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REVIEW

Alternative therapies for Carbapenem-Resistant *Enterobacteriaceae* (CRE)

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Abstract

Background: Increasing antibiotic resistance is a global concern for human health. Carbapenem antibiotics have high sensitivity and are among the last line of antibiotics for treating infections caused by Gram-negative bacteria that are resistant to various classes of drugs. Over 70% were caused by Carbapenem-Resistant Enterobacteriaceae (CRE) infections, a threat in the clinical field. **Objective:** To find alternative antibiotic therapy options for Carbapenem-Resistant Enterobacteriaceae (CRE) infections. **Method:** A narrative review method was used in this study. Articles from several journals with the keyword "*Therapy Alternative of Carbapenem-Resistant Enterobacteriaceae*" in PubMed, Elsevier Article, Cochrane and Indonesian literature from Google Scholar databases were reviewed. **Results:** Recommended alternative therapy options for CRE infections include combinations of carbapenem-containing antibiotics with other antibiotic classes as anti-CRE treatments, ceftazidime/avibactam for KPC and OXA-48-producing infections, *in vitro* efficacy of eravacycline, and prolonged high-dose carbapenem therapy. Additionally, several drugs in the development stages include the combination of new beta-lactamase inhibitor IMI/REL and the novel cephalosporin siderophore cefiderocol, zidebactam, and nacubactam. **Conclusion:** New strategies against CRE, such as the reutilization of older antibiotic classes, higher anti-CRE doses, and combination approaches, have demonstrated clinically effective and improved outcomes and have also gained approval from the FDA.

Introduction

Antibiotics are antimicrobial agents used to treat infections caused by bacteria. Antibiotics are grouped into several classes, including the β-lactams. One of the members of the Beta-lactams is the carbapenems. Carbapenem antibiotics have broad-spectrum antibacterial activity and high sensitivity. Consequently, these antibiotics are often regarded as the last line of defence in treating infections caused by Gram-negative bacteria that have developed resistance to various drug classes. Therefore, the carbapenem class is often referred to as the "*last line*" (Halim *et al*., 2017). Members of the Enterobacteriaceae, including *Escherichia coli* and *Klebsiella pneumoniae*, have been previously identified as antibiotic-resistant bacteria, particularly among multidrug-resistant (MDR) bacteria. Therefore, this has prompted the development of new antibiotics, which have become necessary in various countries. Infections with Enterobacteriaceae are a critical priority because they are resistant to third-generation cephalosporins and carbapenem antibiotics (Lee *et al*., 2017; Rodríguez-Baño *et al*., 2018).

Enterobacteriaceae are significant pathogens responsible for severe infections, including Blood Stream Infections (BSI), Community-Acquired Pneumonia (CAP), Hospital-Acquired Pneumonia (HAP), Ventilator-Associated Pneumonia (VAP), Complicated Urinary Tract Infections (cUTI), and Complicated Intra-Abdominal Infections (cIAI) (Hossain *et al*., 2004; Peleg *et al*., 2005; Leavitt *et al*., 2007; Lee *et al*., 2017). Consequently, antibiotic resistance in these bacteria represents a critical challenge both clinically and socioeconomically (Ting *et al*., 2018). Increasing antibiotic resistance is a global concern for human health (Anthony *et al*., 2008; Lee *et al*., 2009).

In Indonesia, few studies have discussed infections caused by multidrug-resistant (MDR) gram-negative bacilli, as cases of these infections have been increasing, leading to a rise in morbidity and mortality rates (Anggraini *et al*., 2018). The presence of antibiotic-resistant infectious bacteria may result in the deaths of approximately 700,000 patients annually (Lesho & Laguio-Vila, 2019). In 2020, the prevalence of deaths due to Carbapenem-Resistant Enterobacteriaceae (CRE) infections exceeded 70%, posing a significant threat in the clinical field (Dong *et al*., 2020).

