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Review

Prevalence of Carbapenem-Resistant Enterobacterales and Their Diverse Resistance Mechanisms

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This review provides an overview of carbapenem-resistant Enterobacterales (CRE) studies. CRE, called superbugs, has a high mortality rate and an increased resistance rate in several countries. The bacteria representing CRE are *Klebsiella* species and *Escherichia* spp., and they cause urinary tract infections (UTIs) and bloodstream infections (BSIs). CRE acquires resistance due to several mechanisms, typically divided into carbapenemase-producing (CP)-CRE and non-CP-CRE. Furthermore, although there are several antibiotics developed to treat CRE, they have their limitations; thus, antibiotic combination therapies or novel treatments are being developed. Therefore, since research on CRE and the use of appropriate antibiotics is important, some CRE-resistant mechanisms that enhance them are discussed. This review article was written using information obtained from Google Scholar and the National Center for Biotechnology Information website.

Key Words: Carbapenem-resistant Enterobacterale (CRE), Carbapenemases, Resistance mechanisms, Antibiotic therapy

INTRODUCTION

The World Health Organization (WHO) cites an increase in antibiotic-resistant bacteria as one of the biggest threats to global health (Tompkins and van Duin, 2021). The increase in infection rates by multidrug-resistant (MDR) gram-negative organisms poses an important and increasingly urgent challenge for patient care (Goodman et al., 2016). Gram-negative bacteria, Enterobacterales, naturally exist in the intestinal tracts of humans and animals and spread relatively easily among humans *via* environmental, food, and hand carriage routes (Goodman et al., 2016).

Enterobacterales mainly include *Klebsiella* species, *Escherichia* spp., *Enterobacter* spp., and *Salmonella* spp. They may also include *Proteus* spp., *Raoultella* spp., and *Citrobacter* spp. (Goodman et al., 2016; Potter et al., 2016). Enterobacterales are commonly caused by community- and hospital-acquired infections. They cause urinary tract infections (UTIs), bloodstream infections, pneumonia, lower respiratory tract infections, and other diseases (Lutgring and Limbago, 2016; Lee et al., 2017).

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Thus, antibiotic resistance among Enterobacterales is clinically important (Suay-Garcia and Perez-Gracia, 2019). Among antibiotic-resistant bacteria, carbapenem-resistant Enterobacterales (CRE) was listed as one of the top three classes of antibiotic-resistant bacteria by the WHO in 2017, and CRE has been referred to as superbug bacteria (Muscarella, 2014; Ma et al., 2023). CRE infections not only have a higher mortality rate and health costs than carbapenem-susceptible bacterial infections, they also have 60% resistance rates in China, and in certain regions, such as North America, Europe, and South Asia, they are now endemic (Bonomo et al., 2018; Ma et al., 2023). Epidemiological studies show that the most common CRE species are *K. pnuemoniae*, *E. coli*, *E. cloacae*, and *Citrobacter* (Zhang et al., 2018; Ma et al., 2023).

Carbapenem is a β-lactam antibiotic that inhibits bacterial cell wall synthesis and is the last-resort drug that can treat MDR bacterial infections (Papp-Wallace et al., 2011). The main drugs of carbapenem antibiotics are meropenem, doripenem, ertapenem, and imipenem, and if they are resistant to at least one of these drugs, they are defined as CRE (Nicolau, 2008; Tompkins and van Duin, 2021). The Clinical and Laboratory Standards Institute (CLSI) has determined that the standards of resistance are a minimum inhibitory concentration (MIC) of ≥ 2 μg/mL against ertapenem and ≥ 4 μg/mL against meropenem, doripenem, and imipenem.

CRE resistance mechanisms are divided into carbapenemase-producing CRE (CP-CRE), which β-lactam ring hydrolyzes by carbapenemase, and non-CP-CRE, which includes mutations in porin, production of other β-lactamase, and overexpressed efflux pumps (Potter et al., 2016; Lutgring, 2019; Suay-Garcia and Perez-Gracia, 2019; Ma et al., 2023). Carbapenemases come from ambler classes A, B, or D. The most common carbapenemases are *K. pneumoniae* carbapenemase-Class A (KPC), New Delhi-metallo-β-lactamase-Class B (NDM), Verona integron-encoded metallo-β-lactamase-Class B (VIM), imipenemase metallo-β-lactamases-Class B (IMP), and oxacillinase-48-ClassD (OXA-48) (Potter et al., 2016). CP-CRE are more dangerous than non-CP-CRE (Tamma et al., 2017). Since carbapenemase genes are found on mobile genetic elements, they can be transferred among naïve bacteria (Lutgring and Limbago, 2016).

