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# Carbapenem Resistance: Mechanisms and Drivers of Global Menace

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## Abstract

The emergence of carbapenem-resistant bacterial pathogens is a significant and mounting health concern across the globe. At present, carbapenem resistance (CR) is considered as one of the most concerning resistance mechanisms and mainly found in gram-negative bacteria of the *Enterobacteriaceae* family. Although carbapenem resistance has been recognized in *Enterobacteriaceae* from last 20 years or so, recently it emerged as a global health issue as CR clonal dissemination of various *Enterobacteriaceae* members especially *E. coli*, and *Klebsiella pneumoniae* are reported from across the globe at an alarming rate. Phenotypically, carbapenems resistance is in due to the two key mechanisms, like structural mutation coupled with  $\beta$ -lactamase production and the ability of the pathogen to produce carbapenemases which ultimately hydrolyze the carbapenem. Additionally, penicillin-binding protein modification and efflux pumps are also responsible for the development of carbapenem resistance. Carbapenemases are classified into different classes which include Ambler classes A, B, and D. Several mobile genetic elements (MGEs) have their potential role in carbapenem resistance like Tn4401, Class I integrons, IncFIIK2, IncF1A, and IncI2. Taking together, resistance against carbapenems is continuously evolving and posing a significant health threat to the community. Variable mechanisms that are associated with carbapenem resistance, different MGEs, and supplementary mechanisms of antibiotic resistance in association with virulence factors are expanding day by day. Timely demonstration of this global health concern by using molecular tools, epidemiological investigations, and screening may permit the suitable measures to control this public health menace.

**Keywords:** carbapenems, antibiotic resistance, public health, global health concern, *Enterobacteriaceae*

## 1. Antibiotic resistance as a global threat

The global burden of antibiotic resistance is mounting continuously; preferably it piles up the pressure on veterinary medicine and on human. The WHO made a landmark by promoting and declaring AMR as a global health concern. The agenda of global health concerns are at the developmental stages, for example, a book named as *The Evolving Threat of Antimicrobial Resistance: Options for Action* is a precious addition to the archive [1]. Currently, the world is experiencing dramatic pre-antibiotic era, and many of the untreated infection emerge on a large-scale; clinicians often encounter many patients with such infections that normally reported as PDR or MDR bacteria by many laboratories and not responding to already available therapeutics. It has been estimated that yearly about two million people acquire vulnerable infections just because of these antibiotic-resistant pathogens, and as a result of this, about 23,000 people die according to Centers for Disease Control and Prevention (CDC) [2].

In a historical perspective, antibiotic resistance is a mounting and compelling concern. New types of antibiotic-resistant bacteria are taking control of ancient drugs. We may be entering the post-antibiotic era, because of increased persistence, spread, and the emergence of superbugs. It has been reported that annually, in the USA, about 99,000 deaths are caused by antibiotic-resistant pathogen-related hospital-acquired infections [3]. While in America, the annual death rate is about 50,000 caused by two usual HAIs, known as sepsis and pneumonia, which cost around \$8 billion to the economy of the USA. The patients infected with bacterial strains that are resistant to antibiotics must stay in the hospital minimum for 13 days, which adds to 8 million days annually. An annual report of the cost of economy loss with regard to a productivity loss of around \$35 billion has been demonstrated within healthcare settings [3].

## 2. Causes of antibiotic resistance

Currently, the multifarious causes of resistance constitute many factors including improper use and regulations, lack of awareness, aberrant antibiotic usage, the use of antibiotics as a growth promoter in livestock as well as in poultry for infection control, and online marketing [4]. Fundamentally, the reason behind the resistance evolution is the improper and excessive use of antimicrobials. The powerful drivers of antibiotic resistance include infection control standards, sanitation system, drug quality, water hygiene systems, diagnostics and therapeutics, and migration or travel quarantine. Genetic mutations and exchange of genetic material between organisms play a key role in the distribution of antibiotic resistance [5]. MDR organisms in hospital wastes are associated with public health illnesses because they are ultimately disseminated to humans. In this regard, recently a study has been conducted in Pakistan to find the occurrence of ESBL producing *K. pneumoniae* in hospital wastes including hospital sludge and wastewater, operation theater waste. They found the significant percentage of extended-spectrum  $\beta$ -lactamases (ESBL) producing MDR *K. pneumoniae* in these wastes [6]. Similarly another study conducted by [7] reported the patterns of antibiotic-resistant *K. pneumoniae* in clinical isolates with special reference to fluoroquinolones, depicting an alarming threat of antibiotic resistance among *K. pneumoniae*-related nosocomial infections.

## 3. Carbapenems

Carbapenems are effective  $\beta$ -lactam antimicrobials and have very potent efficacy against many ESBL-producing bacteria and are also administered intravenously.

