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Clinical data from studies involving novel antibiotics to treat multidrug-resistant Gram-negative bacterial infections

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ABSTRACT

Multidrug-resistant (MDR) Gram-negative bacteria (GNB) pose a critical threat to global healthcare, worsening outcomes and increasing mortality among infected patients. Carbapenemase- and extended-spectrum β-lactamase-producing Enterobacterales, as well as carbapenemase-producing *Pseudomonas* and *Acinetobacter* spp., are common MDR pathogens. New antibiotics and combinations have been developed to address this threat. Clinical trial findings support several combinations, notably ceftazidime–avibactam (CZA, a cephalosporin-β-lactamase inhibitor combination), which is effective in treating complicated urinary tract infections (cUTI), complicated intra-abdominal infections and hospital-acquired and ventilator-associated pneumonia caused by GNBs. Other clinically effective combinations include meropenem–vaborbactam (MVB), ceftolozane–tazobactam (C/T) and imipenem–relebactam (I–R). Cefiderocol is a recent siderophore β-lactam antibiotic that is useful against cUTIs caused by carbapenem-resistant Enterobacterales (CRE) and is stable against many β-lactamases. Carbapenem-resistant Enterobacterales are a genetically heterogeneous group that vary in different world regions and are a substantial cause of infections, among which *Klebsiella pneumoniae* are the most common. Susceptible CRE infections can be treated with fluoroquinolones, aminoglycosides or fosfomycin, but alternatives include CZA, MVB, I–R, cefiderocol, tigecycline and eravacycline. Multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are increasingly common pathogens producing a range of different carbapenemases, and infections are challenging to treat, often requiring novel antibiotics or combinations. Currently, no single agent can treat all MDR-GNB infections, but new β-lactam–β-lactamase inhibitor combinations are often effective for different infection sites and, when used appropriately, have the potential to improve outcomes. This article reviews clinical studies investigating novel β-lactam approaches for treatment of MDR-GNB infections.

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1. Introduction

The World Health Organization (WHO) has classified antibiotic-resistant bacteria into priority categories. Those ranked as critical priority pathogens for research and development of new antibiotics were all Gram-negative bacteria (GNB) [1] (Fig. 1); these include carbapenem-resistant *Acinetobacter baumannii* (*A. baumannii*) (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (*P. aeruginosa*) (CRPA) and carbapenem-resistant and third-generation (extended-spectrum) cephalosporin-resistant Enterobacterales [1,2]. Similarly, the United States (US) Centers for Disease Control and Prevention (CDC) consider CRAB and carbapenem-resistant Enterobacterales (CRE) as urgent threats [3,4]. Multidrug-resistant (MDR) *P. aeruginosa* and Enterobacterales that produce extended-spectrum β-lactamases (ESBL) were also categorised by the CDC as serious threats [4].

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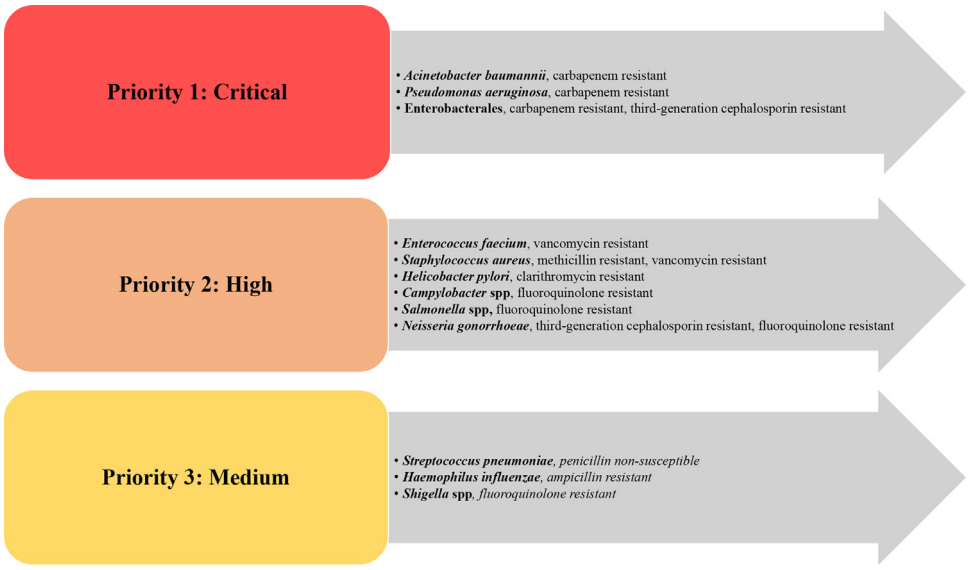

Fig. 1. Priority list of antibiotic-resistant bacteria, other than MDR *Mycobacterium tuberculosis,* for the research and development of new antibiotics.
Priority list classified by the WHO. Republished with permission of Elsevier Science & Technology journals, from Tacconelli *et al.* Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis* 2018;**18**:318–27 [1]; permission conveyed through Copyright Clearance Center, Inc.

Important initiatives such as the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) global non-profit partnership, the 10 x '20 initiative of the Infectious Diseases Society of America (IDSA) and others have partly prompted many small- and medium-sized enterprises and several pharmaceutical companies to dedicate resources to the discovery of novel agents with activity against MDR-GNB [5–7]. This has resulted in US Food and Drug Administration (FDA) approval of several novel antibacterial agents. This review focuses on combinations of old β-lactam antibiotics with novel β-lactamase inhibitors such as ceftazidime–avibactam (CZA), meropenem–vaborbactam (MVB), imipenem–relebactam (I–R), a combination of an old β-lactamase inhibitor with a novel anti-pseudomonal cephalosporin (ceftolozane–tazobactam [C/T]) and a cephalosporin with a novel-entry mechanism of action (cefiderocol).