In therapeutic science, traditional drugs, such as fosfomycin, aminoglycosides, colistin, tigecycline, and aztreonam, are still being used for CRE, but they have limits. Therefore, combination treatments, such as ceftazidime-avibactam, meropenem-varbobactam, ceftazidime-avibactam-aztreonam /ertapenem, and imipenem-relebactam, as well as novel treatments, such as plazomicin, cefiderocol, phage therapy, and zidebactam, are being developed (Potter et al., 2016; Suay-Garcia and Perez-Gracia, 2019; Tompkins and van Duin, 2021). The more potent treatments for CRE infections are meropenem-vaborbactam, imipenem-relebactam, plazomicin, cefiderocol, and aztreonam-avibactam (Tilahun et al., 2021). Moreover, new drugs are currently being developed, such as nacubactam and LYS228 (Tompkins and van Duin, 2021).

In this review, epidemiology, antibiotic resistance mechanisms, and treatment options for CRE were summarized to better understand and manage CRE infections.

1. Resistance mechanisms of CRE

CRE is largely divided into two groups: CP-CRE and non-CP-CRE (Lutgring, 2019). CP-CRE become resistant by producing carbapenemase that hydrolyzes carbapenem belonging to β-lactam. Non-CP-CRE acquire resistance through factors other than carbapenemase. Typically, it has cases that produce other β-lactamase, lose the function of porin, or overexpress the efflux pump (Suay-Garcia and Perez-Gracia, 2019).

1-1. Carbapenem-producing CRE (CP-CRE)

Carbapenemases are enzymes that hydrolyze β-lactam antibiotics such as penicillins, cephalosporins, monobactams, and carbapenems. They are frequently carried by mobile genetic elements, such as plasmids and transposons (Queenan and Bush, 2007; Lutgring and Limbago, 2016). Carbapenemases are potentially dangerous because their resistant genes are likely to spread to naïve bacteria (Lutgring and Limbago, 2016). CP-CRE have a higher MIC, are more virulent, and have a higher mortality rate than non-CP-CRE (Tamma et al., 2017). CP-CRE, which has these characteristics, are the major resistance mechanisms (Suay-Garcia and

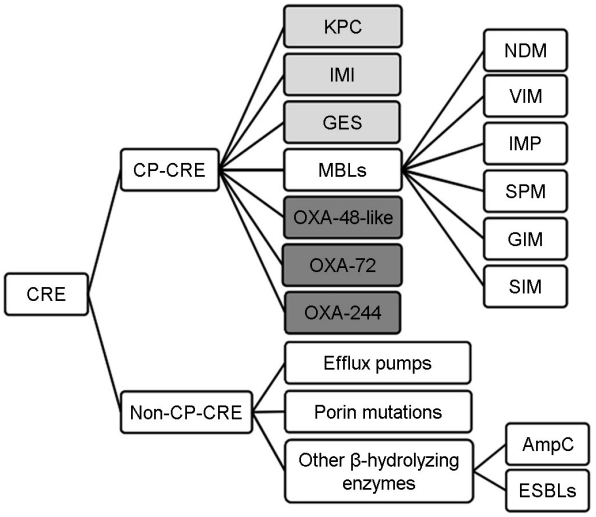

Fig. 1. Classification of CRE by mechanisms of drug resistance. Classification of the different mechanisms of drug resistance in CRE (Light grey: Ambler class A, White: Ambler class B, Dark grey: Ambler class D) (CRE: Carbapenem-resistant Enterobacteriaceae; CP: carbapenemase producing; KPC: *Klebsiella pneumoniae* carbapenemase; IMI: Imipenem-hydrolyzing β-lactamase, GES: Guiana extended-spectrum β-lactamase; MBLs: Metallo-β-lactamase; OXA: oxacillinase; NDM: New Delhi metallo-β-lactamase; VIM: Verona integron-borne metallo-β-lactamase; IMP: Imipenem-resistant *Pseudomonas* carbapenemase; SMP: Sao Paulo metallo-β-lactamase; GIM: German imipenemase; SIM: Seoul imipenemase; AmpC: Type C ampicillinase; ESBLs: Extended-spectrum β-lactamase). The illustration is adapted from Suay-Garcia and Perez-Gracia, 2019.