According to the Global Antimicrobial Resistance and Use Surveillance System (GLASS) study conducted in 2020, there was an increase in antimicrobial resistance in several types of bacteria, including *K. pneumoniae* and *E. coli* (Oliva *et al*., 2017). According to research conducted in Indonesia in 2011, Enterobacteriaceae resistant to meropenem (a carbapenem class) were found to have a prevalence of 50.5% and 84% in hospital emergency departments and neonatal units, respectively. In 2015-2016, out of 1082 major pathogenic bacteria detected in hospitals, about 10.7% of bacteria showed resistance to carbapenems (Santoso & Rostinawati, 2022).

Carbapenems (especially meropenem and imipenem) generally have specific activity against *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and the Enterobacteriaceae family (especially *K. pneumoniae*) (Aurillo *et al*., 2022). However, according to research, the use of carbapenems in hospitals has increased, leading to resistance in Gram-negative bacteria (Aurillo *et al*., 2022). The causes of this resistance are diverse, including factors such as inappropriate use of antibiotics in the early stages of therapy, increased duration of hospitalisation, genetic mutations in bacteria, and colonisation by resistant pathogens (Ventola, 2015; Qu *et al*., 2019).

Resistance to Carbapenems among the Enterobacteriaceae my result from inappropriate use of antibiotics, including 1) the use of carbapenems for infections treatable with effective narrow spectrum antibiotics; 2) the use of carbapenems to treat carbapenems-resistant bacteria; and 3) the administration of carbapenems to patients who have not been proven to be infected (Halim *et al*., 2017). CRE can be mediated through several mechanisms, such as the upregulation of efflux pumps, porin mutations, decreased permeability, changes in transpeptidases, and the production of carbapenemase enzymes that can activate carbapenems. The main groups of enzymes responsible for most carbapenem resistance are KPC (*Klebsiella pneumoniae* carbapenemases) as class A amblers; MBLs (Metallo-ß-Lactamases) as class B amblers; and NDM-1 (MBL New Delhi) and OXA-48-producing CRE (Oxacillinase 48) as class D amblers (Pérez-Gracia, 2019).

The rapid emergence of CRE infections can be prevented by studying and understanding the mechanisms by which Enterobacteriaceae develop resistance to carbapenems through the production of carbapenemase enzymes. In controlling CRE infections, several strategies can be employed, including timely detection, high-dose carbapenem therapy, and anti-CRE antibiotic combination strategies with other classes of antibiotics, as well as the use of old antibiotics and the development of new anti-CRE therapies.

Methods

In writing this article, a narrative review approach was employed, incorporating a systematic review of publications totalling 23,111 articles in Indonesian and English journals. Articles from several journals with the keyword "*Therapy Alternative of Carbapenem-Resistant Enterobacteriaceae*" in PubMed, Elsevier Article, Cochrane and Indonesian literature from Google Scholar databases were reviewed.

Results

Figure 1 illustrates the mechanisms underlying the bacteria's resistance to both broad-spectrum and narrow-spectrum antibiotics. However, therapeutic options such as fosfomycin, aminoglycosides, and meropenem-levofloxacin combination are available in Indonesia. The following describes the therapeutic options for Carbapenem-Resistant Enterobacteriaceae (CRE) in Table I.

