June 2025
Volume 5
Issue 2

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.2.1790

Dissemination of carbapenem and colistin resistance in Gram-negative bacteria: The emerging role of novel β-lactam/β-lactamase inhibitors for managing a global dilemma

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Received on, 13 November 2025 - Accepted on, 08 December 2025 - Published on, 14 December 2025

ABSTRACT:

Antibiotic resistance is imposing an increasing burden on global health. In 2021, an estimated 4.71 million deaths were associated with bacterial antimicrobial resistance, of which 1.14 million were directly attributable to resistant infections; projections estimate nearly 39 million deaths from antimicrobial-resistant diseases between 2025 and 2050. Of particular concern is the rise of carbapenem-resistant Gram-negative bacteria, which has decreased the effectiveness of carbapenems once used against ESBL producers.colistin, previously discontinued because of severe toxicity, was reintroduced as a last-resort therapy, but its usefulness is now threatened by rising resistance driven in part by unregulated veterinary use and the spread of plasmid-mediated mcr genes. Several new β-lactam/β-lactamase-inhibitor combinations and novel agents demonstrate improved efficacy and safety compared with revived older drugs; however, their high cost and limited availability constrain their impact in low- and middle-income countries such as Egypt. This review summarizes the epidemiology and molecular mechanisms of carbapenem andcolistin resistance and evaluates the clinical evidence and mechanisms of action for last-line and novel β-lactam/β-lactamase-inhibitor therapies.

KEYWORDS:

Antibiotic resistance, Carbapenem resistance, Gram-negative bacteria,colistin resistance,β-lactam/β-lactamase inhibitors, Egypt

1. Introduction

Since their discovery, antibiotics have been extensively utilized across all domains to combat bacterial diseases. The unregulated and ongoing use of antibiotics exerted selective pressure on microorganisms, resulting in a global rise in antibiotic resistance (1, 2). The continuous rise in antibiotic resistance, combined with the diminishing discovery of novel treatments to combat emerging antibiotic-resistant bacteria, may propel the globe toward a pre-antibiotic period (2).

Antibiotic resistance exerts considerable strain on global healthcare systems. In 2021, around 4.71 million deaths were linked to bacterial antibiotic resistance, with 1.14 million deaths directly attributed to it. It is projected that approximately 39 million individuals will die from antimicrobial-resistant infections between 2025 and 2050 (3). Moreover, resistance rates are elevated in low-income countries compared to high-income countries, suggesting a correlation between the high prevalence of antibiotic resistance and a nation's level of development. Additionally, significant data deficiencies exist in numerous low-income contexts, implying that the actual resistance situation in these countries may be more severe than previously estimated (4, 5).

Furthermore, the Global Antimicrobial Resistance and Use Surveillance System (GLASS) report published by the WHO in 2025 revealed that one in six laboratory-confirmed bacterial infections, which are frequent among humans worldwide in 2023, showed resistance to antibiotic

treatments. Between 2018 and 2023, antibiotic resistance escalated in almost 40% of the examined pathogen-antibiotic combinations, with an average annual increase of 5–15%. The WHO estimated that antibiotic resistance is most prevalent in the South-East Asian and Eastern Mediterranean Regions, where one in three reported cases exhibited resistance. In the African Region, 20% of infections displayed resistance. Resistance is more prevalent and deteriorating in regions where health systems lack the capacity to diagnose or manage bacterial infections. The recent analysis indicates that drug-resistant Gram-negative bacteria are increasingly becoming a global concern. The impact is most significant in nations least prepared to address the issue. *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) are the predominant drug-resistant Gram-negative bacteria identified in bloodstream infections. These pathogens pose the most critical bacterial infections that frequently lead to sepsis, organ failure, and mortality. Over 40% of *E. coli* and more than 55% of *K. pneumoniae* worldwide are now resistant to third-generation cephalosporins, the preferred therapy for these infections. In the African Region, resistance surpasses 70%. Other critical life-saving antibiotics, such as carbapenems and fluoroquinolones, are becoming less effective against *E. coli, K. pneumoniae, Salmonella* spp., and *Acinetobacter* spp. Carbapenem resistance, once uncommon, is increasingly prevalent, limiting treatment alternatives and necessitating dependence on last-resort medicines. Such antibiotics are expensive, challenging to obtain, and frequently inaccessible in low-and middle-income countries (LMICs) (5).