2. New β-lactamase inhibitors and a new β-lactam

The original β-lactam–β-lactamase inhibitor (BL–BLI) combinations (i.e. amoxicillin–clavulanic acid, ampicillin–sulbactam, cefoperazone–sulbactam, piperacillin–tazobactam and ticarcillin–clavulanic acid) were highly active against class A serine β-lactamases when they were introduced to the market [8,9]. Resistance against these developed with the appearance of four structurally and functionally distinct groups of β-lactamases: the metallo-β-lactamases (MBLs) of class B, AmpC serine β-lactamases belonging to class C, oxacillinases (OXA) – serine β-lactamases of class D and a new class A-like *Klebsiella pneumoniae* (*K. pneumoniae*) carbapenemase (KPC) [8,9]. As a result, a single BL–BLI partnership with activity against all clinically important β-lactamases (e.g. KPC-2, OXA-23, OXA-24/40, AmpC, and New Delhi MBL-1 [NDM-1]) has been lacking, but there are some new combinations such as cefepime–taniborbactam and cefepime–zidebactam currently in development that cover a wide spectrum of these enzymes and may address this need [9,10]. Diazabicyclooctanes (DBO) are synthetic non-β-lactam-based β-lactamase inhibitors; there has been an exponential expansion of this class of inhibitors, with most modifications occurring at the C2 side chain [9]. Most studies indicate that DBOs inhibit class A and class C β-lactamases, with minor activity against class D β-lactamases also observed [9] (Fig. 2). In February 2015, avibactam (AVI) (in combination with ceftazidime [CAZ]) was the first DBO to be approved by the FDA [11]. Although activity is partner dependent (e.g. with CAZ, ceftaroline, aztreonam, cefepime or imipenem [IPM]), β-lactam-avibactam combinations are potentially highly effective against many MDR-GNB pathogens, including Enterobacterales and *P. aeruginosa*, producing class A, C, and some class D enzymes [9,12]. Switching the β-lactam partner of a clinically available β-lactamase inhibitor is another approach to treat infections caused by strains that carry multiple classes of β-lactamases, for example the pairing of tazobactam with the novel cephalosporin, ceftolozane [9,13]. The C/T partnership has a spectrum of activity that includes class A, C, and some class D β-lactamases, but not carbapenemases [14]. Another DBO that has been developed is relebactam (REL), and although it has a similar spectrum of activity to AVI (activity against MBLs and most OXAs is lacking), greater activity against OXA-48 has been observed for AVI [15,16] (Fig. 2). Additionally, vaborbactam (VAB) (approved for use in combination with meropenem) is the first FDA-approved β-lactamase inhibitor containing a cyclic boronate pharmacophore; this forms a covalent adduct with the catalytic serine side chain of serine β-lactamases, and can inhibit various class A and C β-lactamases [14,17,18].

Finally, cefiderocol, the first in its class, is an injectable siderophore cephalosporin that combines a catechol-type siderophore and cephalosporin core with side chains like cefepime and CAZ [19]. This structure and mechanism confer enhanced stability against hydrolysis by many β-lactamases, including ESBLs such as CTX-M and carbapenemases such as KPC, NDM, Verona integron-encoded MBL (VIM), imipenem-hydrolysing MBL (IMP), OXA-23, OXA-48-like, OXA-51-like and OXA-58 (Fig. 2) [19].

3. Five new β-lactam approaches for various Gram-negative infections

Key recent clinical studies of novel β-lactam antibiotics and combinations in the treatment of MDR-GNB are summarised in Table 1 .

Table 1
Design and findings of key clinical studies of novel β-lactam antibiotics in combination with β-lactam inhibitors and other antibiotics in the treatment of multidrug-resistant Gram-negative bacteria.

Trial (n)	Reference	Infection	Investigational drugs	Design	Treatment groups and dose	Primary endpoint	Results (% of patients)
REPROVE n =726 (cMITT), n = 527 (CE)	Torres et al. 2018 [24]	NP, including VAP	CZA vs. MEM	Randomised, double-blind, Phase III non-inferiority	CZA 2 g/0.5 g q8h vs. MEM 1 g q8h. Duration: 7–14 days CZA: 2 h-infusion, MEM: 30-min infusion	Clinical cure (at TOC visit)	**Clinical cure rate, cMITT** CZA: 68.8% MEM:73.0% **Clinical cure rate, CE** CZA: 77.4% MEM:78.1% (CZA non-inferior in the treatment of NP)
ASPECT-NP n = 726 (ITT)	Kollef et al. 2019 [44]	Ventilated NP	C/T vs. MEM	Randomised, controlled, double-blind, Phase III non-inferiority	C/T 3 g q8h vs. MEM 1 g q8h. Duration: 8–14 days, both given by 1-h infusion	28-day all-cause mortality in ITT population	C/T: 24.0% MEM: 25.3% (C/T non-inferior for 28-day mortality)
ASPECT-cIAI n = 806 (microbiological ITT)	Solomkin et al. 2015 [45]	cIAI	C/T + MZL vs. MEM	Randomised, prospective, double-blind, non-inferiority	C/T 1.5 g + MZL 500 mg q8h vs. MEM q8h. Duration: 4–14 days	Clinical cure at TOC in microbiological ITT population	**Clinical cure at TOC in microbiological ITT population** C/T + MZL: 83% MEM: 87.3% **Clinical cure at TOC in microbiologically evaluable (secondary) population** C/T + MZL: 94.2% MEM: 94.7% (prespecified non-inferiority margin met)
ASPECT cUTI n = 800 (mMITT)	Wagenlehner et al. 2015 [46]	Complicated lower UTI or pyelonephritis	C/T vs. LVX	Randomised, double-blind, double-dummy, non-inferiority	C/T 1.5 g q8h vs. LVX 750 mg OD. Duration: 7 days	Composite of microbiological eradication and clinical cure 5–9 days post treatment in mMITT population	C/T: 76.9% LVX: 68.4% (C/T non-inferior to LVX for composite cure)
TANGO I n = 374 (microbiological mITT population) n = 347 (microbiological evaluable population)	Kaye et al. 2018 [116]	cUTI, including acute pyelonephritis	MVB vs. PPN–TAZ	Randomised, multicentre, double-blind, double-dummy, active-control, Phase III	MVB (2 g/2 g over 3 h) vs. PPN–TAZ (4 g/0.5 g over 30 min) q8h for 15 doses. Mean duration, IV and oral stepdown therapy: 10 days	**FDA:** Overall success (clinical cure or improvement and microbial eradication composite) at end of IV treatment in microbiological mITT population **EMA:** microbial eradication at TOC visit in the microbiological mITT and microbiological evaluable populations	**FDA endpoint, overall success** MVB: 98.4% PPN–TAZ: 94.0% **EMA endpoint (microbiological mITT):** MVB: 66.7% PPN–TAZ: 57.7% **EMA endpoint (microbiological evaluable):** MVB: 66.3% PPN–TAZ: 60.4% (non-inferiority criterion met)
TANGO II n = 47 (mCRE-MITT)	Wunderink et al. 2018 [36]	Carbapenem-resistant Enterobacterales infections[a]	MVB vs. BAT[b]	Randomised controlled, multinational, open-label, Phase III	MVB (2 g/2 g over 3 h, q8h for 7–14 days) vs. BAT	Clinical cure, Day 28 all-cause mortality, microbiological cure, and overall success (clinical cure + microbiological eradication)	**Cure rate at end of treatment** MVB: 65.6% BAT: 33.3% **Cure rate at TOC:** MVB: 59.4% BAT: 26.7% **Day 28 all-cause mortality** MVB: 15.6% BAT: 33.3%
APEKS-cUTI n = 371 (mITT)	Portsmouth et al. 2018 [51]	cUTI +/- pyelonephritis or acute uncomplicated pyelonephritis	CDL vs. IPM	Phase II, multicentre, double-blind, parallel-group non-inferiority	CDL 2 g q8h vs. IPM (imipenem/cilastatin 1 g/1 g) q8h. Duration: 7–14 days	Composite clinical and microbiological outcomes at TOC (7 days after treatment end)	**Microbiological eradication at TOC in mITT population** CDL: 73% IPM: 56 % **Clinical response rate at TOC in mITT population** CDL: 90% IPM: 87% (prespecified non-inferiority margin met)

