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REVIEW

Emerging Carbapenem-Resistant *Enterobacteriaceae* Infection, Its Epidemiology and Novel Treatment Options: A Review

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Abstract: Infections due to multidrug-resistant *Enterobacteriaceae* have become major international public health problem due to the inadequate treatment options and the historically lagged pace of development of novel antimicrobial drugs. Inappropriate antimicrobial use in humans and animals coupled with increased global connectivity aided to the transmission of drug-resistant *Enterobacteriaceae* infections. Carbapenems are the medications of choice for extended-spectrum beta-lactamase and AmpC producers, but alternatives are currently needed because carbapenem resistance is increasing globally. This review pointed to discuss emerging drug-resistant *Enterobacteriaceae*, its epidemiology and novel treatment options for infections, which date back from 2010 to 2019 by searching Google Scholar, PubMed, PMC, Hinari and other different websites. The occurrence of carbapenem-resistant *Enterobacteriaceae* is reported worldwide with great regional variability. The rise of carbapenem-resistant *Enterobacteriaceae* poses a threat to all nations. Enzyme synthesis, efflux pumps, and porin mutations are the main methods by which *Enterobacteriaceae* acquire resistance to carbapenems. The major resistance mechanism among these is enzyme synthesis. Most carbapenem resistance is caused by three enzyme groups: *Klebsiella pneumoniae* carbapenemase (Ambler class A), metallo-ß-lactamases (Ambler class B), and oxacillinase-48 (Ambler class D). Ceftazidime–avibactam, which was newly licensed for carbapenemase producers, is the most common treatment option for infections. Meropenem–vaborbactam, imipenem–relebactam, plazomicin, cefiderocol, eravacycline, and aztreonam–avibactam are recently reported to be active against carbapenem-resistant *Enterobacteriaceae*; and are also in ongoing trials for different populations and combinations with other antibacterial agents. Overall, treatment must be tailored to the patient's susceptibility profile, type and degree of infection, and personal characteristics.

Keywords: multidrug resistance, antimicrobial therapy, carbapenemase, *Enterobacteriaceae*

Introduction

The causative agent of an infectious disease whose incidence is increasing following its appearance in a new host population or whose incidence is increasing in an existing population as a result of long-term changes in its underlying epidemiology or the development of antimicrobial resistance has been defined as an emerging antibiotic-resistant pathogen.[1] Carbapenem-resistant *Enterobacteriaceae* (CRE) infections result in longer hospital admissions, higher healthcare costs, and increased mortality than carbapenem-susceptible bacterial infections.[2]

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The Enterobacteriaceae family includes many bacteria that are commonly isolated from clinical cultures, including *Escherichia coli, Klebsiella* spp., and *Enterobacter* spp. Because *Enterobacteriaceae* are a common cause of both community and healthcare-related diseases, they are particularly important in the context of antibiotic resistance.[3] The Enterobacteriaceae family has developed through time and has an innate ability to proliferate by developing resistance to antimicrobial chemicals provided, rendering existing antibacterial ineffective, and emerging as resistant to carbapenem, a last-line antibiotic.[4,5]

In the human and animal colons, *Enterobacteriaceae* is mostly found as part of the normal flora. According to the World Health Organization's antimicrobial resistance report, *Enterobacteriaceae* resistant to carbapenem are classified as a critical group and developing drug-resistant infections.[6,7] According Centers for Disease Control (CDC) description of the antimicrobial-resistant pathogens, CRE such as *Klebsiella* species, *Escherichia coli* (*E.coli*) and *Enterobacter* species are the most crucial emerging resistance threats in the global.[8]

Bacterial infections caused by CRE, which are resistant to all classes of current antimicrobial drugs, have become a serious endpoint in the fight against bacterial infections in public health.[9–11] Furthermore, the rise of carbapenem resistance and rapid dissemination of the *Enterobacteriaceae* family are referred to as "superbugs bacteria".[12,13]