The most concerning pathogens include multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) bacteria. MDR, XDR, and PDR bacteria are defined, respectively, as nonsusceptibility to ≥1 agent in ≥3 antimicrobial classes, susceptibility limited to ≤2 classes, and nonsusceptibility to all antimicrobial classes (6). Classical resistant pathogens are part of the ESKAPE group, comprising *Enterococcus faecium*, *Staphylococcus aureus* (*S. aureus*), *K. pneumoniae*, *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Enterobacter spp.* The most alarming pathogens presently include carbapenem-resistant *Enterobacterales* (CRE), particularly carbapenem-resistant *K. pneumoniae* (CRKP), methicillin-resistant *S. aureus*, extended-spectrum-β-lactamase (ESBL)-producing *Enterobacterales*, vancomycin-resistant *Enterococci*, multidrug-resistant *P. aeruginosa*, and multidrug-resistant *A. baumannii* (7, 8).

In 2024, the WHO recognized CRE as one of the top four drug-resistant bacteria necessitating urgent antibiotic discovery (Critical group), alongside carbapenem-resistant *A. baumannii,* third-generation cephalosporins-resistant *Enterobacterales*, and rifampicin-resistant *Mycobacterium tuberculosis.* Conversely, carbapenem-resistant *P. aeruginosa* was categorized as a high-priority group, thus deemed a lesser threat than the previously mentioned species. The WHO indicated that although *P. aeruginosa* is challenging to treat, emerging evidence suggests a global decline in its resistance profile. Additionally, its low transmissibility relative to other carbapenem-resistant species influenced the WHO's decision to prioritize the issue of carbapenem-resistant *P. aeruginosa* as less critical (9).

Although emerging medications effective against Gram-positive bacteria offer a temporary reprieve (10), the 2020 global antibiotic clinical pipeline included merely 23 candidates exhibiting activity against Gram-negative bacteria, none of which were from a novel class. In fact, the last antibiotic approved by the United States (US) Food and Drug Administration (FDA) with a new mechanism of action targeting Gram-negative bacteria was identified nearly 60 years ago, resulting in infections caused by antibiotic-resistant Gram-negative bacteria emerging as a significantly greater threat (11-13).

Antibiotic-resistant microorganisms and their resistance genes are increasingly recognized as environmental pollutants. Once largely confined to point sources such as hospitals, sewage systems, and agricultural sites, they now contaminate relatively pristine rivers, lakes, and soils (1,14). LMICs are particularly vulnerable because of weak surveillance and diagnostics, poorly regulated antibiotic use in humans and animals, overcrowded hospitals, inadequate hygiene, rapidly expanding meat and fish production, higher infectious-disease burdens, and limited access to costly second- and third-line drugs. These vulnerabilities are amplified by insufficient waste- and wastewater management, which releases resistant fecal bacteria and antibiotic residues into the environment; excessive manufacturing emissions have also been reported from major producers such as China and India. Because resistance crosses borders, addressing the problem in LMICs is a global imperative; therefore, cost-effective measures that overlap with water, sanitation, and hygiene improvements should be prioritized, and sewage surveillance offers a promising, less-resource-demanding complement to conventional clinical monitoring. The One Health Concept emphasizes that successfully managing this global health

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
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challenge is critical, as it requires understanding the connections between the human, animal, and environmental microbiota due to the common crossing of species and environmental boundaries by bacteria and genes (14).

The unprecedented rise and prevalence of XDR and MDR bacteria have necessitated the reintroduction of last-resort antibiotics, includingcolistin, which had previously been discontinued due to their toxic side effects, primarily nephrotoxicity and neurotoxicity. However, considering these significant circumstances, they have resurfaced to combat these formidable bacterial infections (1, 15). Alternative antimicrobials, such as the novel β-lactams and β-lactam/β-lactamase inhibitors, meropenem/vaborbactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam, and the siderophore cephalosporin cefiderocol, have been deemed superior and have largely supplantedcolistin in the treatment of carbapenem-resistant Gram-negative infections. (16).colistin may be necessary for treating carbapenem-resistant *A. baumannii* infections, and in cases when the novel β-lactams and β-lactam/β-lactamase inhibitors have limited accessibility (16, 17).

