceftazidime-avibactam is currently FDA and EMA approved for the treatment of complicated intra-abdominal infections (cIAIs), complicated urinary tract infections (cUTIs), and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) [19]. Moreover, ceftazidime-avibactam is also EMA approved for treatment of serious infections due to Gram-negative bacteria with limited or no treatment options,

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Article highlights

- The increasing incidence of carbapenem-resistant Gram-negative bacteria represents an urgent public health concern as they have spread worldwide.
- Among old antibiotics, regimens including high-dose colistin or aminoglycosides have been associated with increased rates of relevant side effects and non-negligible toxicity.
- New antimicrobials that have been recently approved in clinical practice (e.g. ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, cefiderocol, eravacycline, and plazomicin) are usually well-tolerated with a favorable safety profile.
- Future real-world studies are needed to confirm the efficacy and safety observed in randomized clinical trials.

This box summarizes key points contained in this article.

including carbapenemases producing Gram-negative rods [20].

In randomized controlled trials (RCTs) assessing the efficacy and safety of ceftazidime-avibactam [21–24], rates of adverse events (AEs) and serious AEs (SAEs) in general were similar between ceftazidime-avibactam and comparators. In the REPROVE trial, ceftazidime-avibactam was compared with meropenem for treatment of nosocomial pneumonia including ventilator-associated pneumonia [21]. This study demonstrated that comparable efficacy of ceftazidime-avibactam or meropenem treatment and the incidence of AEs (74.6% with ceftazidime-avibactam versus 74.2% with meropenem) or SAEs (18.5% with ceftazidime-avibactam versus 13.4% with meropenem) were similar. Of importance, in this study, 4.0% of patients receiving ceftazidime-avibactam and 2.7% with meropenem discontinued the study drug because of treatment-related AEs. In most cases, AEs comprised diarrhea, hypokalemia, anemia, constipation, and vomiting. No changes of concern were observed regarding hematological values or clinical chemistry parameters (Table 2) [21].

Consistent findings were also observed in the REPRISE trial, a randomized, open-label phase 3 trial in which a combination of 2000 mg ceftazidime plus 500 mg avibactam, administered via a 2-h intravenous infusion every 8 h, was compared with the best available therapy (BAT) for treatment of cUTI (n = 281) or cIAI (n = 21) due to ceftazidime-resistant *Enterobacterales* and *P.aeruginosa*. BAT consisted of carbapenem monotherapy in all except 7 patients who received colistin (n = 2), aminoglycoside (n = 2), and piperacillin-tazobactam, carbapenem plus fluoroquinolone, or carbapenem plus aminoglycoside, one each. In this study, 31.1% in the ceftazidime-avibactam group and 39.3% in the BAT group had experienced AEs, the majority of which were considered as mild or moderate in intensity [23]. Gastrointestinal AEs were the most frequent treatment emergent AEs with both ceftazidime-avibactam (12.8%) and BAT (17.9%). Overall, 9/164 (5.5%) and 10/164 (6.1%) patients belonging to ceftazidime-avibactam and BAT groups experienced SAEs, respectively, but none were considered related to study drug (Table 2) [23]. A further study (RECLAIM trial), comparing ceftazidime-avibactam with meropenem in cIAI, showed a similar number of AEs between groups (45.9% with ceftazidime-avibactam versus 42.9% with meropenem) [24]. Most common AEs for ceftazidime-avibactam included diarrhea (7.6%), nausea (6.8%), vomiting (4.5%), and pyrexia (4.5%) (Table 2) [24]. In the RECAPTURE trial demonstrating the noninferiority of ceftazidime-avibactam versus doripenem for the treatment of hospitalized patients with cUTI or acute pyelonephritis, at least one AE occurred in 185/511 (36.2%) and 158/509 (31.0%) ceftazidime-avibactam and doripenem recipients, respectively [22]. AEs were generally mild and moderate, and balanced across study groups and mainly consisted of headache (7.4%), nausea (2.9%), diarrhea (2.7%), or constipation (2.2%) (Table 2) [22]. Although randomized trials specifically targeting carbapenem-resistant pathogens have not been performed yet, data coming from real-life studies appeared promising [16,25–27]. Shields et al. [26] reported the use of ceftazidime-avibactam versus other treatment regimens in 109 patients with CR *K. pneumoniae* bloodstream infection (BSI). In this study, clinical success and survival were significantly improved for patients with CR *K. pneumoniae* BSI receiving ceftazidime-avibactam. Moreover, colistin or aminoglycoside-containing treatment was associated with increased rates of nephrotoxicity ($p = 0.002$) [26]. Further evidence supporting the safety of ceftazidime-avibactam in CR *Enterobacterales* infections comes from CRACKLE, a prospective, observational study of 137 patients treated with a ceftazidime-avibactam-based regimen or a colistin-based regimen [27]. Using intent-to-treat analyses with partial credit and desirability of outcome ranking approaches, these investigators found that patients initially treated with ceftazidime-avibactam were 62% more likely to have an improved safety outcome, defined as discharged to home without renal failure [27]. Finally, Vena et al reported no drug-related AEs among 41 patients with multidrug-resistant (MDR) GNB infections treated with ceftazidime-avibactam, most of which were due to carbapenem-resistant strains [12].