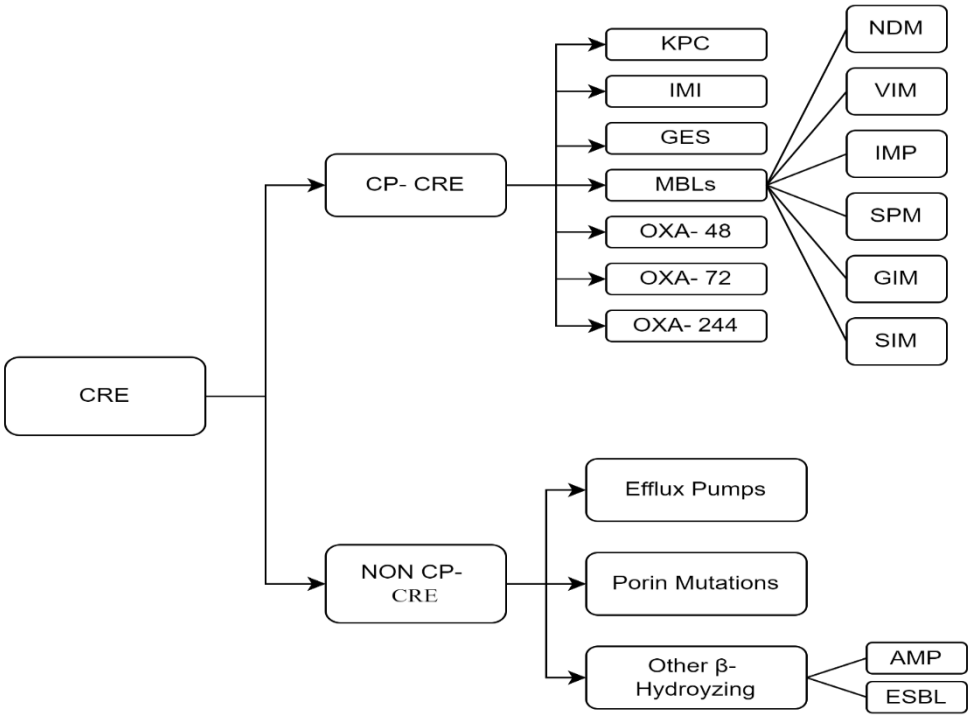
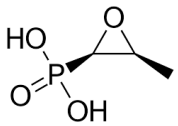
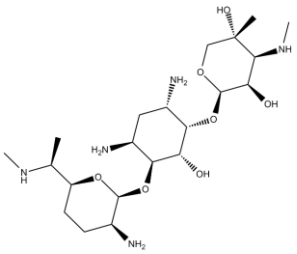
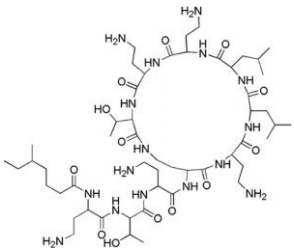
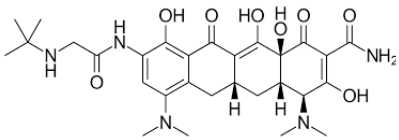
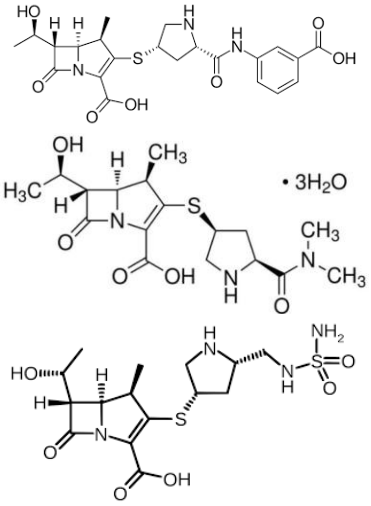
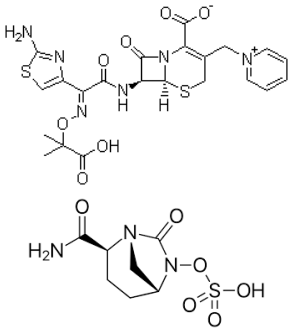
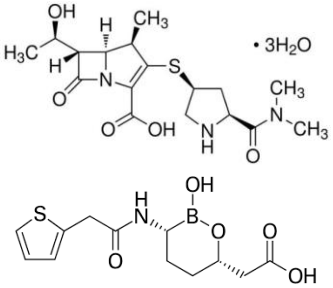
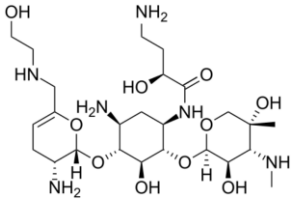
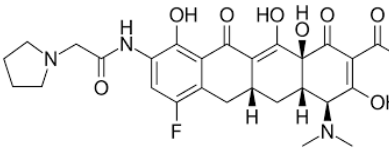
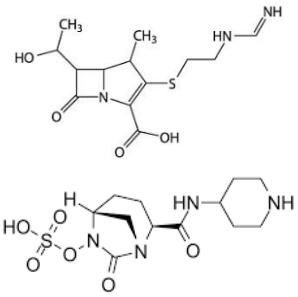
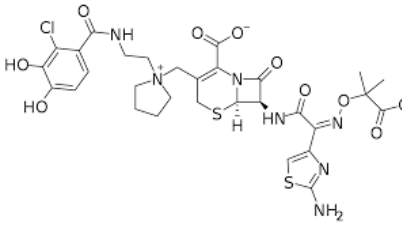
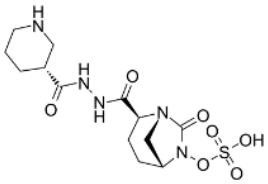
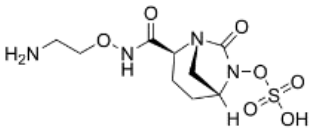