This review provides a comprehensive overview of the epidemiological data, mechanisms of action, and resistance associated with last-resort antibiotics, particularly carbapenems andcolistin, and highlights the emerging role of novel β-lactams and β-lactam/β-lactamase inhibitors in combating these vicious pathogens.

2. Burden and impact of antimicrobial-resistant bloodstream infections

Bacteremia, defined as the presence of bacteria in the bloodstream, constitutes an important public health threat (18) that can lead to devastating diseases (19, 20) and incur annual costs in the billions of dollars to the world economy (21, 22). Clinical bacteremia is linked to sepsis, a critical organ failure resulting from an aberrant host response to infection (23). The WHO has identified sepsis as a global health issue (18), with data from 2017 indicating 48.9 million cases and 11 million sepsis-related deaths worldwide, accounting for nearly 20% of all global deaths (24). Sepsis is associated with a variable but incredibly high mortality rate (25-27) and can cause permanent dysfunction, including cognitive impairment or organ failure (26, 28).

Bloodstream infections (BSIs) by themselves are associated with substantial morbidity and mortality (29, 30). In 2019, BSIs accounted for 2.91 million deaths worldwide. Nearly half of these fatalities were attributed to Gram-negative bacteria, which are known to be linked to elevated mortality rates (31, 32). Carbapenem-resistant isolates accounted for 26.3% of these fatalities. *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* were the predominant carbapenem-resistant infections associated with mortality (32). A study conducted between 2019 and 2021 on patients suffering from hospital-acquired BSIs concluded almost the same results (33). This highlights the significance of carbapenem resistance and its global impact on the mortality associated with BSIs. Furthermore, the GLASS report published by the WHO in 2025 identified significantly elevated levels of antibiotic resistance in bacteria responsible for BSIs (5).

Moreover, antibiotic resistance correlates with inferior outcomes compared to typical cases. A study of 131 US hospitals demonstrated a significant correlation between antimicrobial resistance in BSIs and *in vitro* susceptibility-discordant empiric antibiotic therapy, leading to increased crude mortality, extended total hospital stay, and heightened intensive care unit admissions (34). Previous research from Turkey indicated that carbapenem resistance in bloodstream pathogens was associated with a 30-day fatality rate reaching 66% (35). Furthermore, CRE are associated with increased length of hospital stay and mortality compared to carbapenem-susceptible *Enterobacterales* in LMICs (36).

Antimicrobial resistance substantially increases both the mortality and economic burden associated with BSIs in LMICs. A recent systematic review and meta-analysis conducted across diverse LMIC settings found that BSIs caused by antibiotic-resistant bacteria were associated with significantly higher mortality rates than infections due to susceptible strains, with CRKP yielding the highest mortality risk among the pathogens studied. Furthermore, the direct medical costs for antimicrobial-resistant BSIs were estimated to be approximately USD 12,442 higher per patient compared to infections with susceptible organisms. The economic impact was further compounded by premature mortality, contributing an additional average cost of USD 41,103 per patient (37).

3. Carbapenems as a last resort for ESBL-producing Gram-negative bacteria

Carbapenems, a broad-spectrum β-lactam antibiotic, are structurally related to penicillin (38). Carbapenems have a carbon instead of a sulfone at the fourth position of the β-lactam ring, differing from other β-lactams. The unique structure plays a major role in their stability against β-lactamases (39). Carbapenems enter bacteria through outer-membrane porins and bind penicillin-binding proteins (PBPs). By acylating PBPs via their β-lactam ring, they inhibit peptidoglycan cross-linking, trigger autolytic enzymes, and cause osmotic cell lysis. (38, 39). A key advantage of carbapenems is their ability to bind to several PBPs (40).

ESBLs are enzymes that deactivate most β-lactam antibiotics, including penicillins, cephalosporins, and Aztreonam. Nonetheless, ESBL-producing *Enterobacterales* typically retain susceptibility to carbapenems. Carbapenems were regarded as the preferred treatment for these resistant pathogens (41), as ESBLs do not deactivate non-β-lactam drugs. Organisms possessing ESBL genes frequently have supplementary genes or mutations that enhance their resistance to a wide array of antibiotics. Globally, the majority of ESBLs are classified into various categories of sulfhydryl reagent variable (SHV) β-lactamases, Temoniera (TEM) β-lactamases, and cefotaxime-M (CTX-M) β-lactamases (16, 42). Recent outbreaks of ESBL have primarily been linked to the CTX-M type rather than the TEM or SHV types, with CTX-M-15 being the most widespread ESBL globally (16, 43, 44).