3. Ceftolozane-tazobactam

Ceftolozane-tazobactam is a new cephalosporin-β-lactamase inhibitor combination approved by FDA and the EMA for treatment of cIAIs, cUTIs, and HABP/VABP in adult patients [28]. Ceftolozane is stable by itself against multiple resistance mechanisms including overexpression of AmpC, and the combination with tazobactam confers it activity against ESBL-producing *Enterobacterales* [29]. Currently, ceftolozane-tazobactam has proven to be the most active β-lactam against *P. aeruginosa*, retaining remarkable activity also against MDR or extensively drug-resistant (XDR) isolates, even when it is carbapenem-resistant in the absence of carbapenemase production (e.g. MBL or serine carbapenemases). However, it lacks activity against *P. aeruginosa* strains carrying metallo-β-lactamases, CR *Enterobacterales, A. baumannii,* or *S. maltophilia* [18]

Based on data extrapolated from clinical trials, AEs due to ceftolozane-tazobactam do not considerably differ from those observed during treatment with other cephalosporins. Most common AEs were nausea, diarrhea, *C. difficile* infection, headache, pyrexia, and abnormal liver function test [30–32]. In two prospective studies using ceftolozane-tazobactam at a dosage of 1.5 gr every 8 hours, AEs were reported in 34.7% to 44.0%

Table 1. Spectrum of action of new treatment options with activity against carbapenem-resistant Gram-negative bacteria.

	Activity							
	Enterobacterales						Carbapenem-resistant Gram-negative pathogen-directed clinical trials	
DRUG	Class A carbapenemases (e.g. KPC)	Class B carbapenemases (e.g. VIM and NDM)	Class C carbapenemases (e. g. AmpC)	Class D carbapenemases (e. g. OXA-48)	*P. aeruginosa*			
A. baumannii								
Ceftazidime-avibactam	Yes	No	Yes	Yes	Yes	No	No	
Ceftolozane-tazobactam	No	No	Yes	No	Yes	No	No	
Meropenem-vaborbactam	Yes	No	Yes	No	Yes/No*	Yes/No*	Yes	
Imipenem-cilastatin-relebactam	Yes	No	Yes	No	Yes	No	Yes	
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Eravacycline	Yes	Yes	Yes	No	No	Yes	No	
Plazomicin	Yes	Yes/No**	Yes	Yes	Yes	No	Yes	

*Yaborbactam does not appear to improve the activity of meropenem against resistant nonfermenting Gram-negative bacilli, notably *Acinetobacter* spp or *Pseudomonas aeruginosa*. ** Caution should be exercised when using plazomicin to treat NDM producing *Enterobacterales* because of frequent coexpression of 16s rRNA methyltransferases.

and drug-related AEs in 17.5% to 19.0%, respectively. In these two trials, most common AEs included gastrointestinal effects, insomnia, and abnormal liver function tests (Table 2) [31,32]. Interestingly, in the ASPECT-NP study, the only RCT using high dose of ceftolozane-tazobactam (3 gr every 8 hours) [30], the severity and frequencies of AEs leading to study drug discontinuation were similar between patients who received ceftolozane-tazobactam and patients who received meropenem [30]. The most commonly reported treatment-related AEs in the ceftolozane-tazobactam group were abnormal liver function tests (3%), *C. difficile* infection (1%), and diarrhea (1%).

As for studies coming from real-life experiences, Munita et al [33] reported only 2 cases of AEs among their study population including 35 patients infected with carbapenem-resistant *P. aeruginosa* treated with ceftolozane-tazobactam (one patient developed self-limited diarrhea with a negative *C. difficile* molecular assay, and the other was found to have peripheral eosinophilia and eosinophiluria without acute kidney injury). Lower rates of AEs were observed by Bassetti et al, who reported only 3 patients experiencing drug-related AEs, among 101 patients treated with C/T [34]. In this study, AEs consisted of gastrointestinal symptoms (i.e. nausea, abdominal pain, and diarrhea), rash, and an asymptomatic increase in liver function test results. In this study, all except one patient experiencing AEs were treated with standard dosage of ceftolozane-tazobactam (1.5 g every 8 hours) and the time from starting study drug to AE onset varied widely from 5 days to 72 days. All episodes were considered as mild in severity. Nonetheless, ceftolozane-tazobactam was discontinued early in 2 out of 3 patients experiencing AEs [34].

In another retrospective, multicenter, observational cohort study, patients who received ceftolozane-tazobactam were compared with those treated with either polymyxin or aminoglycoside-based regimens for infections due to drug-resistant *P. aeruginosa* [35]. This study encompassed a total of 200 ill patients (100 in each treatment arm), of whom 69% were in the intensive care unit, 63% mechanically ventilated, and 42% in severe sepsis or septic shock at infection onset. The most common infection type was VABP (52%), and 7% of patients were bacteriemic. In this study, after adjusting for differences between groups, receipt of ceftolozane-tazobactam was independently associated with clinical cure (aOR, 2.63; 95% CI, 1.31–5.30) and protective against acute kidney injury (aOR, 0.08; 95% CI, 0.03–0.22). Of interest, the number needed to harm with acute kidney injury with a polymyxin/aminoglycoside-based regimen was 4 [35].