Figure 1: Classification of various mechanisms of CRE drug resistance

Table I: Treatment options in Carbapenem-Resistant Enterobacteriaceae (CRE) infections

	Anti-CRE	Mechanisms	Structure	Toxicity
Old antibiotics	Fosfomycin	Inhibits cell wall synthesis		IV: Hypokalemia (26%), local pain (4%), heart failure (3%)
	Aminoglycosides: Gentamicin Amikacin	Protein synthesis inhibitors		Nephrotoxicity, ototoxicity
	Colistin Polymyxin B	Cell membrane disruptors		Colistin: Nephrotoxicity (50%-60%), neurotoxicity Polymyxin B: Nephrotoxicity (20%-40%), neurotoxicity
	Tigecycline	Protein synthesis inhibitors		Nausea (26%), vomiting (18%), and diarrhoea (12%).

	Anti-CRE	Mechanisms	Structure	Toxicity
Combination therapy	Ertapenem + Meropenem/ Doripenem	Cell wall synthesis inhibitor		Ertapenem: Gastrointestinal effects (2%-12%), local phlebitis/thrombo-phlebitis (2%), headache (4%-7%), hypersensitivity reactions (rash-1-3%), hematologic reactions (1%-7%), elevated liver enzymes (7%-9%), fever (2%-5%), and seizures (<1%). Meropenem: Local phlebitis/thrombophlebitis (1%), hypersensitivity reactions (rash-3%), headache (2%-8%), gastrointestinal effects (1%-8%), hematologic changes (<6%), seizures (1%). Doripenem: Headache (3%-16%), gastrointestinal effects (4%-12%), local phlebitis (2%-8%), hypersensitivity reactions (rash 2%-7%), hematologic changes (<1%), elevated liver enzymes (2%-7%), and seizures (<1%).
	Ceftazidime/ Avibactam	Cell wall synthesis inhibitors/β-lactamase inhibitors		No clinical trials yet
	Meropenem/ Vaborbactam	Cell wall synthesis inhibitors/β-lactamase inhibitors		Meropenem: Local phlebitis/thrombophlebitis (1%), hypersensitivity reactions (rash-3%), headache (2%-8%), gastrointestinal effects (1%-8%), hematologic changes (<6%), and seizures (1%).
Novelty	Plazomycin	Protein synthesis inhibitors		Nephrotoxicity, ototoxicity, headache, nausea, vomiting, diarrhoea, hypertension, and hypotension.
	Erevacyclin	Protein synthesis inhibitors		acute pancreatitis, pancreatic necrosis, dysgeusia, pleural effusion, dyspnoea, and hyperhidrosis