(*continued on next page*)

Table 1 (*continued*)

Trial (n)	Reference	Infection	Investigational drugs	Design	Treatment groups and dose	Primary endpoint	Results (% of patients)
APEKS-NP $n = 292$ (mITT)	Wunderink 2021 et al. [52]	Hospital-acquired ventilator-associated or healthcare-associated Gram-negative pneumonia	CDL vs. MEM	Randomised, double-blind, parallel-group, Phase III, non-inferiority	3 h IV infusion CDL 2 g q8h vs. MEM 2 g q8h. Duration 7–14 days	All-cause mortality at Day 14 in mITT population	CDL: 12.4% MEM: 11.6% (prespecified non-inferiority margin met)
CREDIBLE-CR $n = 118$ (CR-MITT)	Bassetti et al. 2021 [53]	Life-threatening carbapenem-resistant Gram-negative infections	CDL vs. BAT	Randomised, open-label, multicentre, parallel-group, pathogen-focused, descriptive, Phase III	3 h IV infusion CDL 2 g q8h vs. BAT. Duration 7–14 days	For NP, BSI and sepsis, clinical cure at TOC in the CR-MITT. For cUTI, microbiological eradication at TOC in the CR-MITT	**NP, clinical cure** CDL: 50% BAT: 53% **BSI/sepsis, clinical cure** CDL: 43% BAT: 43% **cUTI, microbiological eradication** CDL: 53% BAT: 20% (CDL similar efficacy to BAT)
RESTORE-IMI 1 $n = 31$ (mMITT)	Motsch et al. 2020 [117]	Hospitalised patients with HAP/VAP, cIAI or cUTI caused by IPM-resistant pathogens	I–R vs. IPM + CST	Multicentre, randomised, controlled, double-blind, Phase III	I–R (500 mg/250 mg, q6h) vs. IPM (500 mg q6h) + CST (loading dose 300 mg, then maintenance doses up to 150 mg, q12h) Duration: 5–21 days	Favourable overall response (defined by relevant endpoints for each infection) in mMITT population	**Favourable overall response** I–R: 71% IPM + CST: 70% **Day 28 all-cause mortality** I–R: 10% IPM + CST: 30%
RESTORE-IMI 2 $n = 531$ (mITT)	Titov et al. 2020 [38]	HABP or VABP	I–R vs. PPN–TAZ	Multicentre, randomised, controlled, double-blind, Phase III	I–R (500 mg/500 mg/250 mg) vs. PPN–TAZ (4 g/500 mg) q6h. Duration: 7–14 days	Day 28 all-cause mortality in mITT population	**Day 28 all-cause mortality** I–R: 15.9% PPN–TAZ: 21.3% **Favourable clinical response at early follow-up** I–R: 61.0% PPN–TAZ: 55.8%
Dose-ranging study $n = 255$ (ME at DCIV)	Lucasti et al. 2016 [39]	cIAI	REL (2 doses) vs. PBO (all + IPM)	Randomised, multicentre, double-blind, controlled trial	REL (125 mg), REL (250 mg), PBO, IV (all + IPM 500 mg) q6h. Duration 4–14 days	Proportion of ME pts with a favourable clinical response at DCIV	**Favourable clinical response at DCIV** REL 250 mg: 96.3% REL 125 mg: 98.8% PBO (IPM alone): 95.2% (both IPM plus REL doses non-inferior to IPM alone)
Dose-ranging, comparative trial $n = 230$ (ME at DCIV)	Sims et al. 2017 [118]	cUTI or acute pyelonephritis	REL (2 doses) vs. PBO (all + IPM)	Randomised, multicentre, double-blind, controlled, non-inferiority, Phase II dose-ranging	REL (125 mg), REL (250 mg), PBO (all + IPM 500 mg), 30 min IV infusions q6h. Duration 4–14 days	Favourable microbiological response rate (pathogen eradication) at DCIV in ME population	**Favourable microbiological response rate** I–R (REL 250 mg): 95.5% I–R (REL: 125 mg): 98.6% IPM alone: 98.7% (IMI-REL with both REL doses non-inferior to IPM alone)

[a] Bacteraemia, HABP/VABP, cIAI, cUTI/acute pyelonephritis)

[b] BAT, best available therapy including mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline, or ceftazidime–avibactam alone.BAT, best available therapy; BSI, bloodstream infection; C/T, ceftolozane–tazobactam; CE, clinically evaluable; CDL, cefiderocol; cIAI, complicated intra-abdominal infection; cMITT, clinically modified intention-to-treat (population); CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacterales; CR-MITT, carbapenem-resistant microbiological ITT (population); CST, colistin; cUTI, complicated urinary tract infection; CZA, ceftazidime–avibactam; DCIV, discontinuation of IV therapy; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HAP, hospital-acquired pneumonia; HABP, hospital-acquired bacterial pneumonia; IPM, imipenem; I–R, imipenem-cilastatin-relebactam; ITT, intent-to-treat (population); IV, intravenous; LVX, levofloxacin; MEM, meropenem; MVB, meropenem–vaborbactam; mCRE-MITT, microbiologic-CRE modified intent-to-treat (population); ME, microbiologically evaluable; mITT: modified intent-to-treat (population); mMITT, modified microbiological intent-to-treat (population); MZL, metronidazole; NP, nosocomial pneumonia; OD, once daily; PBO, placebo; pt: patient; PPN–TAZ, piperacillin–tazobactam; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours; REL, relebactam; TOC, test of cure; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; VABP, ventilator-associated bacterial pneumonia.