Perez-Gracia, 2019). There is also the Ambler class of CP-CRE. The Ambler class is divided from Classes A to D. The active sites of Classes A, C, and D CP-CRE are serine, and the active site of Class B CP-CE is the zinc ion (Queenan and Bush, 2007). Classes A, C, and D are inhibited by clavulanic acid and tazobactam, and MBL, whose active site is Zn^{2+}, is inhibited by EDTA and dipicolinic acid (DPA) (Ma et al., 2023). However, only A, B, and D are defined as carbapenemase because Class C cannot hydrolyze carbapenem (Queenan and Bush, 2007; Ma et al., 2023) (Fig. 1).

1-1-1. Class A

Class A carbapenemase was first detected in *Serratia marcescens* in 1990 in the United Kingdom (Yang et al., 1990). This class includes non-metallo carbapenemase/ imipenemase (NMC/IMI), *S. marcescens* enzyme (SME), Guiana extended-spectrum (GES), and *Klebsiella pneumoniae* carbapenemase (KPC). All of these enzymes can hydrolyze β-lactams, including penicillins, carbapenems, cephalosporins, and aztreonam, and are inhibited by clavulanic acid and tazobactam (Queenan and Bush, 2007). ^{bla}GES are only extended-spectrum β-lactamases (ESBLs), however, if it has a point mutation, they can confer hydrolytic against carbapenems such as imipenem (Queenan and Bush, 2007; Dang et al., 2016). Plasmid-encoded enzymes are KPC, and GES, and chromosomally encoded enzymes are SME, NMC, and IMI (Queenan and Bush, 2007).

The most common Class A carbapenemase in Enterobacterales is KPC (Potter et al., 2016). The KPC family is located on plasmids; therefore, they have powerful potential, such as acquired multidrug resistance to β-lactams for spread, and they are frequently found in *K. pneumoniae* (Ji et al., 2015; Porreca et al., 2018). KPC was first discovered in a *K. pneumoniae* clinical isolate in 1996 in the United States (Yigit et al., 2001). However, KPC has also been found in *E. coli*, *K. oxytoca*, *S. enterica*, *C. freundii*, *E. aerogenes*, *E. cloacae*, *Proteus mirabillis*, and *S. marcescens*, and *Pseudomonas* species (Suay-Garcia and Perez-Gracia, 2019; Tompkins and van Duin, 2021).

1-1-2. Class B

Class B carbapenemase was first detected in *Bacillus cereus*, which are opportunistic pathogenic bacteria that exist in the environment (Queenan and Bush, 2007). This Metallo-β-lactamase (MBLs) class includes New Delhi metallo-β-lactamase (NDM), Imipenem-resistant *Pseudomonas* carbapenemase (IMP), and Verona integron-borne metallo-β-lactamase (VIM) (Codjoe and Donkor, 2017). All of these enzymes can hydrolyze all β-lactams except monobactams such as aztreonam (Queenan and Bush, 2007). These enzymes, which are located on mobile genetic elements, have a high potential for horizontal transfer, resulting in problems (Walsh, 2005).

The NDM family is the most common gene in this class in Enterobacterales. The most common species are *K. pneumoniae* and *E. coli* (Wu et al., 2019). Plasmids with NDM enzymes may have other β-lactamases and aminoglycosides that have resistance determinants (Suay-Garcia and Perez-Gracia, 2019). In addition, the rate of NDM

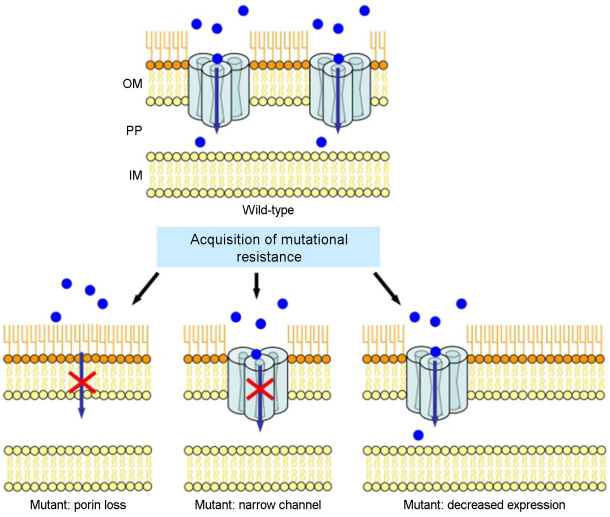

Fig. 2. Resistance mechanism of porins. Examples of different mechanisms of acquiring mutational resistance associated with porins. The blue circles represent the antibiotic molecules, and the red cross indicates that the antibiotic cannot cross the outer membrane. Abbreviations: IM, inner membrane; OM, outer membrane; PP, periplasmic space. The illustration is adapted from Fernández and Hancock, 2012.

infection has increased over the years, resulting in this enzyme being a particular concern given its rapid spread and limited treatment options (Wu et al., 2019; Ma et al., 2023). The IMP was first discovered in this class, and it is common in China, Japan, and Australia (Potter et al., 2016; Tompkins and van Duin, 2021). VIM was first detected in Italy in 1997 (Suay-Garcia and Perez-Gracia, 2019), and it has a high prevalence rate in Greece, Italy, Spain, and Hungary (Tompkins and van Duin, 2021).