In order to treat bacterial infections, carbapenems are considered as the most reliable and the last resort class of antimicrobials. Carbapenem agent has a very unique structure, usually defined by carbapenem coupled to B-lactam ring, which provide protection against the majority of b-lactamases as well as metallo-b-lactamases, and thus possess extended antibacterial activity [8]. Carbapenems work by penetrating the cell wall of bacteria, binding with penicillin-binding proteins (PBPs), and result in inactivation of intracellular autolytic inhibitor enzymes, ultimately killing the bacterial cell.

In addition, carbapenems mainly target “transpeptidase inhibition enzyme” during bacterial cell wall synthesis, preventing peptide cross-linking activity, leading to enhanced autolytic activity, and thus resulting in cell death. Therefore, carbapenems are considered as effective antimicrobials to treat life-threatening and invasive infections due to their “concentration-independent killing effect” on infecting bacteria [9, 10].

4. Carbapenemases

Carbapenemases are versatile b-lactamases, having the capability to hydrolyze carbapenems, cephalosporins, penicillins, and monobactams. Carbapenemases typically belong to two molecular families, namely, “metallo-carbapenemases” in which activity is inhibited by EDTA, used zinc molecule at their active sites, and “serine-based carbapenemases” in which activity is not inhibited by EDTA rather used serine residues at their active sites and inactivated through  $\beta$ -lactamase inhibitors like tazobactam and clavulanic acid [11].

$\beta$ -Lactamases are classified based on two properties: functional and molecular ones. Functional classification was proposed by a scientist “Bush” in 1988, who classified  $\beta$ -lactamases into four functional groups namely, groups 1–4. Carbapenems fall under subgroup the 2f and group 3 [12]. Later on another scientist, Rasmussen, suggested that group 3 can be further divided into three functional subgroups on the basis of substrate specificity [13].

The molecular classification was proposed by scientist “Frere” and colleagues, who classified carbapenemases into class A, class B, and class D carbapenemases (Table 1).

Class A carbapenemases require a serine active site at position number 70 in Ambler numbering system, fall under the group 2f, and have the ability to hydrolyze carbapenems, penicillins, aztreonam, and cephalosporins [14].

Classification	Enzymes	Common bacteria
Class A	SME, NMC, KPC, IMI, GES	All <i>Enterobacteriaceae</i> , rarely <i>P. aeruginosa</i>
Class B	VIM, SPM, GIM, IMP	<i>Acinetobacter</i> species, <i>P. aeruginosa</i> , <i>Enterobacteriaceae</i>
Subclass B1	VIM-2, IMP-1, SPM-1, CcrA and BclI	
Subclass B2	Sfh-1, CphA	
Subclass B3	Gob-1, FEZ-1, CAU-1 & L1	
Class D	OXA	<i>Acinetobacter</i> species

Table 1.  
Molecular classification scheme of carbapenemases [16].

Class B metallo- $\beta$ -lactamases require a zinc ion at their active sites and have the ability to hydrolyze carbapenems, penicillins, and cephalosporins but do not hydrolyze aztreonam [15].

Class D carbapenemases were firstly described in 1993; among these class D OXA  $\beta$ -lactamases are the most important and were anciently named as penicillinases and have the ability to hydrolyze oxacillin, penicillin, cloxacillin, and ceftazidime but do not hydrolyze imipenem [11].

## 5. The emergence of carbapenem resistance

Carbapenem resistance is a leading and major public health concern around the globe. It mainly occurs among the *Enterobacteriaceae* family, particularly in healthcare settings. In the UK and the USA, carbapenem-resistant enteric bacterial strain has been identified and isolated from such patients who recently received medical care in Bangladesh, Pakistan, and India. Such strains possess a gene called New Delhi metallo- $\beta$ -lactamase (NDM), responsible for producing metallo- $\beta$ -lactamase enzyme that causes hydrolysis of carbapenems [17].

Factors that play a critical role in the emergence of carbapenem resistance are improper antibiotic prescription, uncontrolled public access to antimicrobials, poor sales regulation, lack of infection control measures within healthcare centers, the use of sub-therapeutic doses in agricultural settings [18].