Anti-CRE	Mechanisms	Structure	Toxicity
Imipenem/ Relebactam	Cell wall synthesis inhibitors/β-lactamase inhibitors		Imipenem: Neurotoxicity (53%), skin toxicity (26%), haematologic toxicity (13%), and gastrointestinal toxicity (7%). Relebactam: Neurotoxicity, hepatotoxicity, nephrotoxicity, and bone marrow suppression (cytopaenia)
Cefiderocol	Cell wall synthesis inhibitor		No non-clinical data
Zidebactam	β-lactamase inhibitors		Non-clinical data not yet available
Nacubactam	β-lactamase inhibitors		Non-clinical data not yet available

Discussion

CP-CRE can be classified into several kinds of carbapenemases, including class A, class B, and class D β-lactamases (Ambler, 1980). In class A, there is a plasmid-encoded *Klebsiella pneumoniae* Carbapenemase (KPC) enzyme active to hydrolyse carbapenems (Nordmann *et al*., 2009). The KPCs produced by Enterobacteriaceae resist several β-lactam antibiotics (Nordmann *et al*., 2009). Although KPCs were initially found in *K. pneumoniae* isolates, clinical isolates producing KPCs have also been identified in *Escherichia coli*, *Klebsiella oxytoca*, *Salmonella enterica*, Citrobacter *freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Proteus mirabilis*, and *Serratia marcescens* (Miriagou *et al*., 2010; Okoche *et al*., 2015; Abdallah & Balshi, 2018; Boutal *et al*., 2018; Fernández *et al*., 2018).

Furthermore, there is a class B carbapenemase, namely Metallo-β-lactamase (MBL) (Walsh *et al*., 2005). MBL is often a serious problem because it is an inhibitor of drug receptors, has a high potential for gene transfer, and can hydrolyse most β-lactam antibiotics, except monobactams (van Duin & Doi, 2017). Bacteria that produce MBLs often also express ESBLs, so they are primarily associated with multidrug resistance (MDR), which can inactivate monobactams (Tooke *et al*., 2019). In Enterobacteriaceae, the most common types of MBLs found are New Delhi metallo-β-lactamase 1 (NDM-1), discovered in New Delhi, Verona integron-borne metallo-ß-lactamase (VIM), and Imipenem-resistant Pseudomonas carbapenemase (IMP) (Codjoe & Donkor, 2017; Tilahun *et al*., 2021).

The non-CP carbapenem-resistant Enterobacteriaceae have alternative carbapenem resistance mechanisms (Codjoe & Donkor, 2017). First, they produce different types of β-lactamases, such as *Amp*C, which form bonds with carbapenem molecules and prevent them from reaching the target receptors (Queenan *et al*., 2010). This is also often found in *E. coli* and other Enterobacteriaceae species. Secondly, through the expression of Resistance-Nodulation-Division (RND) efflux pump-resistant genes, such as the most common RND type *AcrAB-TolC* (Weston *et al*., 2017). Thirdly, alterations in porin synthesis also play a role in blocking carbapenem penetration into bacterial cells. strains with mutations in porins cannot usually spread in a community setting but can proliferate locally within the

hospital environment (Bialek-Davenet *et al*., 2017). Therapeutic options to overcome bacteria resistant to carbapenems are very diverse, including antibiotic combinations, some of which are not yet available in Indonesia. Examples include ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, and cefiderocol (Doi, 2019). Older antibiotics, which have been used in medicine for many years, are still effective against CRE, such as the fosfomycin class. Fosfomycin-type antibiotics are commonly used to treat Urinary Tract Infections (UTIs) and remain effective against about 80% of CRE cases (Vardakas *et al*., 2016). The aminoglycoside class remains the first choice for treating carbapenem-resistant *K. pneumoniae* infections (Amaldi *et al*., 2018). Gentamicin is the most commonly used aminoglycoside, but amikacin is the only molecule that is still potent and active (Ni *et al*., 2016).