1-1-3. Class D

Class D is called oxacillinase (OXA), and it can hydrolyze penicillin and oxacillin (Queenan and Bush, 2007; Potter et al., 2016). OXA-encoding genes are mostly found in *Acinetobacter* species (Tompkins and van Duin, 2021). Over 1000 OXA enzymes have been identified, the most prevalent of which is OXA-48 (Ma et al., 2023). In Europe, the most common OXA enzyme is OXA-48 (Tompkins and van Duin, 2021). Also, the number of carbapenemase hydrolyzing Class D (CHDLs) appearing in the world is increasing. Furthermore, they occur more frequently than Class A and B carbapenemases (Potter et al., 2016).

1-2. Non-carbapenem-producing CRE (Non-CP-CRE)

The first case involves producing another β-lactamase including ESBL and AmpC cephalosporinase (Suay-Garcia and Perez-Gracia, 2019). ESBL and AmpC type β-lactamase rarely hydrolyze carbapenem, but they become resistant to antibiotics when these enzymes are overexpressed, leading to mutations in the porin located in the outer membrane protein (OMP) and increased efflux pump activity which can case reduced antibiotic inflow (Queenan et al., 2010; Goodman et al., 2016; Codjoe and Donkor, 2017).

The second case involves loss of porin function. Enterobacterales belong to Gram-negative bacteria. Gram-negative bacteria are surrounded by the outer membrane, and the OMP mainly serves as a permeable barrier. Porin is a water-filled channel that facilitates the absorption of hydrophilic compounds (Fernández and Hancock, 2012). Porin has different types for each bacteria. For example, *K. pneumoniae* has ompK35 and ompK36, and *E. coli* has ompF and ompC (Ma et al., 2023). OmpK35 and ompK36 are homologues of ompF and ompC, respectively (Mmatli et al., 2020). These porins allow nutrients and antibiotics to enter the bacteria (Fig. 2). When these proteins are lost or mutated, bacteria become resistant to antibiotics (Tsai et al., 2013). A research paper was published in Seoul, Republic of Korea, in 2007. It states that combinations that produce other β-lactamases, such as AmpC, at the same time as the expression of this OMP, have a high mortality rate (Shin et al., 2012). Additionally, bacteria with a double mutation in this OMP are known to have increased MIC about meropenem (Ma et al., 2023).

The third case is the overexpression of efflux pump. Bacteria operate pumps that can be ejected out of the cell to prevent the accumulation of harmful toxins or antibiotics in the cell. These are called efflux pumps (Fernández and Hancock, 2012) (Fig. 3). There are two main types of efflux pumps: ATP-binding cassette (ABC) transporter and secondary multidrug transporter (Fernández and Hancock, 2012). There are four types of secondary multidrug transporters, one of which is resistance-nodulation-division (RND), which in turn is one of Enterobacterales' multi-resistance mechanisms (Suay-Garcia and Perez-Gracia, 2019). The most common RND pump is AcrAB-TolC of *E. coli* (Fernández and Hancock, 2012). AcrAB-TolC is composed

of acrA, acrB, and tolC, and when there is a mutation in acrR, an inhibitor of acrAB-TolC, acrB is overexpressed, causing the efflux pump to be overexpressed as well, which increases antibiotic resistance (Weston et al., 2018; Ma et al., 2023). These resistant genes could easily be transferred to other microorganisms through plasmids (Courvalin, 1994). Therefore, we need to make sure that this pump gene is only expressed when necessary.

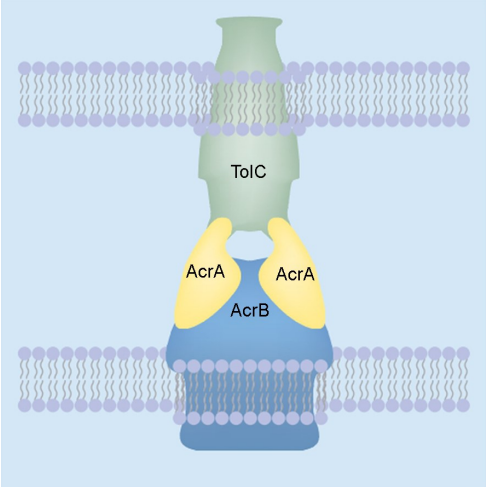

Fig. 3. Schematic diagram of the AcrAB-TolC complex. The illustration is adapted from Colclough et al., 2020.