Because of the emergence of the CRE family, therapeutic approaches are no longer effective, and infections are more difficult to cure with the commonly used medications. As a result, infections would spread, longer hospital admissions would increase economic and social expenses, and death would rise.[14] Carbapenem-resistant bacteria pneumonia, urinary tract infections, septicemia, endocarditis, meningitis, and severe intra-abdominal infections are only a few of the illnesses caused by *Enterobacteriaceae*.[15] Due to the synthesis of extended spectrum beta-lactamase (ESBL), *Enterobacteriaceae* have developed resistance to third-generation cephalosporins, making therapy very challenging.[16] The introduction and spread of bacteria resistant to carbapenems, on the other hand, puts their effectiveness in threat.[17,18] To combat this threat, the medical community turned to broader spectrum agents and carbapenems, which in turn contributed to resistance due to selection and increased the emergence of increasingly resistant organisms.[19]

Carbapenem resistance in Enterobacteriaceae is mostly expressed by the synthesis of carbapenemase enzymes, which are encoded by numerous genotypes and can be transferred among *Enterobacteriaceae* via transferable genetic elements. Commonly pronounced enzymes include Class A *Klebsiella pneumoniae* carbapenemase, Class B metallo-β- lactamases, and Class D OXA β-lactamases.[20] Resistance can also be developed through efflux pumps, permeability changes caused by the loss of outer membrane porin, or target mutations.[21] Resistance is enhancement to be a continuous evolutionary process in the *Enterobacteriaceae* family. Mutation is a type of genetic change that occurs frequently in nature. Mutations in genetic structures can affect a cell's ability to grow and survive in the presence of environmental stresses like antimicrobials.[22]

However, novel medications for treating CRE infection have just been accessible, and several more are in the works. While traditional drugs such as fosfomycin, tigecycline, minocycline, polymyxin and other therapeutic alternatives are still being used as therapy for CRE infections, recently emerged drugs including meropenem–vaborbactam, imipenem–relebactam, plazomicin, cefiderocol, eravacycline, and aztreonam–avibactam are more potent against CRE infections with fewer side effects and toxicities. Moreover, copper oxide nanoparticles, phage therapy and varieties of candidate vaccines have also influenced the development of Shigellosis infection.[23]

This review aims to provide an update on the rising carbapenem-resistant *Enterobacteriaceae*, its epidemiology as well as novel treatment options against these increasingly resistant bacteria.[24]

Literature Review

Natural Habitats and Reservoirs of Antibiotic-Resistant *Enterobacteriaceae*

Carbapenem-resistant Enterobacteriaceae (CRE) infections can arise naturally from bacteria found in a healthy person's intestinal tract, as well as soil, water, sewage, plants (fruit, vegetables, and herbs), dairy products, and raw meat, depending on the species.[25] Colonized/infected patients, biofilms from medical equipment, sinks/hand washing basins, faucets, drains, sink traps, toilets with a rim, sewage/drainage system, and contaminated healthcare personnel's stethoscopes are the main reservoirs or sources of infection in healthcare institutions.[26] Shower heads, bars of soap, liquid soap, artificial fingernails,

pools/hot tubs/water fountains, dialysis tubing, infusion pumps, breathing equipment, and cleaning mops all contribute to a damp humid environment.[25]

Drug-resistant *Enterobacteriaceae* and/or resistance genes can spread in a variety of ways, depending on the microbe's robustness in the environment, virulence, and infectious dosage, among other factors. Contact with colonized patients, air, water, food, beverages, and contaminated equipment can all spread them. Furthermore, increased mobility, environmental changes, overcrowding, poor cleanliness, and poor infection management are all contributing to an increase in the rate of transmission.[27]

Risk Groups for Acquiring Carbapenem-Resistant *Enterobacteriaceae*

Prior and recent antibiotic use, residency in long-term acute care facilities, admission to an intensive care unit, presence of indwelling medical devices, poor functional status, increased age, solid organ or stem cell transplant, and receipt of health care in or travel to endemic areas are all risk factors for acquiring MDR Enterobacteriaceae.[28] Patients who need ventilators (breathing machines), urinary (bladder) catheters, or intravenous (vein) catheters, as well as those on extended courses of particular medicines and those with weaker immune systems, are at risk for CRE infections.[29]