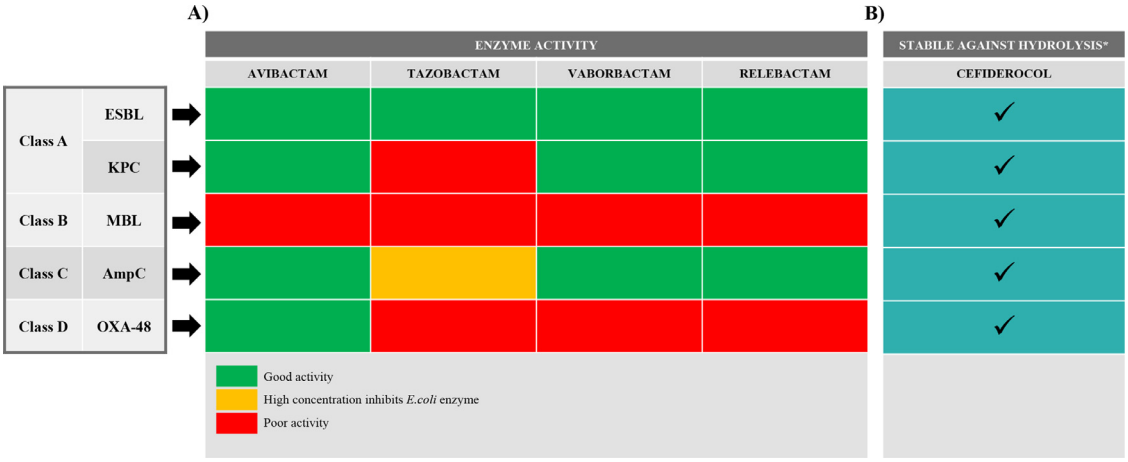

Fig. 2. A) Activity of avibactam, tazobactam, vaborbactam and relebactam against important β-lactamases within different classes; and B) stability of cefiderocol against these enzymes [16,19,50,143,144].
ESBL, extended-spectrum β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; OXA, oxacillinase.
*Enhanced stability to β-lactamases does not always correlate with clinical efficacy.

3.1. Ceftazidime–avibactam (CZA)

The combination CZA is an intravenously administered formulation of the extended-spectrum cephalosporin CAZ and the novel, non-β-lactam β-lactamase inhibitor AVI [20]. Ceftazidime–avibactam has potent activity against Enterobacterales carrying bla_{KPC} and bla_{OXA-48} and the activity of this combination also extends to MDR *P. aeruginosa* [16,21]. It is approved in many countries for the treatment of adults and paediatric patients ($\geq$ 3 months) with cUTI, including pyelonephritis [22,23], complicated intra-abdominal infections (cIAI) [22,23], hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP) [24], and other infections caused by aerobic MDR-GNB in patients with limited treatment options [22,25,26]. The efficacy and safety of CZA has been studied in five Phase III clinical trials. In the RECAPTURE study (CZA versus Doripenem for the Treatment of cUTI, Including Acute Pyelonephritis), CZA was non-inferior to doripenem and both treatments showed similar efficacy against CAZ-non-susceptible pathogens [26]. The REPRISE study was a pathogen-directed, international study of 333 patients with cUTI or cIAI caused by CAZ-resistant Enterobacterales or *P. aeruginosa* who were treated with CZA or best available treatment (BAT) [22]; clinical cure rates were similar between the two treatment arms (91% in both groups).

In another study, CZA plus metronidazole was found to be non-inferior to meropenem in clinical cure at test of cure (TOC) and 30-day all-cause mortality in the treatment of cIAIs. The efficacy of this combination was similar against infections caused by CAZ-susceptible and CAZ-resistant pathogens [22,24]. In the case of HAP and VAP, CZA was found to be non-inferior to meropenem in terms of clinical cure rates and 30-day all-cause mortality [24].

Several studies have assessed the spectrum of activity and the efficacy of CZA in the treatment of infections due to MDR-GNB [14]. A meta-analysis showed in 12 studies that this combination had a pooled clinical success rate of 73% (95% CI 67.7–78.4%) in treating CRE and MDR *P. aeruginosa* infections (mainly pneumonia) [14]. Based on this evidence, the UK Clinical Pharmacy Association recommends CZA for the treatment of KPC- and OXA-48-producing Enterobacterales [27]. In addition, a recent observational study showed a therapeutic advantage for CZA in combination with aztreonam compared with other active antibiotics in patients with bloodstream infections (BSI) due to MBL-producing Enterobacterales [28].

3.2. Meropenem–vaborbactam (MVB)

Intravenous MVB was the first carbapenem–β-lactamase inhibitor combination approved in the US for use in patients with cUTI, including pyelonephritis [18,29]. One component, meropenem, is active against MDR bacteria, except for carbapenemase-producing strains [18]. The other component, VAB, is a potent inhibitor of class A serine carbapenemases and restores meropenem activity against class A and class C carbapenemases, but not against class B or class D carbapenemases [30]. It also restores the activity of meropenem against β-lactamase-producing Enterobacterales, including KPC- and ESBL-producers [29,31]. It may be an alternative for KPC-producing Enterobacterales but has no effect on other MDR bacteria such as *A. baumannii* [30]. Meropenem has good activity against most *P. aeruginosa* strains but not those that have porin mutations or overproduce efflux pumps, and VAB does not restore this activity [32–34]. Of note, some CZA-resistant KPC-3 variants (e.g. V240G and D179Y) have increased susceptibility to meropenem [35], and thus susceptibility to MVB would be expected.

In the Phase III, non-inferiority Targeting Antibiotic Non-Susceptible Gram-negative Organisms (TANGO I) trial in patients with cUTIs, intravenous MVB was found to be non-inferior to intravenous piperacillin–tazobactam for overall success [29]. The TANGO II trial evaluated the safety and tolerability of MVB alone and MVB in combination with a polymyxin (colistin), high-dose meropenem, CZA (n = 1), or an aminoglycoside versus BAT in patients with serious CRE infections [36]. Meropenem–vaborbactam was associated with increased clinical cure, decreased mortality and reduced nephrotoxicity compared with BAT [36]. The use of MVB for treating HAP, including VAP, has been approved by the European Medicines Agency (EMA) [37].

3.3. Imipenem–relebactam (I–R)

Imipenem–relebactam, a novel BL–BLI combination, was recently approved for the treatment of cUTI, cIAI, HAP and VAP [38]. Relebactam is a β-lactamase inhibitor with the ability to inhibit a broad spectrum of β-lactamases such as class A and class C β-lactamases, including carbapenemases [39]. The addition of REL to IPM restores IPM activity against several IPM-resistant bacteria, including MDR *P. aeruginosa* and Enterobacterales such as CRE KPC producers [39,40]. Imipenem–relebactam has also shown clinical activity against several other aerobic (*Escherichia coli, Enterobac-*

ter cloacae, amongst others) and anaerobic Gram-negative bacteria, and it is also active against *Enterococcus faecalis* and methicillin-susceptible *Staphylococcus aureus* [40]. However, REL-IPM is inactive against MBL-producing Enterobacterales and CRAB [40]. In the RESTORE-IMI 1 trial, the efficacy of I–R was found to be comparable with that of colistin–imipenem for treating infections caused by IPM-non-susceptible GNB in patients with HAP and VAP, cUTI and cIAI; the incidence of nephrotoxicity was significantly lower for I–R. In addition, the RESTORE-IMI 2 trial demonstrated non-inferiority of I–R to piperacillin–tazobactam in the treatment of HAP and VAP [38,40]. A recent open-label, noncomparative, Phase III study examined the efficacy of I-R amongst hospitalised patients requiring intravenous antibiotics for cIAI and cUTI, including patients with secondary sepsis. At the end of treatment, 85.7% of patients with cIAI and 100.0% of patients with cUTI achieved clinical or microbiological responses, respectively, and a favourable composite clinical and microbiological response was reported for those with sepsis [41].