2. Prevalence of carbapenemase in different countries

According to studies in various countries, carbapenemase genes are distributed by country (Fig. 4, Table 1). In Greece, the KPC gene was the most common and it is accounting for 75%, and the NDM gene was 25% in *K. pneumoniae* (Tsilipounidaki et al., 2022). In China, the carbapenemase gene was found in most CRE clinical strains. KPC was found to be the most common carbapenemase in *K. pneumoniae* (76.5%) and *Serratia marcescens* (50%), and NDM-5 was mainly observed in *E. coli* (52.1%) and NDM-1 was *E. cloacae* (50.3%), *C. freundii* (54.5%), and *K. oxytoca* (48.3%) (Wang et al., 2018). In the U.S. and Brazil, the proportion of KPC-producing strains was also high. In the U.S., the most of strains that produce carbapenemase are *K. pneumoniae* (80%). The most common are KPC-2 (51%) and KPC-3 (41%) (Van Duin et al., 2020). In Brazil, 94.7% of CRKP strains produced KPC enzymes, and some also

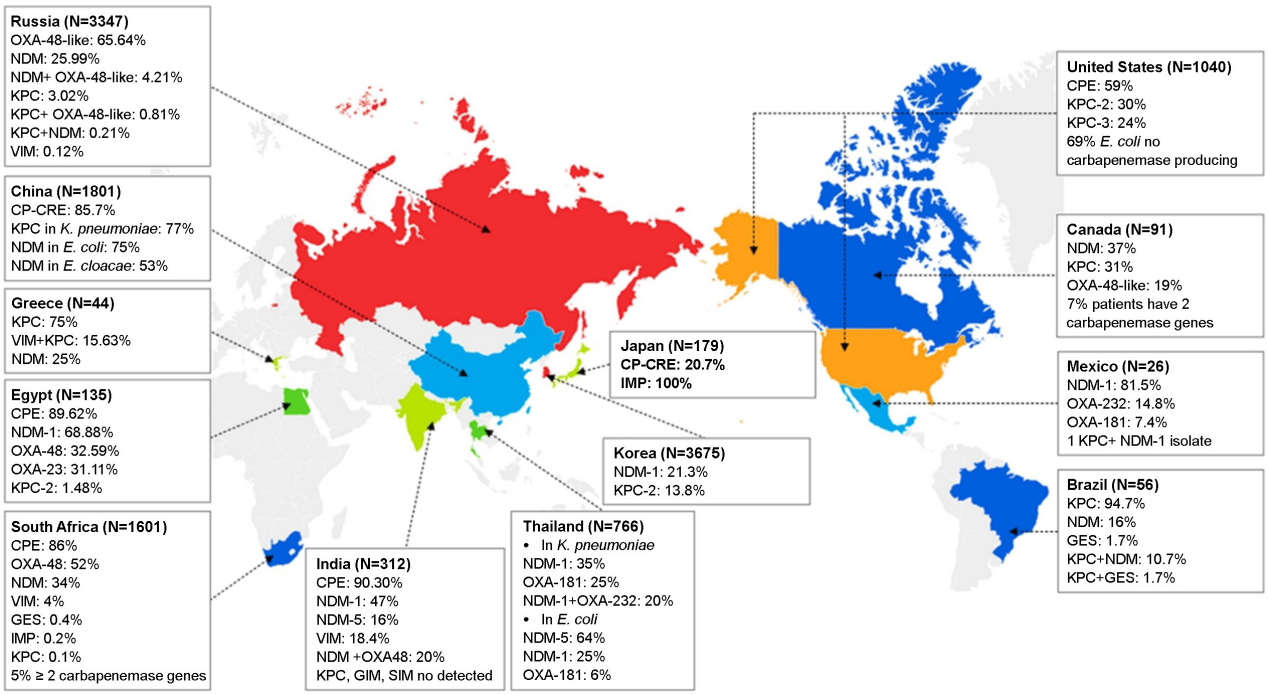

Fig. 4. Carbapenemase distribution in different countries and regions worldwide. Different colors are used to distinguish different countries and regions. The illustration is adapted from Ma et al., 2023.