Emerging Carbapenem-Resistant *Enterobacteriaceae* and Mechanism of Resistance

Global antimicrobial resistance reports show the rising frequency of resistance in species belonging to the Enterobacteriaceae family in various sources including health facilities and the community. The emergence and dissemination of CRE is the most recent and alarming report globally.[30] Carbapenem-resistant bacteria in the Enterobacteriaceae family have spread widely across numerous fronts. On a biological level, resistance genes are frequently carried on plasmids, which are easily transmitted among *Enterobacteriaceae*. This resistant gene exchange can take place both within a host and in the environment.[31,32]

Antimicrobial resistance can also be caused by the production of antibiotic-inactivating enzymes and non-enzymatic mechanisms, which could be intrinsic or acquired.[33] Increased production of intrinsic resistance mechanisms (either antibiotic-inactivating enzymes or efflux pumps) due to chromosomal gene mutations, permeability changes due to loss of outer membrane porin, or target modifications.[21] Horizontal transfers of mobile genetic elements such as plasmids carrying resistance genes producing beta-lactamase enzymes, aminoglycoside-modifying enzymes (AMEs), or non-enzymatic mechanisms such fluoroquinolone resistance in *Enterobacteriaceae* are among the common mechanisms. Because these plasmids frequently include numerous resistance determinants, a single plasmid conjugation may be enough to transmit multidrug resistance to the recipient strain.[34]

Carbapenem resistance in *Enterobacteriaceae* can be caused by a variety of methods, including the synthesis of Carbapenemase enzymes, extended spectrum beta-lactamases (ESBLs), AmpC enzymes (mainly plasmid-mediated), and porin loss, which reduces drug permeability.[35]

Enterobacteriaceae can develop resistance to one or more antibiotic classes that are normally effective against them. *Klebsiella pneumoniae* carbapenemase (KPC), imipenem's metallo-beta-lactamase (IMP), New Delhi metallo-beta-lactamase (NDM), Verona integron-encoded metallo-beta-lactamase (VIM), and oxacillin carbapenemase (OXA) are among the most important acquired resistances.[36]

Acquisition and Spread of Carbapenem Resistance Among *Enterobacteriaceae*

Resistance genes can also be obtained from bacteria that are not resistant to antibiotics. They can be passed between bacteria of the same species as well as bacteria of different species or genera.[21] Transduction, transformation, and conjugation are examples of horizontal gene transfer mechanisms. Plasmids (resistance plasmid 1 is a common example in *Enterobacteriaceae*), transposons, and other vectors can carry one or more resistance genes (eg, Tn5053).[37] Resistance determinants for other antimicrobial classes, such as aminoglycosides and fluoroquinolones, may be carried by ESBLs and carbapenemase expressing plasmids.[21]

For ESBLs genes in *Enterobacteriaceae* families, the possibility of plasmid-mediated horizontal resistance gene transmission between livestock and humans (eg, via the food chain) has been observed.[38–40] Furthermore, excessive use of antibiotic agents, usage without prescriptions, and use of antibiotics in both the health care system and

livestock production may encourage the diffusion of resistance genes, which has a direct effect on the expansion of antibiotic resistance.[41,42]

Epidemiology

Multidrug-resistant Enterobacteriaceae (MDR-E) is thought to have initially arisen in the 1980s, shortly after the widespread use of cephalosporins and other broad-spectrum ß-lactam antibiotics. SHV and TEM were among the first ESBLs found, followed by CTX-M, which have now expanded to become the most common plasmid-mediated ß-lactamases worldwide. Different carbapenemase-producing Enterobacteriaceae are becoming more prevalent in different parts of the world, according to epidemiological data. Carbapenem-resistant strains were initially discovered in the 1980s and rapidly spread over the world.[43]

New Delhi metallo-ß-lactamase-1 is the most common carbapenemase generating resistance in India, Pakistan, and Sri Lanka. KPC-producing Enterobacteriaceae, on the other hand, are found in the United States, Colombia, Argentina, Greece, and Italy, and OXA-48-like enzyme-producers are found in Turkey, Malta, the Middle East, and North Africa.[44] Another study from 2011 to 2014 in the United States found 10% carbapenem resistance in *Klebsiella pneumoniae* and 16–36% third-generation cephalosporin (3rd GC) resistance in *Escherichia coli*.[45] Another study using clinical isolates in Europe found that *K. pneumonia* is resistant to third GC in 31% of the cases, while *E. coli* is resistant to carbapenem in 8% of the cases and third GC in 12% of the cases.[46]