Additionally, colistin remains the primary treatment option for CRE infections (Karaiskos *et al*., 2019b). Currently, CRE, especially *K. pneumoniae*, has begun to resist colistin, reducing its effectiveness as a monotherapy drug (Sader *et al*., 2018). Therefore, colistin is now used in combination therapy with meropenem, which has significantly reduced mortality rates (Daikos *et al*., 2014). Colistin (polymyxin E) and polymyxin B are considered the most effective agents against CRE based on *in vitro* tests. Polymyxin B and colistin have differences in one amino acid (Gales *et al*., 2011). Polymyxin antibiotics are still considered a last resort due to their side effects, such as nephrotoxicity, neurotoxicity, and skin discolouration (Elias *et al*., 2010; Vicari *et al*., 2013; Karaiskos *et al*., 2019b).

The glycyclin-thigesiclin drug class is also still an alternative in treating CRE in certain situations (Ni *et al*., 2016). The superiority of Tigecycline with low-dose concentrations in serum may affect clinical outcomes in patients with nosocomial community pneumonia (Giamarellou & Poulakou, 2011). The initial dose starts at 200 mg, and the maintenance dose is 100 mg every 12 hours (Karaiskos *et al*., 2019b). For standardised doses, the starting dose is 100 mg, and the maintenance dose is 50 mg every 12 hours (Trecarichi & Tumbarello, 2017). The use of these high doses is effective in treating ventilator-acquired pneumonia (VAP) caused by CRE (De Pascale *et al*., 2014). Several studies have demonstrated that high-dose tigecycline regimens for treating CRE infections in critically ill patients are significantly more effective, resulting in lower mortality rates compared to the use of standard doses of tigecycline (Ni *et al*., 2016).

Based on several studies of various antibiotics for the treatment of CRE, combination therapy has proven to be more successful than monotherapy, and it can be recommended to patients infected with CRE bacteria (Qureshi *et al*., 2012; Daikos *et al*., 2014; Machuca *et al*., 2017; Trecarichi & Tumbarello, 2017). Typically, this combination treatment consists of an initial dose of ertapenem, followed by an infusion of meropenem or doripenem lasting three or four hours with an additional dose of meropenem of 2g every eight hours (Bulik & Nicolau, 2011). This therapy has proven effective against CRE because ertapenem has a greater affinity for KPC, making it more difficult for ertapenem to be hydrolysed by carbapenemase. This allows simultaneous administration of a combination of two carbapenems to maintain high concentrations (Anderson *et al*., 2007). Comparative studies have confirmed the efficacy of this type of carbapenem combination therapy with clinical success rates exceeding 70% (Oliva *et al*., 2017; Venugopalan *et al*., 2017).

In case of new antibiotics, these therapies can be divided into two groups, namely 1) antibiotics that have been approved for medical use and 2) molecules that are currently under development. Recent antibiotics approved for the treatment of CRE infections include ceftazidime/avibactam, meropenem/vaborbactam, plazomicin, and eravacycline. Ceftazidime/avibactam is a combination of a β-lactam and a β-lactamase inhibitor. The uniqueness of this combination lies in avibactam, a synthetic, non-β-lactam β-lactamase inhibitor that is effective against Ambler class A, C, and D β-lactamases (De Jonge *et al*., 2016). Although clinical studies using this combination are still limited, preliminary data show a lower mortality rate of 9% compared to colistin, which achieved a mortality rate of 32% (van Duin *et al*., 2018).

The meropenem/vaborbactam combination antibiotic is a novel combination of β-lactam/β-lactamase inhibitors, consisting of carbapenems and serine-β-lactamase inhibitors, which contain compounds that enhance the effectiveness of meropenem (Karaiskos *et al*., 2019b). This combination can inhibit the serine carbapenemases of Ambler classes A and C (Petty *et al*., 2018). An *in vivo* study showed that 991 KPC-producing Enterobacteriaceae isolates were tested, 99% were sensitive to meropenem-vaborbactam (Lomovskaya *et al*., 2017).