3.4. Ceftolozane–tazobactam (C/T)

The C/T combination contains a cephalosporin (ceftolozane) and a β-lactamase inhibitor (tazobactam), and shows in vitro activity against a broad range of GNB**,** including ESBL-producing strains of Enterobacterales and *P. aeruginosa*, and MDR or extensively drug-resistant (XDR) *P. aeruginosa* [13,42]; however, C/T is not active against CRE [13]. Ceftolozane–tazobactam has been approved for the treatment of cUTI, including pyelonephritis, cIAI (in combination with metronidazole), HAP and VAP in adults [43].

In the ASPECT-NP trial, C/T was compared with meropenem for treatment of nosocomial pneumonia, and showed that 3 g q/8 hours of C/T is an effective and well-tolerated treatment for GNB nosocomial pneumonia in mechanically ventilated patients, which is a high-risk, critically ill population [44]. Post hoc analysis showed lower mortality for C/T compared with meropenem in the subgroup of patients with ventilated HAP; however, significance was not demonstrated and additional analyses are planned. Lower mortality for C/T was also observed for the subgroup of those failing prior antibiotic therapy [44]. The Phase III randomised trial (ASPECT-cIAI) compared the efficacy of C/T plus metronidazole vs. meropenem for the treatment of cIAI. In this study, C/T plus metronidazole demonstrated non-inferiority to meropenem, with clinical cure rates of 95.8% and 88.5%, respectively, in patients with ESBL-producing Enterobacterales [45]. The Phase III, ASPECT-cUTI study was a large, international trial evaluating C/T vs. high-dose levofloxacin for the treatment of cUTIs, including pyelonephritis. Five to nine days after treatment, C/T and levofloxacin achieved composite cure rates (microbiological eradication and clinical cure) of 76.9% and 68.4%, respectively, indicating superior efficacy for C/T in this setting [46,47]. Strains of *P. aeruginosa* that are non-susceptible to piperacillin–tazobactam, CAZ or meropenem are less likely to be susceptible to other β-lactams but are more likely to be susceptible to C/T [48]. However, more evidence is needed to confirm its exact role in treating infections caused by ESBL-producing Enterobacterales [49].

3.5. Cefiderocol

As with other β-lactam antibiotics, the principal antibacterial/bactericidal activity of cefiderocol occurs by inhibition of cell wall synthesis by binding to penicillin-binding proteins; however, it is unique in that it enters the bacterial periplasmic space because of its siderophore-like property (Fig. 3) [19,50]. The chemical structure of cefiderocol is similar to both CAZ and cefepime, which are third- and fourth-generation cephalosporins, respectively, but has better stability to a variety of β-lactamases, including AmpC, ESBLs and MBLs [50].

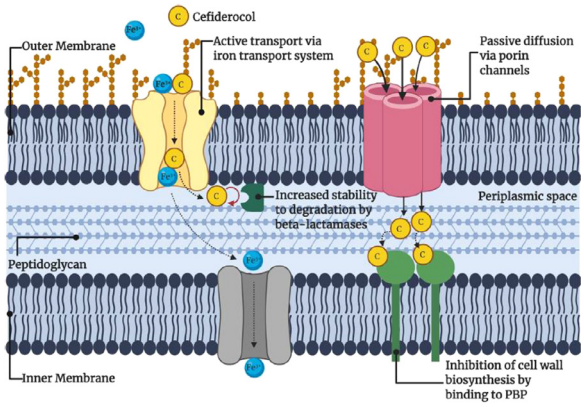

Fig. 3. The mechanism of action of cefiderocol.
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Cefiderocol was compared, in a Phase II, multicentre, non-inferiority trial, with imipenem–cilastatin for the treatment of cUTI in hospitalised adults at risk of MDR Gram-negative infections. At TOC (7 days after treatment cessation), 73% patients treated with cefiderocol and 55% of patients treated with imipenem-cilastatin achieved the composite endpoint of clinical and microbiological response, with a significant (18.6%) treatment difference in favour of cefiderocol [51]. In turn, the Phase III, non-inferiority trial APEKS-NP evaluated the efficacy and safety of cefiderocol vs. high-dose meropenem for the treatment of adults with Gram-negative nosocomial pneumonia [52]. All-cause mortality at day 14 was 12.4% for cefiderocol and 11.6% for meropenem, demonstrating non-inferiority for cefiderocol; similar tolerability was reported [52]. The CREDIBLE-CR study compared efficacy and safety of cefiderocol vs. BAT for the treatment of serious infections caused by CR-GNB. Cefiderocol and BAT had comparable clinical and microbiological efficacy in a heterogeneous patient population [53]. However, numerically more deaths occurred in the cefiderocol group, primarily in the patient subset with *P. aeruginosa* infections, and more so with *Acinetobacter* spp. infections. The IDSA guidance suggests that cefiderocol can be considered in urinary tract infections (UTI) caused by CRE [54]. Additional data on the efficacy of cefiderocol compared with standard therapy for healthcare-associated and hospital-acquired Gram-negative bloodstream infections is expected to emerge from the Phase II, investigator-driven GAME CHANGER trial, which is due to report in March 2023 [55].

4. Clinically important β-lactam-resistant Gram-negative pathogens

An overview of antibiotic-resistant GNB pathogens is given in Table 2, detailing the most clinically relevant drugs to which key pathogens such as *K. pneumoniae, A. baumannii* and *P. aeruginosa* are resistant.

4.1. ESBL-producing Enterobacterales

ESBL-producing Enterobacterales are a major group amongst antibiotic-resistant GNB, and are responsible for significant morbidity and mortality [56–58]. The incidence of infections with ESBL-producing Enterobacterales is rapidly increasing worldwide and is an evolving crisis [59]. In the US, the incidence of ESBL-producing Enterobacterales infections increased by 53% from 2012

Table 2
Multidrug-resistant Gram-negative pathogens – key drugs and characteristics.