Before 2001, the Greek System for Antibiotic Resistant Research showed a carbapenem resistance rate of 1%; by 2008, this had risen to 30% in hospital wards and 60% in intensive care units. According to data from the European Centre for Disease Prevention and Control's EARS-Net, 678 (62.3%) of 1088 Greek *K. pneumoniae* isolates were carbapenem-resistant in 2014.[47] In the state of Israel, in 2008 and 2013, two cross-sectional nationwide surveys of CP Enterobacteriaceae (CPE) in Israeli post-acute-care hospitals revealed a considerable drop in the overall incidence of carbapenem resistance among Enterobacteriaceae isolates (184 of 1147 isolates (16%)). KPC-carrying *K. pneumoniae*, on the other hand, remained the most common CPE, with a growing proportion of ST258 *K. pneumoniae* strains (120 of 184 (65%) in 2008 versus 91 of 113 (80%) in 2013).[48]

The Meropenem Annual Drug Susceptibility Data Gathering surveillance system mentioned 57 isolates in 2006, with 9.5% of the gathering characterized as clonal blaKPC-producing Klebsiella strains, representing a two-fold increase from the previous year; most isolates were from states in the Mid-Atlantic US Census division, and hospital prevalence rates ranged from 2.4% in Ohio to 9.5% in Pennsylvania; most isolates were from states in the Mid-Atlantic.[49,50] The spread of KPC-producing bacteria across the United States is clear; according to the same surveillance program, 28 of 195 Enterobacteriaceae isolates (14.4%) tested from 26 US medical centers had blaKPC-2 or blaKPC-3 by 2010, with 9 of the 28 discovered in Texas.[51] In Egypt and other African countries, carbapenem resistance is common and spreading, with more than half of hospitals (64%) having at least one CRE isolate and half (47.9%) of Enterobacteriaceae isolates being CRE, which is greater than estimates from other Arab, African, and Asian countries.[52]

In general, all countries are at risk of being victims to the emergence of carbapenem-resistant Enterobacteriaceae infection with growing prevalence has been reported worldwide.[74]

Prevention and Control

Infections can be controlled by using a multidimensional, coordinated strategy and following infection prevention principles. Specifically, by reducing CRE transmission from person to person.[75] Essentially, avoiding unnecessary or misuse of invasive equipment such as indwelling urinary catheters or IV lines, medical staff hand washing, greater barrier measures, and isolation of patients colonized or infected with carbapenemase producers. Infection management strategies are primarily focused on stopping the spread of such organisms from patient to patient. Apart from that, the main issues are healthcare professionals' hand hygiene, the use and cleaning of medical equipment, and environmental colonization; early implementation of active surveillance through rectal screening for CRE carriage on hospital admission, environmental cleaning, staff education, case notification/flagging, and contact tracing are all necessary to prevent spreading and outbreaks of carbapenemase-producing bacteria spread and outbreaks.[6]

Generally, educating health care workers, using infection control and antimicrobial stewardship, and active surveillance for halting the chain of transmission should all be part of a proactive approach to tackling

antimicrobial resistance at a regional, national, and international level.[53]

Principal Treatment Options

For infections caused by ESBL and AmpC producers, carbapenems are the preferred treatment options. CRE, on the other hand, are resistant to practically all beta-lactams, with a few exceptions, and older antibiotic groups that have acceptable action. As a result, CRE therapy options are more limited, with older treatments such as aminoglycosides, polymyxins, a glycylcycline, and Fosfomycin being particularly effective.[76] Although polymyxins are effective against CRE, they have nephrotoxicity and neurotoxicity as adverse effects, as well as poor effectiveness against *Proteus, Providencia, Morganella*, and *Serratia* infections.[77]