In a similar study comparing patients with MDR/XDR *P. aeruginosa* infections treated with ceftolozane-tazobactam with those treated with the aminoglycoside- or colistin-based regimen [36], a trend toward more favorable 14-day clinical cure rates was observed in ceftolozane-tazobactam (81.3%) than in the aminoglycoside or colistin group (56.3%, $p = 0.11$). Of importance, although safety data were not separately addressed, acute kidney injury was more frequently reported in patients treated with the aminoglycoside- or colistin-based regimen in comparison to those receiving ceftolozane-tazobactam (25.0% vs 0%, $p = 0.04$) [36].

Table 2. Common adverse events, serious adverse events, and drug discontinuation rates during major clinical trials of new compounds used in the treatment of carbapenem-resistant infections.

Drug	Study type	Treatment-related adverse effects (%)	Serious AE (%)	Drug Discontinuation (%)
Ceftazidime-avibactam	**Phase 3** randomized trial comparing ceftazidime-avibactam versus meropenem in HABP including VABP (REPROVE) [21]	Treatment-related AEs: 16% in ceftazidime-avibactam versus 13% in the meropenem group. More common AEs in the ceftazidime-avibactam group were as follows: - Diarrhea (15%) - Hypokalemia (11%) - Anemia (6%) - Constipation (6%) - Vomiting (6%)	Treatment-related SAEs occurred in 4 patients in ceftazidime-avibactam (1%) SAEs consisted of diarrhea, acute coronary disease, abnormal liver function, and subacute hepatic failure.	4.0%
	Phase 3 randomized trial comparing ceftazidime-avibactam versus BAT in cUTI/cIAI (REPRISE) [23]	Treatment-related AEs: 9% in the ceftazidime-avibactam group versus 9% in the BAT group. Most common AE in the ceftazidime-avibactam group was gastrointestinal.	SAEs occurred in 9 patients in ceftazidime-avibactam (5.5%), versus 10 in the BAT group (6.1%). No SAE was considered to be study drug related.	1.0%
	Phase 3 randomized trial comparing ceftazidime-avibactam plus metronidazole with meropenem in cIAI (RECLAIM) [24]	Overall, AEs were observed in 45.9% in the ceftazidime-avibactam plus metronidazole group versus 42.9% in the meropenem group. Most common AEs observed in the ceftazidime-avibactam group were as follows: - diarrhea(7.6%) - nausea(6.8%) - vomiting(4.5%) -pyrexia (4.5%) -Wound infection (2.5%) -Headache (2.8%) -Hypertension (2.8%)	SAEs were reported in 7.9% of patients the in ceftazidime-avibactam plus metronidazole group.	AEs leading to discontinuation were reported in 2.6% of patients in the ceftazidime-avibactam plus metronidazole group.
	Phase 3 randomized trial comparing ceftazidime-avibactam versus doripenem in patients with cUTI (RECAPTURE) [22]	Treatment-related AEs: 36.2% in the ceftazidime-avibactam group versus 31.0% in the doripenem goup The most AEs in the ceftazidime-avibactam group were as follows: -Headache (7.4%) -Nausea (2.9%) -Constipation (2.2%) -Diarrhea (2.7%)	No SAEs were reported	1.4%
Ceftolozane-Tazobactam	**Phase 3** randomized trial comparing ceftolozane-tazobactam versus meropenem in nosocomial pneumonia (ASPECT-NP) [30]	Treatment-related AEs: 11% in the ceftolozane-tazobactam group versus 8% in the meropenem group	Treatment-related SAEs were reported in 2% of patients in the ceftolozane-tazobactam group	No patient discontinued study drug because of AEs.
	Phase 3 randomized trial comparing ceftolozane-tazobactam with levofloxacin in cUTI (ASPECT-cUTI) [31]	No treatment adverse effects were reported. AEs: 34.7% in the ceftolozane-tazobactam group versus 34.4% in the levofloxacin group. Most common AEs were as follows: -Headache (5.8%) -Constipation (2.9%) -Nausea (3.8%)	SAEs occurred in 2.8% of patients in the ceftolozane-tazobactam group. Two serious adverse events (*Clostridium difficile* infections) in the ceftolozane-tazobactam group were deemed to be related to study treatment.	No patient discontinued study drug because of AEs.
	Phase 3 randomized trial comparing ceftolozane-tazobactam plus metronidazole with meropenem in cIAI (ASPECT-cIAI) [32]	AEs reported were 44.0% in the ceftolozane-tazobactam group versus 42.0% in the meropenem group. Most common AEs were as follows: -Nausea (7.9%) -Diarrhea (6.2%) -Pyrexia (5.2%)	SAEs occurred in 1 patient in each treatment group	Drug-related AEs leading to discontinuation were few, occurring in 3 patients (0.6%) in the ceftolozane-tazobactam plus metronidazole group

(*Continued*)

Table 2. (Continued).