Pathogen	Key drug resistance	Classification of threat [1,2,119]	Common infections/setting	Remarks
Non-fermenting Gram-negative bacteria				
Acinetobacter baumannii	BLs (e.g. cephalosporins, carbapenems), tetracyclines (e.g. tigecycline), colistin, fluoroquinolones	Carbapenem-resistance: critical threat	BSI, UTI, IAI, meningitis, HAP, VAP	*A. baumannii* is an increasing threat worldwide. It is an environmental pathogen that produces biofilms enhancing bacterial survival despite treatment. Infections can be difficult to treat and are associated with high costs, significant morbidity and mortality, especially in ICU patients [89]
Pseudomonas aeruginosa	BLs, carbapenems, fluoroquinolones, polymyxins, aminoglycosides, fosfomycin, rifampin	Carbapenem-resistance: critical threat	VAP/HAP, BSI, CF, UTI, wound, burn	*P. aeruginosa* is a common environmental pathogen that develops biofilms and is strongly associated with respiratory infections, especially in CF. Intrinsically resistant to antibiotics due to low membrane permeability, efflux pumps and β-lactamases [108,120,121]
Enterobacterales				
Escherichia coli	BLs (e.g. third- and fourth-generation cephalosporins, carbapenems), fluoroquinolones, polymyxins, aminoglycosides	Carbapenem-resistance: critical threat Third-generation cephalosporin-resistance: critical threat	GI, UTI, HAI, neonatal meningitis	Most commonly isolated GNB pathogen in multiple different infection sites. High rates of resistance and multi-resistance to antibiotics. Common cause of HAI [122–124]. *E. coli, K. pneumoniae* and *P. aeruginosa* account for 70% of all HAI GNB infections in the US [123]. New antibiotics are needed for the treatment of all ESBL-producing Enterobacterales [1]
Klebsiella pneumoniae	BLs (e.g. carbapenems)	Carbapenem-resistance/third-generation cephalosporin-resistance: critical threat	VAP/HAP, BSI, UTI	Commonly isolated in HAIs. Produces broad-spectrum β-lactamases that are active against cefotaxime and ceftazidime [125,126]
***Enterobacter* spp.**	BLs (e.g. carbapenems, second-generation cephalosporins, monobactams, carbapenems)	Carbapenem-resistance/third-generation cephalosporin-resistance: critical threat	BSI, GI, UTI, RTI	Most commonly isolated *Enterobacter* spp. in HAIs are *E. aerogenes* and *E. cloacae*. Highly motile. Plasmid-encoded resistance. Resistance arises from efflux pump, enzyme secretion and low membrane permeability [127]
***Shigella* spp.**	Fluoroquinolones, third-generation cephalosporins, azithromycin	Fluoroquinolone-resistance: medium threat	GI infection, BSI	Particularly associated with gastroenteritis and associated with large-scale morbidity and mortality in low- and middle-income countries. Increasing multidrug resistance is a serious concern [128,129]
***Salmonella* spp.**	Fluoroquinolones (ciprofloxacin) BLs (e.g. ampicillin, ceftriaxone), azithromycin, tetracyclines, sulfonamide	Fluoroquinolone-resistance: high threat	GI infection, BSI	As with *Shigella* spp., *Salmonella* spp. (Typhi and non-Typhi) are associated with life-threatening GI infections. Multidrug resistance is a serious concern and new antibiotics are needed to tackle this threat [130–133]
***Proteus* spp.**	Third-generation cephalosporins carbapenems, polymyxins, BLs (e.g. mecillinam and pivmecillinam), aminoglycosides, nitrofurantoin, tigecycline, colistin	-	GI infections, pyelonephritis, UTI	Swarming bacterial species responsible for UTI. MDR strains are becoming a problem [134–136].
Serratia marcescens	BLs, tetracyclines	-	BSI, UTI, wound	Environmental opportunistic pathogen causing increasing numbers of HAIs, particularly in ICUs [137,138]
Microaerophiles				
***Helicobacter* spp.**	Clarithromycin, metronidazole	Clarithromycin-resistance: high threat	GI inflammation (peptic ulcer)	Antibiotic resistance among *Helicobacter* spp. has been described as having 'reached alarming levels worldwide affecting the efficacy of treatment' [139]
***Campylobacter* spp.**	Fluoroquinolones, BLs, aminoglycosides, macrolides, tetracyclines, phenicols, fosfomycin	Fluoroquinolone-resistance: high threat	GI infection (gastroenteritis)	Foodborne pathogen that has developed resistance to multiple antibiotics, including high-level fluoroquinolone resistance [140]
Other Gram-negative bacteria				
Haemophilus influenzae	BLs, third-generation cephalosporins, chloramphenicol	Ampicillin-resistance: medium threat	RTI, BSI, neurological infections (meningitis)	Opportunistic pathogen, notable cause of fatal infections in children, particularly among infants and children. Strains resistant to amoxicillin–clavulanate, cefotaxime, and cefuroxime more likely to be isolated from ICUs [141]
Neisseria gonorrhoeae	BLs, third-generation cephalosporins, fluoroquinolones, macrolides	Third-generation cephalosporins/ fluoroquinolones: high threat	STI	Common STI pathogen worldwide. The appearance of antibiotic resistance is a significant threat to health. Strains that are multi-resistant to extended-spectrum cephalosporins and azithromycin are especially dangerous [142]

BL, β-lactam; BSI, bloodstream infection; CF, cystic fibrosis; GI, gastrointestinal; GNB, Gram-negative bacteria/bacterial; HAI, healthcare-associated infection; HAP, hospital-acquired [bacterial] pneumonia; IAI, intra-abdominal infection; ICU, intensive care unit; MDR, multidrug-resistant; RTI, respiratory tract infection; STI, sexually transmitted infection; UTI, urinary tract infection; VAP, ventilator-acquired [bacterial] pneumonia.
Source: WHO 2017 [2]; Morris and Cerceo 2020 [119].

to 2017, most of which were community acquired, although healthcare-associated infections (HAI) are also a major source of these infections [60]. The ESBL-producing Enterobacterales are a serious threat due to their resistance to many extended-spectrum penicillins and other agents, including cephalosporins and aztreonam. Furthermore, they often have additional genes conferring resistance to a wider range of antibiotics, including quinolones. ESBLs are produced across the Enterobacterales, and high rates of these enzymes have been reported in *E. coli, K. pneumoniae, K. oxytoca* and *Proteus mirabilis* [61,62]. The CTX-M ESBL inactivates a wide range of antibiotics, including cefotaxime and ceftriaxone, and over time has become more active against CAZ [63]. Bacteria producing this enzyme are rapidly spreading worldwide and this is the most frequently reported ESBL in the US [61]. This type of ESBL is distinct from β-lactamases such as TEM and SHV, which have a narrower range of action [64,65].