Reduced treatment options, complex infections, increased mortality, and pricey treatments are some of the key concerns for individuals infected with ESBL-producing pathogens (45). Consequently, in critical illnesses such as BSIs, carbapenems are established as the preferred therapeutic option. However, this has led to the rise of carbapenem resistance and the spread of CRE (5).

4. The global spread of carbapenem-resistant Gram-negative bacteria

The Centers for Disease Control and Prevention (CDC) defines CRE as *Enterobacterales* exhibiting resistance to at least one carbapenem *in vitro* (46). In recent years, the global prevalence of CRE transmission has escalated, and the spread of COVID-19 has exacerbated the situation to some degree through enhanced bacterial colonization and patient-staff contact, leading to higher prevalence, longer hospital stays, and worse outcomes in co-infected patients as well as antibiotic misuse during the pandemic (47). Epidemiological investigations of CRE have predominantly focused on the dominant strains of CRKP and carbapenem-resistant *E. coli* (CREco), which together account for over 90% of CRE isolates and are widely disseminated worldwide through several transmission routes (48). Furthermore, imipenem resistance has shown a significant upward trend among Gram-negative bacteria, with *K. pneumoniae* causing BSIs exhibiting the most pronounced increase, rising by approximately 15.3% annually (5).

According to the GLASS report, the WHO published in 2025, carbapenem resistance exhibits marked regional variability. In Africa, imipenem resistance was highest among *K. pneumoniae* bloodstream isolates (20.2%). The Eastern Mediterranean Region showed the largest proportion of imipenem-resistant *Acinetobacter* spp., causing BSIs at 66.5%. Egypt has reported notably high imipenem resistance among *K. pneumoniae*, *E. coli*, and *Acinetobacter* spp. Isolated from bloodstream and urinary tract infections. In Europe, overall imipenem resistance remains relatively low, but several countries in Eastern Europe have experienced sharp increases; for example, Greece reported imipenem resistance of 71.8% in *K. pneumoniae*, 2.1% in *E. coli*, and 93.7% in *Acinetobacter* spp. Causing BSIs. South-East Asia recorded the highest imipenem resistance for bloodstream isolates of *E. coli* and *K. pneumoniae*, at 17.5% and 41.2%, respectively. The Western Pacific Region reported lower overall rates, although the Republic of Korea had a high imipenem resistance proportion for *Acinetobacter* spp. Causing BSIs (72.1%) (5).

Ultimately, these significant regional differences show that while resistance hotspots vary by location, CRE remains a serious global threat that requires specific local monitoring combined with international cooperation.

Figures 1 and 2 illustrate the global percentages of imipenem resistance across WHO regions for BSIs and urinary tract infections, respectively.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.2.1790

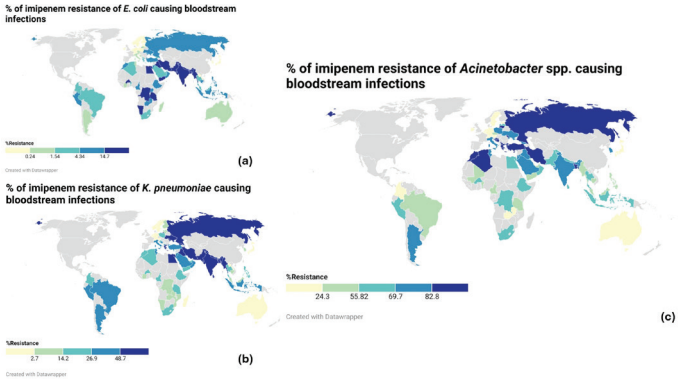

Figure 1: Global distribution of imipenem resistance percentages among different bloodstream pathogens (a) *E. coli*, (b) *K. pneumoniae*, and (c) *Acinetobacter spp.* (5).