Meropenem-Vaborbactam	**Phase 3** randomized trial comparing meropenem-vaborbactam with piperacillin-tazobactam in cUTI (TANGO I) [39];	Treatment-related AEs: 15.1% in the meropenem-vaborbactam group versus 12.8% in the piperacillin-tazobactam group	SAEs were reported in 2.6% of patients in the meropenem-vaborbactam group	2.6%
	Phase 3 randomized trial comparing meropenem-vaborbactam with BAT for CRE infections (TANGO II) [40]	Treatment-related AEs: 24.4% in the meropenem-vaborbactam group versus 44.0% in the BAT group. Most common AEs were as follows: -Diarrhea (12%) -Hypokalemia (10%) -Anemia (10%)	SAEs were reported in 0% of patients in the meropenem-vaborbactam group	Study-drug discontinuation due to TEAEs was 10% in the meropenem-vaborbactam group
Imipenem-cilastatin-relebactam	**Phase 3** randomized trial comparing imipenem-cilastatin-relebactam with colistin plus imipenem-cilastatin for imipenem-nonsusceptible bacterial infection (RESTORE IMI-1 trial) [48]	Treatment-related AEs: 16.1% in the imipenem- cilastatin-relebactam group versus 31.3% in colistin plus imipenem-cilastatin patients.	SAEs were reported in 0% of the imipenem-cilastatin-relebactam group	0%
	Phase 3 randomized trial comparing imipenem-cilastatin-relebactam with piperacillin-tazobactam for HABP/VABP (RESTORE IMI-2 trial) [47]	Treatment-related AEs: 11.7% in the imipenem- cilastatin-relebactam group versus 9.7% in the piperacillin-tazobactam group. Most common AEs were as follows: -Blood and lymphatic system disorders (1.5%) -Diarrhea (3.4%) -Skin and subcutaneous tissue disorders (2.3%)	SAEs were reported in 1.1% in the imipenem-cilastatin-relebactam group	2.3%
Cefiderocol	**Phase 3** randomized trial comparing cefiderocol with high-dose, extended infusion meropenem for Gram-negative nosocomial pneumonia (APEKS – NP) [58]	Treatment-related AEs: 9% in the cefiderocol group versus 11% in the meropenem group. Most frequent AEs in the cefiderocol group were as follows: - Urinary tract Infections (16%) - Hypokalemia (15%	Drug related serious AEs reported for 1.3% of the patients.	1%
	Phase 3 randomized trial comparing cefiderocol with BAT with carbapenem-resistant infections (CREDIBLE-CR) [56]	Treatment-related AEs: 15.0% in the cefiderocol group versus 22.0% in the BAT group.	SAEs related to drug therapy were reported in 1% of patients.	Drug-releted AEs led to discontinuation of study drug in 3% of patients
	Phase 3 randomized trial comparing cefiderocol with imipenem-cilastatin for cUTI (APEKS-cUTI) [59]	Overall AEs: 41% in the cefiderocol group versus 51% in the imipenem-cilastatin group.	SAEs were reported for 5% of patients receiving cefiderocol	Not reported
Eravacycline	**Phase 3** randomized trial comparing eravacycline with meropenem for cIAI (IGNITE 4) [63]	Treatment-related AEs: 37.2% in the eravacycline group versus 30.9% in the meropenem group. Less than 50% of AEs in both groups were considered as study drug related. Most common AEs were as follows: -Nausea (4.8%) -Vomiting (3.6%) - Infusion site phlebitis (3.2%) - Infusion site thrombosis (2.4%)	Information regarding SAEs was not reported.	1.6%
	Phase 3 randomized trial comparing eravacycline with ertapenem in cUTI (IGNITE 1) [64]	Treatment-related AEs: 41% in the eravacycline group versus 27% in the ertapenem group. Most common AEs were as follows: - Nausea (8.1%) - Phlebitis (3.0%)	SAEs reported in the eravacycline group were 5.6%	Not reported

(*Continued*)

Table 2. (Continued).

Plazomicin	**Phase 2** randomized trial comparing plazomicin with levofloxacin in cUTI (EPIC) [76]	Study drug-related AEs were reported in 9.1% of patients in the plazomicin 10 mg/kg group, 20.3% of patients in the plazomicin 15 mg/kg group, and 27.3% in the levofloxacin group. Most common AEs were as follows: -Headache (8.1%) -Diarrhea (5.4%) - Vomiting (5.4%)	SAEs were reported in 1.4% of patients in the plazomicin 15 mg/kg group	AEs leading to study drug discontinuation were reported in 5.4% of patients in plazomicin

AEs: Adverse Events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BAT: Best available therapy; cIAI: Complicated intra-abdominal infection; CRE: Carbapenem-resistant *Enterobacterales*; cUTI: complicated urinary tract infection; HABP: hospital-acquired bacterial pneumonia; MDR: Multidrug resistant; RCT: randomized control trial; SAE: serious adverse events; TEAE: Treatment Emergent Adverse Event; VABP: ventilator-acquired bacterial pneumonia; XDR: extensively drug-resistant.