The MERINO trial did not support the use of piperacillin–tazobactam vs. meropenem in *K. pneumoniae* or *E. coli* BSIs with ceftriaxone resistance [66]. Following these results, carbapenems were considered the standard of care for the treatment of bacteraemia with ESBL-producing Enterobacterales infections. However, this is controversial as there is a counter argument that carbapenems are not necessary for all patients with infections caused by ceftriaxone-resistant Enterobacterales, and that BL–BLIs can be used in appropriate settings [67]. This challenge is based on a report that some of the MICs in the MERINO trial may have been incorrectly determined by local laboratories who used MIC strip tests, and the observation that piperacillin–tazobactam was not administered as an extended infusion [67,68]. Isolates from patients with worse outcomes were frequently found to be non-susceptible to piperacillin–tazobactam when MICs were determined using reference methods [67]. Alternative new drugs and combinations with in vitro activity against ESBL-producing Enterobacterales include: CZA, C/T, I–R, MVB, cefiderocol and plazomicin [50,59].

4.2. Carbapenem-resistant Enterobacterales

The CREs are a more serious threat than ESBLs; they account for > 13 000 nosocomial infections and > 1000 deaths per year in the US [54]. Carbapenemase-producing isolates are the cause of ca. 50% of all CRE infections in the US [69,70]. There is heterogeneity within the CRE, with differing sets of carbapenemases being produced, and consequently there is resistance to various carbapenem antibiotics. The most common of the Ambler classes A, B and D enzymes are KPCs of the class A type, and these can be produced by any of the species belonging to the Enterobacterales. In the US, the most prominent type of carbapenemases are KPCs; other types such as class B MBLs (e.g. NDM, VIM, IMP) and class D oxacillinase (e.g. OXA-48-like) are much less frequently reported [71,72]. It should be noted that carbapenem resistance not only arises from carbapenemase production but also decreased porin expression and increased efflux pump action [73,74].

Carbapenem-resistant *K. pneumoniae* are the most common and clinically important of the CRE reported worldwide [75]. The geographic variation of the carbapenem resistance genes varies across continents [75]. When comparing studies, it is important to note that phenotypic definitions of carbapenem-resistant *K. pneumoniae* (CRKP) may differ. In South-East Asia, NDM and other MBLs (e.g. IMP, VIM) and OXA-48–type are predominant carbapenemases in CRE [76]. In the European Survey on carbapenemase-producing Enterobacteriaceae (EuSCAPE), 37% of the tested CRKP had a carbapenemase gene: KPC (42%) and OXA-48 (38%) were predominantly encoded [77]. In the US, the CDC Gram-negative initiative surveillance revealed that 47.9% of tested CRE isolates were KPC-producing species [78]. In another study from the US (CRACKLE-2), where > 500 patients had CDC-defined CRKP, 83% were carbapenemase producers and 94% of these expressed KPC [70].

The site of infection and knowledge of carbapenemase production are important, as these factors will guide treatment decisions [54]. Similar to infections with other MDR pathogens, poor source control and failure to implement early rapid diagnostics can delay proper management(manuscript submitted for publication). The lack of availability of new drugs such as the newer BL–BLI agents, plazomycin, cefiderocol and eravacycline, in some countries may hinder adequate treatment and force clinicians to use alternative drugs with lower efficacy and higher toxicity.

Whenever bacterial pathogens are susceptible, preferable treatments for CRE infections such as cystitis are ciprofloxacin, levofloxacin, trimethoprim–sulfamethoxazole, nitrofurantoin, fosfomycin or a single dose of an aminoglycoside [54]. Alternatively, CZA, MVB or cefiderocol can be used. For pyelonephritis or cUTI, preferred treatments are CZA, MVB, I–R, or cefiderocol, or, alternatively, aminoglycosides [54].

For non-UTI infections or where KPC has been identified, preferred treatment options are CZA, MVB and I–R. Cefiderocol (for indications other than BSI) and eravacycline or tigecycline (for non-bacteraemic intra-abdominal infection [IAI] only or in combination) are alternative options, depending on the resistance profile of the pathogen (notably resistance to ertapenem or meropenem) [54]. In cases in which an MBL is detected, the preferred treatment options are CZA plus aztreonam or cefiderocol [54]. In cases where an OXA-48-like carbapenemase has been detected, the preferred treatment is CZA, or alternatively cefiderocol (for indications other than BSI), tigecycline or eravacycline (for cIAI only). Combination therapies such as a β-lactam with an aminoglycoside, fluoroquinolone or polymyxin are not recommended for treating CRE infections if the pathogen is susceptible to a β-lactam [54].

For cystitis caused by CRE that are resistant to ertapenem but susceptible to meropenem, without available carbapenemase testing, a standard infusion of meropenem may work due to high achievable concentrations in the urine [54]. In cases of cystitis caused by CRE that are resistant to meropenem and other agents such as aminoglycosides, including amikacin and plazomicin, alternative options include CZA, MVB, I–R and cefiderocol [54]. For isolates producing MBLs (NDM, IMP or VIM), CZA plus aztreonam, aztreonam–avibactam or cefiderocol are preferred [53,79]. Colistin (not polymyxin B), notwithstanding the side effects, is also an alternative, although not preferred [54,80].

Complicated UTI and pyelonephritis caused by CRKP that is resistant to both ertapenem or meropenem are best treated with CZA, MVB, I–R or cefiderocol [54]. Oral fosfomycin should be avoided [81,82]. For infections outside the urinary tract caused by *K. pneumoniae* that are resistant to both ertapenem and meropenem, it is important to identify the specific carbapenemase gene to give specific treatment [75,83].

For KPC producers, the preferred options are CZA, MVB and I–R, with cefiderocol as an alternative [81]. For IAIs, depending on the severity of the infection, tigecycline is an alternative treatment but can be limited by gastrointestinal side effects, particularly when high doses are used; eravacycline is a newer alternative but data are limited for this monotherapy [54,81,84]. For isolates producing MBLs, such as NDM, IMP or VIM, the preferred drugs are CZA with aztreonam or cefiderocol alone [54]. For Enterobacterales producing OXA-48-like carbapenemases, CZA is preferred [54].

4.3. Carbapenem-resistant Acinetobacter baumannii

Acinetobacter baumannii is found in many healthcare environments and is a highly effective human coloniser in hospitals [85]. *Acinetobacter baumannii* can easily survive on multiple surfaces, causing hospital infections and leading to numerous global out-

breaks [86,87]. Furthermore, there have been reports of CRAB strains being transmitted from countries with high antimicrobial resistance rates to countries where the rates are usually low, such as from Spain to Norway [87]. Infections due to *A. baumannii* are frequently found in intensive care units (ICUs), where they are implicated as the cause of VAP, UTIs and bacteraemia [88]. The prevalence of *A. baumannii* infection and colonisation is higher in ICUs since patients with severe clinical conditions are often hospitalised in these facilities.

Antibiotic resistance in *A. baumannii* is frequently due to low outer membrane permeability, antibiotic binding-site modifications and efflux pump expression [89,90]. The acquisition of carbapenemases is also an important mechanism of resistance for CRAB and resistance genes can also be gained through the acquisition of mobile genetic elements [89,91].