Table 1. Prevalence of carbapenemase in different countries

Country	Dominant enterobacteriaceae	Common carbapenemase gene	Reference
Greece	*K. pneumoniae*	KPC (75%), NDM (25%)	Tsilipounidaki et al., 2022 Wang et al., 2018 Van Duin et al., 2020 Ma et al., 2023 Garg et al., 2019 Jamal et al., 2021 Garza-González et al., 2021 Tawfick et al., 2020 Perovic et al., 2020
China	*K. pneumoniae*	KPC (76.5%)	
	S. marcescens	KPC (50%)	
	E. coli	NDM-5 (52.1%)	
	E. cloacae	NDM-1 (50.3%)	
	C. freundii	NDM-1 (54.5%)	
	K. oxytoca	NDM-1 (48.3%)	
U.S.	*K. pneumoniae*	KPC-2 (51%), KPC-3 (41%)	
Brazil	*K. pneumoniae*	KPC (94.7%), NDM (16%)	
Thailand	*K. pneumoniae*	NDM (65%)	
India	*E. coli*	NDM (63%)	
Republic of Korea	*K. pneumoniae*	NDM (21.3%)	
Canada	*K. pneumoniae*	NDM (37%), KPC (31%)	
Mexico	*E. cloacae*	NDM (81.5%)	
Egypt	*K. pneumoniae*, *E. coli*	NDM-1 (68.88%), OXA-48 (32.59%)	
South Africa	*K. pneumoniae*	OXA-48 (52%), NDM (34%), VIM (4%)	
Russia	*E. coli*	NDM (71.92%)	
	K. pneumoniae	OXA-48-like (65.54%)	
Japan	*E. cloacae*, *K. aerogenes*	IMP (100%)	

produced NDMs (16%) (Ma et al., 2023). Similarly, NDM (65%) was the most common carbapenemase in Thailand (Ma et al., 2023). Also, NDM (63%) was the majority in India, and the most common strain was *E. coli* in Enterobacteriacae (Garg et al., 2019). This trend has also been observed in other countries. In the Republic of Korea, NDM (21.3%) was more common than KPC (13.8%) (Ma et al., 2023). In addition, KPC-2 accounted for 97.95% of the KPC type, and NDM-1 accounted for 79.25% of the NDM type (Baek and Shin, 2023). In Canada, the majority isolate was *K. pneumoniae* (44%). NDM (37%) and KPC (31%) are competing carbapenemase genes (Jamal et al., 2021). In Mexico, NDM (81.5%) appeared exclusively, and in Egypt, NDM-1 (68.88%) and OXA-48 (32.59%) were mainly observed. *E. cloacae* showed higher resistance to carbapenems in Enterobacteriaceae isolates in Mexico, and in Egypt, *K. pneumoniae* and *E. coli* were the majority isolates (Tawfick et al., 2020; Garza-González et al., 2021). In Russia, NDM (71.92%) was the most common carbapenemase in *E. coli*, and OXA-48-like (65.54%) was in *K. pneumoniae* (Ma et al., 2023).

Finally, there were various distributions of carbapenemase genes in South Africa and Japan, OXA-48 (52%), NDM (34%), and VIM (4%) were common types, and the predominant species is *K. pneumoniae* in South Africa. *E. cloacae* complex and *K. aerogenes* were found more than *K. pneumoniae* and *E. coli* in Japan, and IMP carbapenemase was observed in all strains which are dominant species (Perovic et al., 2020; Ma et al., 2023). The different distributions of carbapenemase genes in each country and region indicate that different response strategies and attention must be paid to cross-border movement in each region.

3. Current antibiotic therapy of CRE infection

Carbapenem continues to be used as a treatment for Enterobacterales (Suay-Garcia and Perez-Gracia, 2019). However, it has been clinically noted that resistance to this drug is rising. Furthermore, depending on the type of CRE in question, it may be resistant to various antibiotics. These CREs can be treated with traditional antibiotics, a combin-