4. Meropenem-vaborbactam

Vaborbactam is a new no β-lactam β-lactamase inhibitor derived from boric acid, developed to restore the activity of β-lactams against β-lactamase produced by Gram-negative bacteria, particularly *K. pneumoniae* carbapenemase [37]. It inhibits a variety of Amber class A such as CTX-M, SHV, TEM, SME, and KPC producing isolates, as well as class C β-lactamases. However, meropenem-vaborbactam has no activity against class B or Class D (OXA-48) carbapenemases [38]. As such, the primary role of vaborbactam is inhibition of KPC carbapenemases.

Meropenem-vaborbactam is EMA- and FDA-approved for use in adult patients with cUTI, including pyelonephritis [39,40]. More recently, it has been approved by EMA for cIAI, HABP including VABP, and infections due to aerobic Gram-negative micro-organisms with few or no treatment options [40].

Two phase 3 RCT studies of meropenem-vaborbactam have been completed (Table 2). As for safety, in TANGO I trial (efficacy and safety of meropenem-vaborbactam compared to piperacillin-tazobactam in adults with cUTI and acute pyelonephritis), the proportion of patients who experienced any AEs (39.0% vs 35.5%), drug-related AEs (15.1% vs 12.8%), severe AEs (2.6% vs 4.8%), or life-threatening AEs (1.1% vs 0%) were similar between meropenem-vaborbactam and piperacillin-tazobactam groups [41]. Only 2.6% of patients in the meropenem-vaborbactam group discontinued treatment because of an AE in comparison to 5.1% of piperacillin-tazobactam recipients. Most common AE reported during meropenem-vaborbactam was headache (8.8%) followed by diarrhea (3.3%) and nausea (1.8%) [41]. In TANGO II trial (Efficacy and safety of meropenem-vaborbactam monotherapy versus BAT in adults with serious infections due to CRE), a lower rate of treatment emergent AEs were reported in patients receiving meropenem-vaborbactam as monotherapy (2–2 g) via IV infusion over 3 hours every 8 hours compared with BAT (24.4% vs. 44.0%). In most cases, treatment emergent AEs included diarrhea, anemia, and hypokalemia. Of importance, a lower incidence of postbaseline increases in serum creatinine (14.0% vs 24.0%) as well as fewer renal-related AEs (4.0% vs 24.0%) was observed with meropenem-vaborbactam [42]. This is not surprising because BAT regimens usually contained aminoglycosides and polymyxins.

Although meropenem has been generally reported as having lower epileptogenic activity in comparison to imipenem [43], to date, there is no evidence supporting vaborbactam increase in the epileptogenic activity of meropenem alone. Finally, evidence regarding meropenem-vaborbactam use in real-life settings is scarce [44,45] but generally concordant with data reported in pivotal trials. In a retrospective study analyzing 40 critically ill patients treated with meropenem-vaborbactam for GNB infections, only one patient experienced related AEs, considered as mild and consisting of skin rash [45].

5. Imipenem-cilastatin-relebactam

Imipenem-cilastatin-relebactam is the combination of *i)* the well-known carbapenem iminipenem, with *ii)* cilastatin, a dehydropeptidase-I inhibitor, which reduces renal metabolism of imipenem; and *iii)* the novel β-lactamase inhibitor with a DBO core, relebactam. Relebactam protects imipenem-cilastatin from the degradation by Amber class A (i.e. KPC) and class C (i.e. AmpC) β-lactamases. However, it shows no activity against class B metallo β-lactamase (i.e. NDM, VIM, and IMP) or class D oxacillinases (i.e. OXA-48). Its presence substantially restores the activity of imipenem-cilastatin against the majority of KPC-producing CR-GNB strains and CR-*P.aeruginosa*, but not those of *A. baumannii* or *S. malthophilia* [46]. Imipenem-cilastatin-relebactam is currently FDA- [47] and EMA [48]-approved for the treatment of adults patients with HABP/VABP, cUTI, and cIAI and patients with other serious Gram-negative infections with few or no therapeutic options.

Based on current evidences coming from pivotal trials, imipenem-cilastatin-relebactam is generally well-tolerated and shows a good safety profile consistent with that established for imipenem-cilastatin alone [49,50]. In RESTORE IMI-1 trial (an RCT comparing the efficacy and safety of imipenem-cilastatin-relebactam 500 mg-500 mg-250 mg iv every 6 hours vs colistin 300 mg loading dose followed by 150 mg every 12 hours plus imipenem-cilastatin 500 mg-500 mg every 6 hours in patients with imipenem-nonsusceptible bacterial

infections) [50], treatment emergent nephrotoxicity was significantly less frequent (p = 0.002) with imipenem-cilastatin-relebactam than with colistin plus imipenem-cilastatin (10% vs 59%) (Table 2). In this study, the most common AEs reported with imipenem-cilastatin-relebactam were pyrexia (13%) and increased in aspartate aminostransferase (AST) (13%) or in alanine aminotransferase (ALT) above the upper limit of normal range (ULN) (11%). Although the incidence of pyrexia was similar between groups, a significantly lower percentage of patients receiving imipenem-cilastatin-relebactam (0%) than colistin plus imipenem-cilastatin (13%) experienced clinically relevant elevations in hepatic transaminases (elevations in hepatic transaminases were per protocol defined as AST or ALT ≥3 X ULN and total bilirubin ≥ 2 X ULN and alkaline phosphatase >2 X ULN or AST or ALT ≥ 5 X ULN) [50].