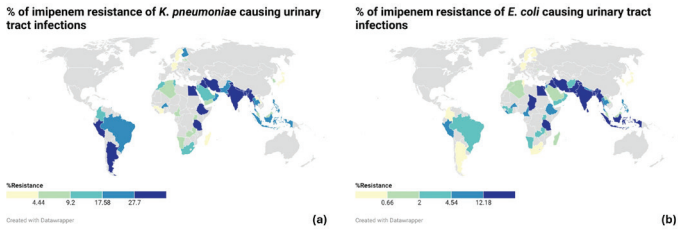

Figure 2: Global distribution of imipenem resistance percentages among different urinary tract pathogens: (a) *K. pneumoniae*, (b) *E. coli* (5).

5. Insights into the different mechanisms of resistance to carbapenems

The mechanisms of resistance to carbapenems among CRE and some non-*Enterobacterales* including carbapenem-resistant *A. baumannii* and carbapenem-resistant *P. aeruginosa* involve (i) antibiotic degradation, (ii) obstruction of antibiotic entrance into bacterial cells, (iii) alteration of antibiotic binding sites, (iv) deletion or mutation of pore proteins, (v) hyperactivation of efflux pumps, (vi) modifications in PBP and (vii) biofilm formation (47).

5.1. Production of carbapenemases

Carbapenemase production is a significant resistance mechanism in Gram-negative bacteria, especially within *Enterobacterales*, which hydrolyzes carbapenems and other β-lactam antibiotics. Carbapenem-resistant pathogens can be categorized into carbapenemase-producers and non-carbapenemase-producers, where carbapenem resistance in the latter results from alternative resistance mechanisms, including the overexpression of other β-lactamases like ESBL (16).

β-lactamases are commonly grouped by the Ambler classification into four classes: A, B, C, and D (49). Carbapenemases fall within classes A, B, and D, whereas class C enzymes are not considered true carbapenemases. However, class C β-lactamases have a low but measurable ability to hydrolyze carbapenems, and their overproduction can contribute to carbapenem resistance when combined with reduced outer-membrane permeability and/or efflux pump overexpression (50). **Figure 3** illustrates the Ambler molecular classification of the major carbapenemase classes, providing a brief description of each, including the antibiotics they affect and their structural differences.

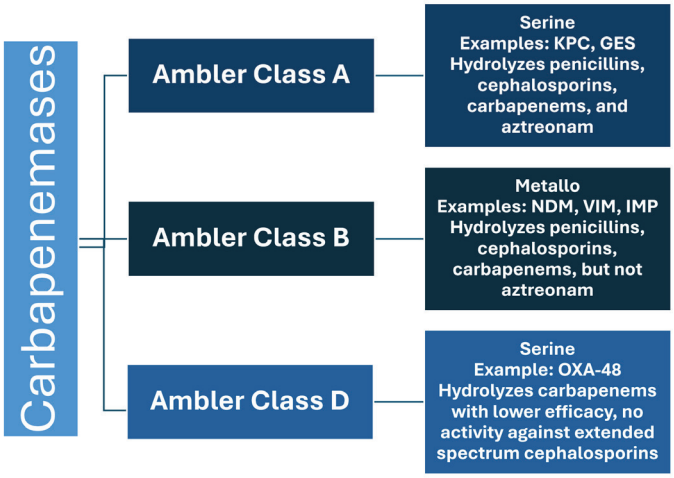

Figure 3: Ambler classification of carbapenemases (51).

5.1.1. Class A carbapenemases

The predominant class A carbapenemases comprise *K. pneumoniae* carbapenemase (KPC), imipenem-hydrolyzing β-lactamase (IMI), non-metallo carbapenemase of class A (NMC-A), Guiana extended-spectrum β-lactamase (GES), and *Serratia marcescens* enzyme (SME) (52). Class A carbapenemases include a serine residue at their active sites and are distinguished by their capacity to hydrolyze penicillins, cephalosporins, carbapenems, and Aztreonam (52). bla_{KPC} is the most prevalent carbapenemase-encoding gene in CRE and is the most frequently identified in the US (47, 52).

5.1.2. Class B carbapenemases

Class B carbapenemases are characterized by metallo-β-lactamase (MBL) structures (52). This class contains amino acids at the binding site that interact with zinc (53). Class B enzymes include NDM (New Delhi metallo-β-lactamase), IMP (Imipenemase), and VIM (Verona integron-encoded metallo-β-lactamase) (52). Most class B carbapenemases

degrade all β-lactams, excluding Aztreonam (53). Class B carbapenemases-encoding genes are typically located on plasmid vectors and other transposable elements, facilitating their dissemination across bacteria (53).