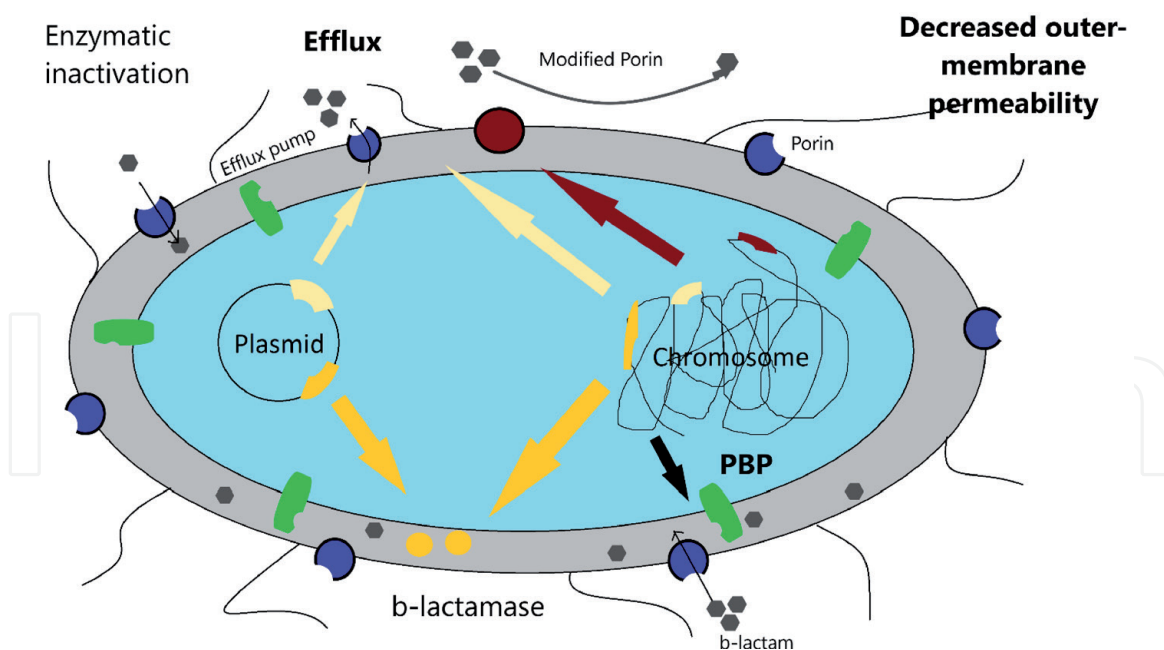
In gram-negative bacteria, the development of carbapenem resistance (particularly in the presence of carbapenemases) is a leading factor associated with the emergence of MDR pathogens which may ultimately lead to the development of pandrug resistant (PDR) bacterial strains. Undoubtedly, among the carbapenemase-producing organisms, resistance to the last resort agents rapidly emerge and spread particularly when such agents are used in healthcare centers [18]. It has also been demonstrated that this carbapenem-resistant-nosocomial pathogens continually emerge, thus accruing more carbapenem resistance determinants, mechanisms, as well as carbapenem encoding genes that ultimately lead to increase carbapenem MICs ruling out yet the best therapeutic choice against such carbapenemase producers [18].

## 6. Mechanisms of carbapenem resistance

The emergence of resistance against these antibiotics reflects a growing health concern around the globe. Carbapenem resistance is mainly caused by two basic mechanisms including the production of carbapenemases (carbapenem-hydrolyzing enzymes) and  $\beta$ -lactamase activity coupled with structural mutations (ESBLs and AmpC cephalosporinases) [19, 20] (**Figure 1**).

Carbapenem resistance can be developed either due to acquired or intrinsic resistance mechanisms or sometimes both, since the bacteria have acquired numerous resistance mechanisms including mutations in the target site, efflux pumps, and enzymatic inactivation. Among these, enzymatic inactivation [acquired carbapenemases (plasmid-mediated)] is the most emerging and well-established mechanism. Acquired carbapenem resistance mechanisms include (1) destruction of carbapenems which are resistant to hydrolysis by plasmid AmpCs in conjunction with ESBL enzymes, contributing insusceptibility towards carbapenem agent [21]; (2) transfer of ESBL genes between the organisms; and (3) porin mutation with expression modulation. Loss of *OprD* porin and efflux pump overexpression is a usual mechanism of carbapenem resistance in the case of *Pseudomonas aeruginosa* [22]. Intrinsic carbapenem resistance mechanism includes reduced uptake (due to altered porin channels) and reduced outer membrane permeability of  $\beta$ -lactam drugs [16].





**Figure 1.**  
Mechanism of carbapenem resistance in *Enterobacteriaceae*. (1) Reduced membrane permeability through modified porins, expression loss or shift in porin proteins in outer-membrane; (2) enzymatic inactivation by plasmid mediated or chromosomal enzymes (having hydrolytic activity); and (3) antibiotic efflux through efflux pump.

Several mobile genetic elements have their potential role in carbapenem resistance like Tn4401, Class I integrons, IncFIIK2, IncF1A, and IncI2 [17]. Transposon Tn4401 contains *tnpR* and *tnpA* genes, coding for “resolvase” and “transposase,” respectively, and is mainly associated with *bla*<sub>KPC-2</sub> type [23]. Plasmids IncFIIK2, IncF1A, and IncI2 belong to ST101 *K. pneumoniae* type-2 found from bloodstream infections in the Asian region particularly in India.