In RESTORE IMI-2 trial [49], imipenem-cilastatin-relebactam 500 mg-500 mg-250 mg iv every 6 hours was compared to piperacillin-tazobactam 4 g-500 mg iv every 6 hours for treatment of HABP/VABP. In this study, imipenem-cilastatin-relebactam was associated with a similar rate of treatment-related AEs (11.7% vs 9.7%) and serious treatment-related AEs (1.1% vs 0.7%) of those observed for piperacillin-tazobactam. Imipenem-cilastatin-relebactam was discontinued because of treatment-related AEs in 2.3% of the patients compared to 1.5% of those treated with piperacillin-tazobactam (Table 2) [49]. Diarrhea (2.3%) and increase in ALT or AST above the ULN (2.3%) were the most common treatment-related AEs reported with imipenem-cilastatin-relebactam [49].

No evidence of central nervous system AEs, such as seizures, confusion, or myoclonic activity, occurred during the clinical trials with imipenem-cilastatin-relebactam [47,48]

6. Cefiderocol

Cefiderocol is a new modified cephalosporin with a catechol side chain that forms a chelated complex with ferric iron. This mechanism facilitates its penetration into bacterial cells, where cefiderocol inhibits cell wall synthesis by binding to penicillin-binding proteins and inhibiting peptidoglycan synthesis [51–53].

Cefiderocol exhibits excellent stability against hydrolysis by a variety of β-lactamases, including class A (e.g. KPC and ESBL), class B (e.g. NDM, VIM, and IMP), class C (AmpC), and class D (e.g. OXA-48, OXA-23, and OXA-48) [53]. Accordingly, it shows great in vitro activity against clinical relevant CR *Enterobacterales* and against CR *P.aeruginosa, A. baumannii*, and *S.malthophilia* [54–57]. It is currently approved for treatment of cUTI and for HABP/VABP. However, cefiderocol has an FDA label warning for higher all-cause mortality when administered for the treatment of MDR Gram-negative bacterial infections, as shown in the recent CREDIBLE-CR trial reporting higher mortality rate with cefiderocol in comparison to the BAT (34% vs 18%) [58].

Cefiderocol was associated with a similar risk for experiencing AEs as other cephalosporins. In the APEKS-cUTI study, a phase 2 RCT comparing cefiderocol 2 g every 8 hours with imipenem-cilastatin 1 g-1 g every 8 hours for treatment of cUTI, the frequency of overall AEs (41% vs 51%) and serious AEs (5% vs 8%) did not differ significantly between groups [59]. Diarrhea (4%) and constipations (3%) were the most frequently reported AEs with cefiderocol, with no differences between study groups. In this trial, only 3 patients experienced *C. difficile* infection (one patient in the cefiderocol group) and no death was considered as related to the study drug [59]. In the APEKS-NP study, comparing the efficacy and safety of cefiderocol 2 g every 8 hours versus meropenem 2 g every 8 hours for adults with nosocomial pneumonia, a higher percentage of AEs was reported in both arms (88% and 86% in cefiderocol and meropenem, respectively), with only 1.3% and 3.3% of drug-related serious AEs observed in cefiderocol and meropenem groups, respectively. Overall, the most common AEs were urinary tract infections and hypokalemia (Table 2) [60]. The CREDIBLE-CR study [58] is a randomized, open-label, multicenter, pathogen-focused, phase 3 study comparing cefiderocol 2 g every 8 hours versus BAT in adults with serious carbapenem-resistant Gram-negative infections. Most patients belonging to the BAT group received combination therapy (27/38: 71%), consisting of the colistin-based regimen in 66% of the cases . According to the results of this trial (Table 2) [58], the frequency of AEs that are considered to be treatment related was 15.0% and 22.0% in the cefiderocol and BAT arm, respectively. Diarrhea (2%) and abnormal liver function tests (2%) were the most frequent AEs reported in the cefiderocol group, whereas acute kidney injury (8%) was the most common reported treatment-related, treatment emergent AE in the BAT group. As for treatment-related serious AEs, there was only 1 out of 101 patients receiving cefiderocol who discontinued the drug because of an increase in the transaminase level. Discontinuation due to treatment-related AEs occurred in 3% of the patients with cefiderocol in comparison to 4% of patients receiving BAT [58].