5.1.3. Class D carbapenemases

Oxacillinase (OXA) enzymes constitute class D carbapenemases (52). Similar to class A carbapenemases, class D carbapenemases include a serine amino acid at their binding sites (52). They differ from class A carbapenemases due to their diminished hydrolytic activity against carbapenems and penicillins, lack of activity against extended-spectrum cephalosporins, and resistance to earlier β-lactamase inhibitors (e.g., clavulanic acid, tazobactam, or sulbactam) (52, 54). Nonetheless, the majority is hindered by avibactam (54). OXA-48 is the predominant carbapenemase enzyme in this category and is usually identified in *K. pneumoniae* (53).

5.2. Outer membrane protein deletion or alteration

Bacteria can restrict the penetration of carbapenems into the periplasmic region, where PBPs reside. This process entails modifications in porin expression or variations in the porin encoding gene, resulting in either a total loss or deficiencies in the corresponding porin (55). The primary mechanism of resistance to carbapenems in *P. aeruginosa* isolates is the downregulation of the gene encoding the OprD porin (56). Additionally, the modified expression of OmpK35 and OmpK36 in *K. pneumoniae* was found to confer significant resistance to ertapenem (57).

5.3. Overexpression of efflux pumps

Efflux pumps typically recognize several substrates, as their affinity is determined by physicochemical qualities (e.g., electric charge, aromatic or hydrophobic characteristics) rather than by chemical structures. This elucidates the existence of MDR efflux pumps capable of expelling numerous structurally diverse antimicrobials (58). Gram-negative bacteria, including *P. aeruginosa* and *Acinetobacter spp.*, are recognized for their efflux-mediated β-lactam resistance (59). The overexpression of efflux pumps active on carbapenems may lead to carbapenem resistance (60, 61).

5.4. Penicillin-binding protein alterations

PBPs are essential proteins for the synthesis of peptidoglycans in bacterial cell walls. Carbapenems exert their antibacterial activity by covalently binding to PBPs, leading to stable acylated complexes that obstruct cell wall production (62). Drug resistance is largely caused by structural changes, increased PBP production, decreased antibiotic affinity, and the emergence of new PBPs. In 2019, Ranjitkar et al. (63) found that mutations in the *mrdA* gene, responsible for encoding the PBP2 protein, were found to reduce *E. coli*'s sensitivity to carbapenems. Moreover, the co-existence of *mrdA* mutations with modifications in the *ftsI* gene, which encodes PBP3, intensified the decline in antibiotic susceptibility. It has been suggested that although PBP mutations lead to elevated minimum inhibitory concentration (MIC) values, these mutations alone do not significantly correlate with clinical carbapenem resistance. Instead, they may contribute to clinical drug resistance in combination with reduced porin production or increased carbapenemase production (64).

5.5. Altered biofilm components

For bacteria, biofilm is a technique to protect themselves and fight against hostile circumstances. Its components include LPS, flagella, and type I and III fimbria (65). Modulating biofilm components can govern biofilm synthesis and enable bacteria to endure antibiotic stress, thereby demonstrating antibiotic resistance. The principal surface structures implicated in the biofilm formation of *K. pneumoniae* are type III bacterial fimbriae and capsular polysaccharide; the former facilitates bacterial adhesion, while the latter affects biofilm architecture and intercellular communication (66). Sharma et al. (67) indicated that CRKP can downregulate flagella and bacterial pili proteins under meropenem stress to complete biofilm remodeling and promote bacterial survival under meropenem stress. However, Cusumano et al discovered that CRKP had a 91% reduced likelihood of developing robust biofilm-forming capabilities, indicating a negative link between biofilm development and antibiotic resistance (68). In 2021, the experimental findings of Fang et al. demonstrated that, unlike carbapenem-susceptible *K. pneumoniae*, CRKP exhibited diminished biofilm-forming ability due to the absence of the *mrkH* gene, which governs biofilm formation (65).