Because tigecycline has a higher binding affinity with ribosomal sites than tetracycline, it has been shown to be an effective therapeutic against *Enterobacteriaceae* that are resistant to tetracycline.[78] Tigecycline is effective against practically all ESBLs and multidrug-resistant (MDR) *E. coli* isolates, as well as the vast majority of ESBL and MDR *Klebsiella* isolates. However, their activity against *Proteus*, Providencia, and *Morganella* is limited.[78] Nevertheless, due to its low penetration and quick tissue diffusion after being intravenously administered, tigecycline has unsatisfactory clinical effects in both urinary tract and main blood infections, making it ineffective.[79]

Fosfomycin is an antibacterial drug that works against CRE by inhibiting the enzyme UDP-N-acetylglucosamine enol pyruvyl transferase (MurA), which catalyzes one of the first steps in bacterial cell wall production. However, it has limited use to treatment for lower urinary tract infections. In vitro and retrospective investigations suggest that, at least for KPC infections, combined therapy with a carbapenem (eg, polymyxin–carbapenem or aminoglycoside–carbapenem) is more effective.[80]

In the case of OXA-48 and NDM infections, a recent retrospective observational analysis concluded that combined therapy with colistin is the best treatment option. Because existing antimicrobial medicines have limitations, new and effective antimicrobial drugs are required for CRE infections.[81] Except for the monobactam aztreonam, aztreonam/avibactam MBLs can hydrolyze any beta-lactams (ATM). However, due to the fact that MBL-producing *Enterobacteriaceae* frequently produce serine-lactamases, which can hydrolyze aztreonam, aztreonam is only effective against about 30% of these isolates. As a result, combining ATM with a -lactam/-lactamase inhibitor like ceftazidime–avibactam (CAZ-AVI) has proven to be an appealing combination with synergistic in vitro efficacy, especially against infections that produce both metallo- and serine-lactamases.[82] Cefiderocol is a new siderophore cephalosporin that enters the bacterial cell via iron transporters, avoiding resistance induced by porin channel mutations and efflux pump overproduction. Cefiderocol also has other chemical structural characteristics that offer greater efficacy against Gram-negative bacteria that are difficult to treat, as well as stability against hydrolysis by different beta-lactamases in vitro, including MBL.[83]

Scientists are concentrating on developing new antibacterial medications to address these pressing challenges b-lactamase inhibitor (NB-BLI) which is avibactam combination with ceftazidime. Ceftazidime–avibactam (CAZ-AVI) is an intravenous cephalosporin/beta-lactamase, which is currently available on the market, and it is also being tested in conjunction with aztreonam and ceftaroline.[84]

Contrasting to other β-lactamase inhibitors, avibactam is not a β-lactam. Rather, its diazabicyclooctane structure mimics a β-lactam and is capable of hindering β-lactamases belonging to Strider classes A and C, and some class D enzymes.[85] Despite not possessing antibacterial activity on its own, avibactam broadens the spectrum of ceftazidime's activity. In isolates of *E. coli*, *Enterobacter* spp., and *Klebsiella* spp. that are carbapenem-resistant or express extended-spectrum B-lactamases, AmpC, OXA-48, KPC, and other resistance mechanisms, this combination enhances sensitivity to ceftazidime by 16- to 1024-fold.[85,86]

Despite the fact that combination therapy is now the gold standard for treating CRE infections, resistance, treatment failure, and toxicity have prompted the development of new therapeutic approaches.[87] Unfortunately, several drugs with anti-CRE activity are in late-stage research. Among these under pipelines agents are plazomicin, relebactam + imipenem, eravacycline, zidebactam and meropenem + novel β-lactamase inhibitor. Each drug is detailed in Table 2.