Table 2. CRE therapy options

Antibiotic option	Agent	Mechanism	Reference
Traditional	Fosfomycin	Inhibitor of cell wall production	Blais et al., 2018 Krause et al., 2016 Lin et al., 2017 Liu et al., 2020 Lomovskaya et al., 2017 Ma et al., 2023 Rahman and Koh, 2020 Potter et al., 2016 Shankar et al., 2017 Shields and Doi, 2019 Shirley, 2018 Silver, 2017 Suay-Garcia and Perez-Gracia, 2019 Tilahun et al., 2021 Wu et al., 2020 Zou et al., 2023
	Aminoglycosides	Protein synthesis inhibitors	
	Colistin (Polymixin)	Inhibit cell membrane production	
	Tigecycline (Tetracycline)	Protein synthesis inhibitor	
Combination therapy	Ceftazidime+avibactam +aztreonam/ertapenem	Cell wall production inhibitor/ B lactamase inhibitor	
	Meropenem+vaborbactam	Cell wall production inhibitor/ B lactamase inhibitor	
	Imipenem+relebactam	Cell wall production inhibitor/ B lactamase inhibitor	
Novel drug	Plazomicin (Aminoglycoside)	Protein production inhibitor	
	Eravacycline (Tetracycline)	Protein production inhibitor	
	Cefiderocol (Cephalosporin)	Cell wall synthesis inhibitor	
Novel therapy	Phage therapy	–	
Currently in development	Zidebactam	B lactamase inhibitor	
	Taniborbactam	B lactamase inhibitor	
	LYS228 (monobactam)	Cell wall production inhibitor	
	Nacubactam	B lactamase inhibitor	

ation of antibiotics, novel drugs, and newly developed drugs (Karaiskos et al., 2019; Tompkins and van Duin, 2021). We indicated the characteristics of these options in Table 2.

3-1. Traditional antibiotics for treatment of CRE infection

Traditional antibiotics show activity in several CREs. These antibiotics include fosfomycin, aminoglycosides, colistin, and tigecycline (Tompkins and van Duin, 2021). Fosfomycin is an antibiotic that is effective against gram-positive and gram-negative bacteria, especially a wide range of bacteria acting as antibiotics that inhibit cell wall synthesis against Enterobacterales (Silver, 2017). However, it is not suitable for upper urinary tract infections and is also sparingly used for the treatment of lower UTIs (Tilahun et al., 2021; Tompkins and van Duin, 2021). Aminoglycoside is a powerful and extensive antibiotic that acts through protein synthesis inhibition (Krause et al., 2016). It is still considered a primary treatment for carbapenem-resistant *K. pneumoniae* (CRKP) infections. Among aminoglycosides, gentamicin is the most commonly used; however, amikacin could be considered a useful alternative in certain situations (Suay-Garcia and Perez-Gracia, 2019). Colistin and polymyxin have long been used as antibiotics to treat resistant gram-negative bacteria, especially CRE. However, resistance to these antibiotics is gradually developing. The drugs are also considered nephrotoxic and have negative side effects. Nevertheless, colistin plays a particularly important role in the treatment of CRE infections and can reduce mortality when used as a combination therapy, such as colistin meropenem (Suay-Garcia and Perez-Gracia, 2019; Tompkins and van Duin, 2021). Tigecycline is the first glycylcycline antibiotic to act as a broad-spectrum antibiotic for gram-positive and gram-negative infections, and most Enterobacterales isolates are known to be sensitive to this antibiotic (Shankar et al., 2017). Tigecycline has been successfully used to treat CRE; however, recent studies have shown that monotherapy has limited effectiveness, and combination therapy is expected to be more effective (Tilahun et al., 2021).

3-2. Combination therapy for the treatment of CRE infection

Combination therapy is an approach to treating infections with two or more antibiotics. These therapeutic strategies

are used to discourage the development of resistance to a single antibiotic and to more effectively suppress bacteria.

There are Ceftazidime+avibactam+aztreonam / ertapenem, meropenem+vaborbactam, and imipenem+relebactam which are β-lactam / β-lactamase inhibitor combinations (Suay-Garcia and Perez-Gracia, 2019; Tompkins and van Duin, 2021). Ceftazidime+avibactam is effective against β-lactamase from ambler Classes A, C, and D. However, this therapy is not effective against Class B MBLs (Shirley, 2018). With this approach, the use of ceftazidime+avibactam with aztreonam, which has activity against mannose-binding lectins (MBLs), has been shown to improve activity against MBLs (Ma et al., 2023). This therapy is considered a very promising treatment option for the NDM-producing-Enterobacterales. The important point at this time is that aztreonam can be degraded by other β-lactamases that accompany MBLs (Shields and Doi, 2019). Additionally, the use of ceftazidime+avibactam with ertapenem has been used to successfully treat multi-drug resistant *K. pneumoniae* expressing ^{bla}NDM-1 in the U.S. hospital (Potter et al., 2016).

Meropenem+varbobactam is largely effective against Class A carbapenemase, especially KPC. However, it is not effective against Class B and Class D carbapenemase (Lomovskaya et al., 2017). Therefore, it can have limited utility in areas where MBLs and OXA-48-like enzymes mainly appear.

Imipenem+relebactam is the most recent drug combination, and it is effective against Class A carbapenemase. On the other hand, it is not effective against MBLs and shows little or no activity against OXA-48-like carbapenemase (Tompkins and van Duin, 2021).