Plazomicin is the latest generation of aminoglycosides to overcome bacteria that produce aminoglycoside drug-modifying enzymes (Petty *et al*., 2018). Based on studies conducted, plazomicin has a higher potential compared to other aminoglycosides in overcoming Enterobacteriaceae that produce KPC (Lomovskaya *et al*., 2017). The results of research on plazomicin demonstrated broad activity against both Gram-positive cocci and Gram-negative bacilli, with a

minimum inhibitory concentration (MIC90) of ≤2 mg/L (Walkty *et al*., 2014). Although aminoglycosides are not typically employed as monotherapy, plazomicin demonstrates a broad spectrum of activity and low nephrotoxicity, making it a viable monotherapy option for treating multidrug-resistant Enterobacteriaceae, particularly in urinary tract infections (Castanheira *et al*., 2018).

The therapeutic option of eravacycline antibiotics has broad-spectrum antimicrobial activity against gram-positive, gram-negative, and anaerobic bacteria (Zhanel *et al*., 2016). Eravacycline has several advantages over tigecycline, including more potent in vitro antibacterial activity, better oral bioavailability, lower potential for drug interactions, and a better ability to overcome microbial biofilms (Bassetti & Righi, 2014). In addition to the previously approved agents, six novel molecules are currently in the early stages of development. These include imipenem/cilastatin combined with relebactam, cefiderocol, SPR741, zidebactam, nacubactam, and VNRX 5133. The mechanism of action for imipenem/cilastatin and relebactam resembles that of avibactam (Blizzard *et al*., 2014) and demonstrates superior efficacy compared to colistin/imipenem in treating infections caused by KPC-producing Enterobacteriaceae (Motsch *et al*., 2020). Cefiderocol, the first antibiotic in the siderophore-conjugated cephalosporin class to reach advanced stages of development, functions through a unique mechanism. Its catechol substituent forms a chelating complex with iron, facilitating transport via the active system of Gram-negative bacteria, particularly CRE, thereby bypassing other permeability barriers. Cefiderocol exhibits MIC50 and MIC90 values of 1 µg/mL and 4 µg/mL, respectively (Saisho *et al*., 2018).

Meanwhile, zidebactam and nacubactam demonstrate high affinity for Ambler class A and class C β-lactamases (Karaiskos *et al*., 2019a). Additionally, both compounds bind Penicillin-Binding Proteins (PBPs) and enhance β-lactam activity (Papp-Wallace *et al*., 2018). The cefepime and zidebactam combination is undergoing phase two clinical trials for treating Gram-negative bacterial infections. On the other hand, nacubactam, combined with meropenem, is currently in Phase 1 trials targeting Gram-negative pathogens responsible for urinary tract infections (Monogue *et al*., 2018). Research findings indicate that the combination of meropenem and nacubactam yields higher MIC values than meropenem monotherapy while also being effective against isolates resistant to ceftazidime/avibactam.

Lastly, VNRX 5133, a broad-spectrum β-lactamase inhibitor with activity against Ambler classes A (including ESBL and KPC), B (such as NDM and VIM), C (*Amp*C), and D, is currently in clinical trials. This compound, a cyclic boronate, is being evaluated with cefepime to combat bacteria resistant to multiple antibiotics (Asempa *et al*., 2018).

Conclusion

Carbapenem-Resistant Enterobacteriaceae are rapidly increasing worldwide, especially in Indonesia. These bacteria possess a variety of antibiotic resistance mechanisms, rendering the control and early detection of infections caused by Enterobacteriaceae a challenging task. The treatment options for serious CRE infections are currently limited; therefore, the most suitable treatment strategy is to optimise the dose of available drugs and combine therapy. Anti-CRE development strategies, such as reusing existing antibiotic classes, increasing anti-CRE doses, and combining anti-CRE therapies, have shown effective and improved clinical results in several experimental studies. There is an urgent need to establish new therapeutic guidelines to address CRE infections, including the development of novel drugs such as plazomicin, eravacycline, or cefiderocol.

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Conflict of Interests

The authors declare no conflict of interest.

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