Overall, therapy must be tailored to the patient's susceptibility profile, type and degree of infection, and personal characteristics. Beyond those unique treatment options, nano-strategies (using nanoparticles) to combat multidrug-resistant bacteria, such as carbapenem-resistant Enterobacteriaceae, and other strategies, such as phage

Table 1 Summary of the Global Prevalence of Carbapenem-Resistant *Enterobacteriaceae*

Study Area		Prevalence of CRE	Authors (Reference)
Europe and America	Belgium	3.46%,	[53]
	Turkey	2.8%,	[54]
	USA	5.7%, 0.08%,	[30,55]
	Latin America	6.6%,	[56]
	Russia	11.6%,	[57]
	Australia	0.1%	[58]
	Poland	17.3%,	[59]
	Italy	7.5%,	[59]
	Greece	7.4%,	[59]
	Romania	5.0%	[59]
Asia	India	13.95%, 12.26% and 37.9%	[60–62]
	Pakistan	69%,	[63]
	Kuwait	8%,	[64]
	China	18.1%	[65]
	Saudi Arabia	1.77%	[66]
	Malaysia	5.76%	[67]
	South India	8%	[68]
	Thailand	97%	[69]
Africa	Nigeria	15.2%	[62]
	Ethiopia	12.12%	[70]
	Uganda	28.6%	[12]
	Egypt	62.7%, 54.5%	[52,71]
	Senegal	5.1%	[72]
	Morocco	2.8%	[73]
	Ethiopia	16.2%	[70]

therapy and vaccine strategies, are being developed to overcome these types of resistance.[96–98]

Ceftazidime–avibactam (CAZ-AVI), ceftolozane–tazobactam (TOL-TAZ), meropenem–vaborbactam (MERVAB) and imipenem/cilastatin–relebactam (IMI-REL) are recently reported to be active against Enterobacteriaceae, including ESBL-producing, AmpC-producing and carbapenemase producing isolates; and are also in ongoing trials for different populations and combinations with other antibacterial. Moreover, β-lactam–sulfone β-lactamase inhibitor combinations including cefepime–tazobactam and cefepime–enmetazobactam (AAI101), β-lactam–diazabicyclooctane β-lactamase inhibitor combinations including cefepime–zidebactam (WCK 5107), aztreonam–avibactam, sulbactam–durlobactam (ETX2514), meropenem–nacubactam (FPI-1465) and cefpodoxime proxetil-ETX0282; and β-lactam–boronate β-Lactamase inhibitor combinations such as cefepime–taniborbactam (VNRX-5133) and QPX7728 are in development processes and under clinical trials, which could be promising future treatment options against ESBL and carbapenemase-producing bacteria.[99]

Possibly in the future many clinical trials and investigations have looked into the efficacy and resistance patterns of CAZ/AVI. Interestingly, the International Network for Optimal Resistance Monitoring (INFORM) studied more than 30,000 strains of *Enterobacteriaceae* obtained from patients with diverse bacterial illnesses and found that these microbes were more susceptible to the CAZ/AVI combination (99.5%).[100]

Ceftazidime–avibactam is the primary treatment for CRE infections that produce OXA-48-like proteins. Ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–cilastatin–relebactam have action against *Enterobacteriaceae* that produce KPC enzymes, which are the most frequent carbapenemase in the US.[101]

Nanoparticles

Because of their bactericidal properties, nanoparticles (NPs) have increased in popularity in recent years and have demonstrated broad-spectrum antibacterial efficacy against pathogenic microorganisms.[96] Nanoparticles typically kill bacteria, causing damage to membrane load cells and their integrity, as well as the production of free oxygen radicals. They can usually be given effectively as antibacterial agents. The bactericidal action of graphene oxide/Cu/Ag NPs against *E. coli* and *K. pneumonia* has recently been discovered, possibly because to a synergy between several harmful pathways.[102] Copper oxide nanoparticles have also been identified as a potential antibacterial agent for the treatment of Shigella spp.[103]

Table 2 List of Antibiotics Used for CRE Infection Treatment and Under Pipeline Development for Future Treatment of CRE Infections