7. Eravacycline

Eravacycline is a fluorocycline belonging to the tetracycline class. Similar to other tetracyclines, it inhibits protein synthesis by binding to the 30s ribosomal subunit of bacteria. Eravacycline shows *in vitro* activity against carbapenem-resistant Gram-negative pathogens including *Enterobacterales* and CR *A. baumannii* and *S.malthophilia*, but not against *P. aeruginosa*. It also has a potent activity against Gram-positive pathogens (including methicillin-resistant *S. aureus*, and vancomycin-resistant enterococci) and many anaerobic species [61–63]. Eravacycline was recently approved by the US FDA and the EMA as a single-agent treatment for cIAI, based on the results of two clinical trials of nearly identical designs comparing eravacycline 1 mg/kg every 12 hours with ertapenem 1 g every 24 hours [64] or meropenem 1 g every 8 hours [65]

According to these trials (Table 2), the overall percentage of patients who experienced at least one AE was higher in the eravacycline group with respect to comparators, although no differences between groups were observed when only serious AEs or all-cause mortality was considered. Similar to what has been observed for other tetracyclines, nausea was the most frequent treatment emergent AEs with eravacycline, followed by vomiting [64,65]. Of importance, the percentage of patients

experiencing gastrointestinal side effects was lower in comparison to that reported in older trials evaluating the efficacy and safety of tigecycline [66]. In addition to gastrointestinal AEs, infusion site reactions were also common in the pooled analysis, but no patients required discontinuation of the study drug [64,65,67].

8. Plazomicin

Plazomicin is semisynthetic aminoglycoside, which, through the insertion of an additional hydroxyethyl group to the amine at C-6′ [68], is able to evade almost all clinically relevant aminoglycoside-modifying enzymes [69]. Plazomicin is broadly active against the *Enterobacterales, P.aeruginosa*, and *A. baumannii*, including those isolates considered to be MDR and/or carbapenem-resistant [70–74]. To date, two indications have been pursued for plazomicin: cUTI and serious infections including BSI, HABP, or VABP [69].

Overall, safety and efficacy of plazomicin have been evaluated in two phase 3 clinical trials across which the drug has demonstrated to have a safe AE profile (Table 2) [75,76]. Nonetheless, it has been FDA-approved with a Black Box warning for aminoglycoside class effects as it has for other aminoglycosides (nephrotoxicity, ototoxicity, neuromuscular block, or pregnancy risk) [77]. In the largest trial performed to date (EPIC trial), a similar rate of clinically significant decrease in renal function was observed in patients receiving plazomicin (3.7%) or meropenem (3.0%), but most patients in the plazomicin group had full renal recovery at the end of the study (81.0%). Other common AEs reported in the plazomicin group were diarrhea (2.3%), hypertension (2.3%), headache (1.3%), and nausea (1.3%) [76]. Ototoxicity events were rarely reported in clinical trials, but patients should be monitored for development of this complication, as patients with previous history of ontological disease or patients with anatomical abnormalities were excluded from participation.

9. Potential new anti-infectives targeting carbapenem-resistant infections

Thanks to a considerable boost in scientific research, other molecules have been considered as part of the arsenal for combating infections with CR strains. In this section, we will consider those that are at an advanced stage of investigation.

Aztreonam-avibactam is a unique compound with *in vitro* activity against MBL-producing strains [78,79]. In the REJUVENATE phase 2a open-label multicenter study [80] analyzing the safety of aztreonam-avibactam for treating cIAI, the observed AEs were consistent with the known safety profile of aztreonam alone (hepatic enzyme increases in 26.5% of the patients and diarrhea in 14.7%), with no safety concerns identified.

Enmetazobactam is a new β-lactamase inhibitor [81], exhibiting a potent inhibition of class A β-lactamase, including ESBL and KPC. In addition, the intrinsic activity of cefepime against isolates expressing AmpC also makes the combination suitable for the treatment of organisms that coproduce such β-lactamases. In the ALLIUM phase 3 clinical trial, cefepime-enmetazobactam showed superiority in overall treatment outcomes (a composite of clinical cure and microbiological eradication at test of cure) when compared to piperacillin-tazobactam for treatment of adult patients with cUTI and acute pyelonephritis (NCT03687255). Treatment discontinuation was seen at comparable levels in 5.2% and 4.0% in cefepime-enmetazobactam and piperacillin-tazobactam, respectively. Cefepime-enmetazobactam was well-tolerated with 4.3% of patients reporting serious adverse events, suggesting a comparable safety profile than piperacillin-tazobactam (SAEs observed in 3.7% of the patients) (NCT03687255).

Finally, zidebactam is a new β-lactamase inhibitor active against class A and C β-lactamase and is currently being investigated in combination with cefepime [29]. The combination of cefepime with zidebactam possesses a potent *in vitro* activity against MDR Gram-negative bacteria, including ESBL, KPCs, AmpC, and OXA-48-producing *Enterobacteriales* [82]. Cefepime-zidebactam is showed to be safe and well-tolerated in subjects with normal and impaired renal function [83].