Various antimicrobials are used against CRAB, including polymyxins (such as polymyxins B or E [colistin]), tetracyclines (such as tigecycline and minocycline), β-lactams in combination with β-lactamase inhibitors (such as sulbactam) and other combinations such as trimethoprim–sulfamethoxazole. However, many *A. baumannii* strains show high-level resistance to these agents and there are pharmacokinetic limitations with polymyxins and tetracyclines: high and potentially toxic doses are necessary to achieve good tissue levels [92]. However, the newer tetracycline, eravacycline, shows efficacy against CRAB infections with low MIC values. This drug was shown to be non-inferior to ertapenem and meropenem against CRAB in two randomised clinical trials but is only approved for use for cIAI. However, in two further Phase III clinical trials, eravacycline was inferior to levofloxacin and ertapenem in the treatment of cUTI [92,93]. Cefiderocol has shown efficacy in CRAB infections and non-inferiority to IPM in the treatment of cUTIs has been demonstrated [19,92]. Although it is now approved for the treatment of cUTIs, the CREDIBLE-CR study (where patients with pneumonia, sepsis and UTI participated, and where CRAB isolates were identified in 46% of patients) all-cause mortality at the end of the study was higher when using cefiderocol (50%) compared with BAT (18%) in patients with *Acinetobacter* spp. positive cultures [53].

The OXA (class D) are the most prevalent types of carbapenemases among *A. baumannii* isolates worldwide. Among these are six subclasses: OXA-51-like, OXA-23-like, OXA-24/40-like, OXA-58-like, OXA-143-like and OXA-235-like [94]. To address such resistant infections, new approaches are being developed for treating resistant *A. baumannii* infections, including new β-lactam inhibitors in combination with existing β-lactams and non-β-lactams, new polymyxins, a new aminoglycoside (apramycin), monoclonal antibody treatments and bacteriophages [93].

4.4. *Carbapenem-resistant* Pseudomonas aeruginosa

Pseudomonas aeruginosa is increasingly associated with nosocomial infections, particularly in immunocompromised patients and those with indwelling devices [95]. Carbapenem-resistant *P. aeruginosa* is associated with a high risk of mortality. Worldwide, MBLs are the most prevalent type of carbapenemase produced by clinical isolates of CRPA; VIM MBLs are the most widely disseminated, followed by imipenemases [96]. In many territories, carbapenem resistance is due to MBLs that diminish the usefulness of β-lactamase inhibitors in the treatment of CRPA infections [97]. In the US, 10–20% of *P. aeruginosa* isolates are resistant to at least one carbapenem, making this resistance a serious problem [98,99]. Compared with worldwide literature, India reports increasing MBLs (NDM and VIM) in addition to other resistance mechanisms, which further compromise the efficacy of the newer BL–BLIs [100], whilst KPC-producing *P. aeruginosa* is becoming a concern in China [101].

An analysis of seven studies (total = 1613 patients) found that patients with CRPA BSIs were at higher risk of death than non-CRPA BSIs (pooled ORs, 3.07 and 1.46) [102] and showed that 8–18.4% of deaths in this study were attributable to carbapenem resistance. Risk factors for CRPA infection include carbapenem use, other antibiotic use [103,104] such as fluoroquinolones, medical devices and ICU admission [105]. Additionally, a study in Japan showed a clear correlation between carbapenem consumption and the prevalence of CRPA on a national scale [95].

Alternative treatments to carbapenems include antipseudomonal drugs (e.g. antipseudomonal cephalosporins such as CAZ, cefepime and piperacillin–tazobactam) and are usually partnered with another active agent such as an aminoglycoside (e.g. amikacin) [103]. Carbapenems should be reserved for polymicrobial infections or *P. aeruginosa* isolates that are resistant to other β-lactams [106]. Resistance to antipseudomonal drugs is increasing and MDR *P. aeruginosa* showing resistance to three or more drug classes has emerged and spread across different regions worldwide [107].

The C/T combination is one of the preferred treatment options for MDR/XDR *Pseudomonas* infections [108]. In an analysis of 11 clinical studies (number of strains ranged from 38 to 3229), the susceptibility of MDR/XDR *P. aeruginosa* to C/T ranged from 55–96.6% [108]. When compared with other agents, C/T had a lower probability of co-resistance in β-lactam-resistant *P. aeruginosa* [48]; however, dosing and infusion need to be optimised according to indication. Other notable effective approaches to treating CRPA infections include cefiderocol, CZA and I–R [81].

5. Real-world evidence

Various observational studies have added to the body of clinical trial evidence showing the viability of using monotherapies and antibiotic combinations to treat MDR-GNB infections in regular clinical practice. A recent study involving 22 clinical centres from Italy (n = 577) showed that CZA is an effective option for treating KPC infections (e.g. BSIs and UTIs) when used alone [109]. More investigations are needed to support its use in lower respiratory tract infections and the potential benefits of longer infusion times [109]. A retrospective cohort study (n = 203) found that CZA did not impact clinical failure in the overall population, or high-risk subgroups or 30-day mortality among those with CRE or *Pseudomonas* spp. infections [110]. However, receipt of CZA within 48 hours of infection onset was associated with improved clinical outcomes [110]. It was concluded that CZA can be an effective therapy for CRE and MDR *Pseudomonas*, but that there is a need for advances in the treatment of vulnerable patients with pneumonia and severe renal impairment.

Real-world studies and observational studies have shown the efficacy and safety of C/T in a range of different MDR/XDR *P. aeruginosa* infections, including UTI, IAI, HAP, VAP and skin/soft tissue infections [42,108,111–113]. The C/T combination has also shown lower toxicity than BATs such as polymyxin or aminoglycosides in the treatment of *P. aeruginosa* infections [114].

Although the body of real-world evidence is growing, more of these studies are needed to determine the value of new antibiotic combinations in everyday use in critically ill patients, and to evaluate their usefulness compared with older treatment options such as polymyxins, tigecycline, fosfomycin and aminoglycosides [20,115].

6. Conclusions and final recommendation

Antimicrobial resistance in GNB is a global concern and significantly affects outcomes in patients with limited options for treatment. To date, there is no single agent BL–BLI with a spectrum

that covers all MDR-GNB in empiric or targeted therapy. Whilst cefiderocol provides broad coverage, further analyses are warranted to fully understand its effectiveness against certain MDR Gram-negative pathogens such as *Acinetobacter* spp. and difficult-to-treat resistance *Pseudomonas aeruginosa*. The availability of new antibiotics and the use of novel combinations, such as the new BL–BLI combinations, provide hope for the successful management of various pathogens at different sites of infection. Effective and well-managed antimicrobial stewardship policies are essential to ensure that these agents are properly used, and thus maintain their potency and help limit or slow resistance development.

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