3-3. Novel drugs and newly developed drugs treating of CRE infections

Plazomicin is a novel semi-synthetic aminoglycoside that inhibits protein synthesis. Plazomicin has extensive activity against Enterobacterales and is effective against ESBL enzymes and various CRE enzymes, including KPC, VIM, IMP, and OXA-48. However, its effect against MBLs, such as NDM-1, may be limited (Tompkins and van Duin, 2021).

Eravacycline is a novel, fully synthetic fluorocycline that inhibits protein synthesis in bacteria. It has extensive antimicrobial activity against gram-positive, gram-negative, and anaerobic bacteria. It is also effective against bacteria resistant to other antibiotic families. However, it is inactive against *Pseudomonas* species (Zou et al., 2023). Eravacycline is effective against CRE enzymes such as KPC, VIM, NDM-1, and OXA-48 and has a lower MIC than tigecycline (Tompkins and van Duin, 2021).

Cefiderocol is a novel cephalosporin that facilitates cell membrane synthesis and stops overexpression-related resistance of pump and porin channel mutations (Rahman and Koh, 2020). Cefiderocol is active against CRE enzymes, such as KPC, NDM, VIM, IMP, and OXA-48 enzymes, in *in vitro* studies (Wu et al., 2020).

Phage therapy, which is a treatment method that utilizes a naturally occurring virus called bacteriophage to infect and destroy bacteria, is being re-examined. These bacteriophages attach to the surface receptors of the target bacteria and transfer viral genetic information into the bacterial cells. Bacteria use this genetic information to generate copies of viruses and package new viral particles to destroy them through cell rupture. This kills infected bacterial cells and causes new viral particles to infect the target bacteria in a self-replicating process which may require repeated administration in clinical practice (Lin et al., 2017; Tompkins and van Duin, 2021).

Various drugs are currently being developed, including zidebactam, nacubactam, LYS228, and taniborbactam (Tompkins and van Duin, 2021). Zidebactam and nacubactam have a high affinity to beta-lactamase, which corresponds to Ambler Classes A and C (Suay-Garcia and Perez-Gracia, 2019). Zidebactam, in particular, is active against KPC, OXA-48, and several Class B carbapenemases when combined with cefepime (Tompkins and van Duin, 2021). Nacubactam exhibits strong *in vitro* activity against Class A, D carbapenemase, and Class C ESBL enzymes when combined with meropenem (Tompkins and van Duin, 2021). Taniborbactam, a pan-spectrum β-lactamase inhibitor, inhibits ambler Classes A, B, C, and D beta lactamase (Liu et al., 2020). LY228 is a monobactam antibiotic similar to aztreonam that is effective against ESBLs, SBLs such as Class A, C, and D, and MBLs such as Class B in *in vitro* studies (Blais et al., 2018).

CONCLUSION

The number of patients with suppressed or decreased immunity is increasing rapidly due to existing surgical practices, drug treatments, and immunosuppressive treatments. CRE infections are rapidly spreading in medical institutions, where many of these patients are being cared for. Furthermore, as resistance to various antibiotics increases, these bacteria cause various diseases, such as sepsis through bloodstream infections and urinary tract infections, making them difficult to treat. The most common of these CRE species are *K. pneumoniae* and *E. coli*.

CRE becomes resistant by forming enzymes, mutation porin or efflux pumps, or producing another β-lactamase. The most common resistance mechanism is the production of carbapenemase enzymes. These enzymes vary by country. In China, Greece, the U.S., and Brazil, KPC is the main enzyme. NDM is the main enzyme in the Republic of Korea, Egypt, Canada, Mexico, Thailand, and India. Oxa-48 is the main enzyme in South Africa, and Russia. IMP is the main enzyme in Japan.

The latest antibiotics approved and already being used to treat CRE infections are ceftazidime+avibactam, meropenem +varbobactam, plazomicin and eravacycline. CRE is a gram-negative bacteria, unlike gram-positive bacteria, that has an outer membrane, so it can interact with various bacteria. Therefore, CRE is more dangerous because antibiotic-resistant genes are likelier to be transferred to other types of bacteria.

These infections are also expanding into communities.

In conclusion, this review paper was introduced various antibiotic resistance mechanisms and treatment options for CRE and present the importance of infection control for CRE. Therefore, new attempts are needed to further identify the antibiotic resistance in CRE, development of diagnostic tests to quickly detect it, and efforts to provide efficient preventative treatment and infection control within hospital or the community.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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