Finally, meropenem-nacubactam is highly efficacious against KPC, MBLs, and OXA-48 producing Gram-negative strains. Although limited, data regarding safety of meropenem-nacubactam are encouraging; in a single placebo-controlled study including healthy participants, only eight out of 30 participants receiving nacubactam (26.7%) reported one or more AEs in comparison to 4 of the 10 (40%) participants in the placebo group. Most AEs were mild, and all AEs resolved without sequelae [84].

10. Conclusions

The management of patients with CR infections is evolving toward a more complex clinical reasoning, in which, besides efficacy data and the spectrum of activity, careful consideration of the safety profile of each single agent is becoming paramount for maximizing cost-effectiveness.

11. Expert opinion

For many years, antibiotic therapy for CR infections was limited to the combination of colistin, aminoglycoside, or tigecycline with or without the addition of high doses of carbapenems. However, adverse events with these antibiotics were frequent and often dose and treatment-limiting events. As for colistin, the main side effect was nephrotoxicity that has been observed in 20–76% of the patients during treatment [85–87]. Nephrotoxicity usually occurred during the first week of therapy, was a dose-dependent side effect, and occurs reversibly [86,87]. Colistin has also been associated with development of neurotoxicity in up to 7% of the patients [85]. Neurotoxicity usually presents with paresthesia, but other clinical manifestations including vertigo, mental confusion, seizure, or even a myasthenia-like syndrome with respiratory muscles paralysis have been described [88]. Other adverse events, such as chest tightness or bronchospasm, have been rarely reported following colistin nebulization for respiratory infections [89]. Similar concerns were also related to aminoglycoside therapy as nephrotoxicity was observed in between 10 and 25% of patients during treatment [90,91]. Acute kidney injury was the consequence of an acute tubular necrosis, and

recovery was typically observed several days after discontinuation of therapy [92]. Another important side effect was ototoxicity. Accordingly, attention should be paid to monitoring clinical symptoms of vestibular or cochlear impairment during aminoglycoside therapy [93]. Tigecycline has been commonly associated with presentation of gastrointestinal adverse events, such as nausea (ranging from 30% to 55%), vomiting (from 18% to 30%) [94], and diarrhea [95]. Tigecycline may also induce coagulopathy, manifesting as progressive prolongation of active partial thromboplastin or prothrombin time (3% of the patients) [96,97]. Other rare adverse events associated with tigecycline included cholestatic jaundice, pancreatitis, increased aminotransferase levels, paresthesia, or Steven-Johnson syndrome [85].

The development of new well-tolerated compounds has now radically expanded the options for treatment of these infections, providing hope for clinicians. From the information provided above and considering the principles of the antibiotic stewardship program (e.g. optimizing clinical outcomes while minimizing adverse effects and toxicity), we opine that polymyxin- or aminoglycoside-based regimens should no longer be considered as first-line agents for infections due to CR-GNB, even if a pharmacological "low-cost" choice (e.g. colistin or aminoglycosides) could be attractive. These aspects highlight the importance of administering these agents upon the constant and valuable advice by infectious disease specialists in terms of indications, dosage, mode of infusion, and length of therapy. We also acknowledge the expert guidance of clinical microbiologists because, in our opinion, the full potential of those new treatments may only be realized with the adoption of rapid molecular diagnostics.

Although anticarbapenem-resistant Gram-negative antibiotics are characterized by a very low toxicity and lack of significant drug-drug interactions, it should be noted that data regarding their safety profile for the treatment of CR infections in special population (e.g. pregnant, liver failure, critically ill, and elderly patients) are scarce. In addition, the increasing challenge of the "adequate" antimicrobial dosing for the treatment of severe infections occurring in critically ill patients is also worth mentioning. In this sense, most of the newly approved molecules do not provide indications for dosing in patients receiving continuous renal replacement therapy or extracorporeal membrane oxygenation. Similarly, to the best of our knowledge, no information regarding dosage of newly approved antibiotics in obese patients is available to date. Thus, studies aiming at considering the need for therapeutic drug monitoring or continuous/prolonged infusions or higher dosage in these specific populations are warranted with the aim of avoiding unexposure and potential development of resistance while minimizing toxicity.

In conclusion, the cumulative assessment of the data suggests that, in contrast to "old drug" regimens, treatment with new compounds is not generally associated with development of serious adverse events. In any case, when adverse events occur, they generally appear to be mild and clinically not relevant, as suggested by the low proportion of patients stopping their study drug because of adverse events. Resources should be gathered to further support the value of these antibiotics to patients and clinicians in the real world of difficult infections due to carbapenem-resistant bacteria.

Funding

This paper was not funded.

Declaration of interests

Outside the submitted work, M Bassetti has received funding for scientific advisory boards and travel and speaker honoraria from Angelini, Astellas, AstraZeneca, Basilea, Bayer, BioMérieux, Cidara, Correvio, Cubist, Menarini, Molteni, MSD, Nabriva, Paratek, Pfizer, Roche, Shionogi, Tetraphase, Thermo Fisher, and The Medicine Company. Outside the submitted work, DR Giacobbe reports honoraria from Stepstone Pharma GmbH and unconditional grants from MSD Italia and Correvio Italia. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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