RX. of CRE	Action Mechanism	Mechanism of Action	S/E	Authors
Antibiotics from the past	Fosfomycin	Inhibitor of cell wall production	Appearance of resistance	[88]
	Aminoglycosides	Protein synthesis inhibitor	Appearance of resistance	[15]
	Colistin	Inhibit Cell membrane production	Other serious side effects include nephrotoxicity	[87]
	Tigecycline	Protein synthesis inhibitor	Low concentration in tissue	[89]
Double treatments	Ertapenem with meropenem/ doripenem	Cell wall production inhibitor		[90]
	Ceftazidime or avibactam	Cell wall production inhibitor/ß-lactamase inhibitor	Appearance of resistance	[91]
	Meropenem or vaborbactam	Cell wall production inhibitor or ß-lactamase inhibitor	Inadequate clinical data	[91]
New treatments	Plazomicin	Protein production inhibitor	Unreactive against MBL-producers	[92]
	Eravacycline	Protein production inhibitor	Phase 3 RCT	[86]
	Imipenem or relebactam	Cell wall production inhibitor or ß-lactamase inhibitor	Phase 3 RCT	[93]
	Cefiderocol	Cell wall synthesis inhibitor	Phase 3 RCT	[94]
	Zidebactam	ß-Lactamase inhibitor	Phase 3 RCT	[87]
	Nacubactam	ß-Lactamase inhibitor	Phase 3 RCT	[95]

Abbreviations: ß-Lactamase, Beta lactamase; CRE, carbapenem-resistant *Enterobacteriaceae*; MBL, metallo-β-lactamase; RCT, randomized clinical trial; RX, treatment; S/E, side effects.

Phage Therapy

Phage therapy is increasing in popularity due to a number of benefits, including high specificity to target bacteria without affecting the human body's normal microflora, replication at the infection site, bactericidal activity against antibiotic-resistant bacteria, and fewer side effects than other therapies. Because phages are self-limiting, they can linger on target sites at a low level after killing their bacterial targets.[97] The use of phages as an alternative to antibiotics for treating MDR *S. dysenteries* isolated from wastewater has been studied[104] despite the fact that there have been no reports of serious side effects during the long history of phage therapy in humans.

Vaccine Strategies

To prevent infection by *Shigella* spp., a number of candidate vaccines have been developed, the majority of which are still being tested for safety and immunogenicity. Vaccination provides protection in humans and animals, according to current studies.[98] Glycoconjugate vaccines, such as recombinant glycoconjugate, synthetic glycoconjugate, and O-polysaccharide covalently coupled to immunogenic carrier proteins, are potential candidates for *Shigella* vaccinations,[105] vir G-based live attenuated (WRSS1, WRSs3, WRSf3, WRSf2G12, WRSf2G15 and WRSd1) recombinant outer-membrane proteins, live attenuated vaccines,[106] invasion-plasmid antigens B, C, and D.[107] In addition to this, DNA-based vaccines, Ty21a typhoid vaccine expressing Shigella LPS,[108] and whole-cell-killed and *Shigella* trivalent inactivated whole-cell and heat-killed multi serotype *Shigella*[109] as well as novel antigen candidates, such as triacylated S-LPS, GMMA protein particles currently have been developed.[98] However, there is no licensed vaccine available against this pathogen.

Conclusion and Recommendations

Finally, it is clear that carbapenem resistance in *Enterobacteriaceae* has developed substantially, posing

a serious threat to global health. CRE have once again become a concern to civilization, as evidenced by a steady stream of publications describing resistant strains and sometimes novel resistance mechanisms. Dissemination and acquisition can go undetected, posing serious problems for infection control. Because the Enterobacteriaceae are a typical part of the gut microbiota, people might be colonized asymptomatically and unintentionally serve as a reservoir for spreading the bacteria to others; a subset of people will get illnesses as a result of these bacteria. Drug resistance mechanisms are varied and adaptable in these bacteria, making control and early identification of CRE infections difficult. As a result, a holistic approach must be adopted, which includes continued health-care professional education, infection control, interrupting the infection chain, antimicrobial stewardship in both humans and animals, and increased regional and international collaboration to slow the emergence of resistances. Existing antibiotics such as Fosfomycin, aminoglycosides, and colistin are currently used as therapeutic options for CRE infections, while Avibactam combined with carbapenem-containing regimens is a newly developed antibiotic. Plazomicin, eravacycline, cefiderocol, zidebactam, and nacubactam are among the novel agents in development as new agents for various *Enterobacteriaceae*.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report that they have no conflicts of interest.

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