## 7. Drivers of carbapenem resistance

To date, drivers for the acquisition of Carbapenem resistance among gram-negative bacteria have not been emphasized. But some of the known drivers for carbapenem resistance are prior long-term use of metronidazole and imipenem drugs in hospital settings, prior long-term hospital stays, and the presence of biliary drain catheters. It has been described that the disruption of normal flora by metronidazole increases the frequency of translocation, hence promoting carbapenem resistance among *Enterobacteriaceae* [24].

It has also been demonstrated that carbapenem resistance accelerated, once the gene for these enzymes became associated with acquired genetic elements like integrons and plasmids [25]. Thus the circulation of carbapenem-resistant genes among different strains isolated from clinic and hospital sewerage system coupled with the transfer of such genes by bacteriophage carrying B-lactamases genes coding for OXA-B-lactamases is now been considered as potential drivers for the increased spread and emergence of Carbapenem resistance [26].

## 8. Carbapenem-resistant *Enterobacteriaceae*: a mounting health concern

The *Enterobacteriaceae* is responsible for causing healthcare-related infections. Recent studies reported by the regulatory authority “Centre for Disease Control

and Prevention” reveal that more than 21.3% of healthcare-related infections are due to *Enterobacteriaceae* [27]. Spread and the emergence of Carbapenem-resistant *Enterobacteriaceae* is a mounting health concern around the globe [28]. Regulatory authority “Centre for Disease Control and Prevention” defines CRE as “*Enterobacteriaceae* that seems to be tested as resistant to any carbapenem agent including ertapenem or may demonstrate as carbapenemase production through molecular or phenotypic assay” [29].

The emergence of carbapenem resistance among *Enterobacteriaceae* (CRE) possessing additional resistance genes to a variety of antimicrobial classes had led to the creation of organisms nearly resistant to all available therapeutics [30]. Carbapenem-resistant *Enterobacteriaceae* are a family of bacteria, responsible for causing significant mortality and morbidity, and hence are very difficult to treat. Among the *Enterobacteriaceae*, *E. coli* and *Klebsiella* species can easily become carbapenem resistant. CRE infections commonly occur in healthcare and hospital settings as well as in nursing homes, while the patients on-going long-term antibiotic treatment are also highly susceptible to these CRE infections [31].

Epidemiological data on carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) varies country to country. An important carbapenemase-producing carbapenem resistance (KPC) was the first identified carbapenemase in the USA in 1996, and the prevalence is distributed unevenly among the US states [32]. Since epidemiology of CRE varies differently, so in this regard, KPC is endemic in Israel, while VIM, IPM, NDM, and OXA-48 carbapenemases are endemic in Greece, Japan, India, and Turkey, respectively, and are also disseminated successfully around the globe [33]. The continuous movement of subjects infected or colonized with CP-CRE in conjunction with the continuous exposure of these subjects to medical care is a significant contributor to the spread of CP-CRE [34]. Therefore, the decisive detection of CP-CRE may be the initial step to combat such a mounting health concern [29].

## 9. Treatment options

Since CRE infections are very difficult to treat, some of the treatment options for addressing the threat of “Carbapenem-resistant *Enterobacteriaceae*” include tigecycline, polymyxins, aminoglycosides, fosfomycin, meropenem/vaborbactam, and ceftazidime/avibactam. Combinations of B-lactamase are also available and are safer and more effective for treating CRE infections. It has been reported that polymyxin monotherapy can also lead to the emergence of resistance; therefore, polymyxin in combination with carbapenems must be administered in an appropriate dose [35]. Similar is the case with fosfomycin. The use of fosfomycin intravenously is recommended for urinary tract infections [36]. Clinicians should be vigilant in exploring new treatment options as well as for detection of CRE infections. Many of the new treatment options are in process, but none of them represent a magic bullet to address this concerned threat.

## 10. Conclusion

The rapid spread of carbapenem resistance as well as carbapenem-resistant *Enterobacteriaceae* into the community is a growing and emerging threat to public health. Despite of the large efforts being made to control this public menace, it is very essential to look for some definite solution which still seems to be far off. Until a potential alternative solution to overcome this problem is found,

application of infection control measures whenever CR is detected, rationalization of antibiotic use as well as ensuring active surveillance system may be some steps to control this menace.

An interdisciplinary and global assess should be examined for the formulation of new diagnostic and screening tools. In this regard, alternative strategies to antibiotics like the use of phage therapy and probiotics can reduce this resistance burden. The spread of resistance can be minimized by immunization, application of infection control measures, rationalization of antibiotic usage, proper screening and treatment, and education and awareness programs. At global, national, and regional level, tracking and bio-surveillance system and preventive approaches of MDR and AMR pathogens can control this “global resistome.”

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