6. Polymyxins: Last–Resort for Carbapenem-Resistant

Polymyxins are non-ribosomal, cyclic oligopeptide antimicrobials that are structurally comprised of a cyclic heptapeptide with five

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.2.1790

major chemical compounds: polymyxins A, B, C, D, and E. Polymyxin B and polymyxin E (Colistin) are used extensively in clinical practice (69).

Colistin is a polypeptide antibiotic discovered from the bacterium *Paenibacillus polymyxa* subspecies*colistinus* in 1947 (70). In the 1950s, it was introduced as an intravenous formulation. In 1959, the FDA authorized the use ofcolistin as a therapeutic option for various forms of diarrhea and UTIs, deeming it a "miracle" antibiotic due to its potent bactericidal efficacy against Gram-negative bacteria while maintaining a low resistance profile (71). Nonetheless, owing to its deleterious side effects, especially nephrotoxicity and neurotoxicity, its use was ultimately discontinued in the 1980s in favor of less hazardous alternatives. Despite this, it continued to be utilized as a viable clinical alternative for individuals with cystic fibrosis suffering from pseudomonal lung infections, as well as in topical formulations combined with other antimicrobials for the treatment of ocular or aural infections. Moreover, it kept being used as a viable option in veterinary medicine for decades (72, 73).

In response to the persistent and unprecedented rise in antibiotic resistance, especially to carbapenems, regarded as a last-resort antibiotic for numerous MDR pathogens,colistin was reintroduced in the 2000s to address MDR bacteria. This resurgence has subsequently resulted in the emergence ofcolistin-resistant strains that currently afflict the global population. In 2015, the discovery ofcolistin resistance mechanisms, mediated by plasmids and referred to as mobilecolistin resistance genes (*mcr* genes), was particularly alarming since it indicated the potential for horizontal transfer of this resistance (1, 74). **Figure 4** illustrates the history ofcolistin, from its discovery to the identification of *mcr* genes.

In Egypt, the situation is particularly concerning. A recent systematic review reported that approximately 9% of Gram-negative isolates exhibitcolistin resistance, increasing to nearly 31% among carbapenem-resistant strains (75).

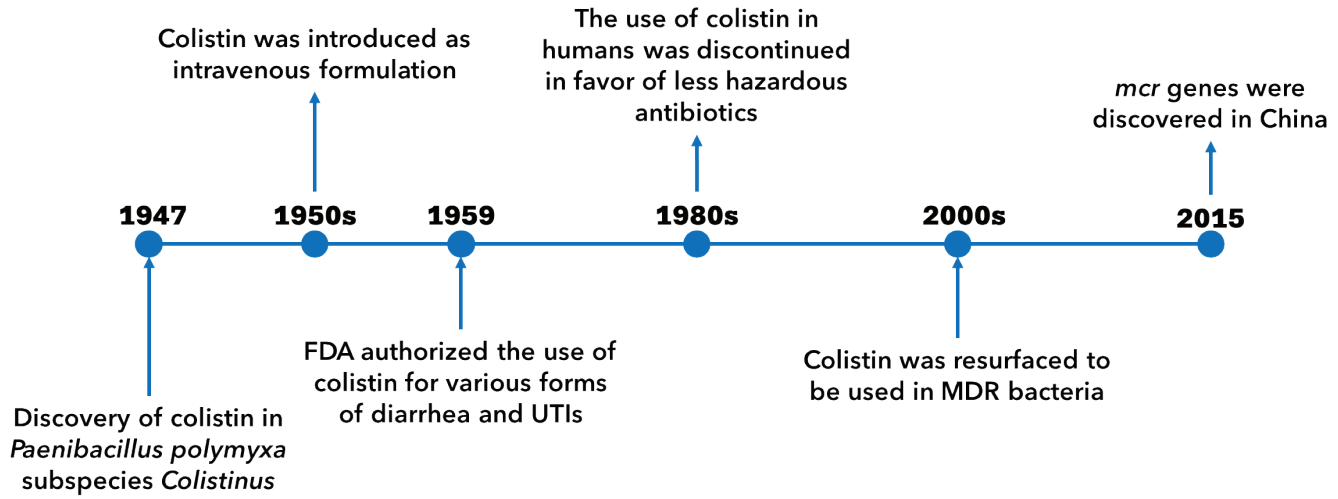

Figure 4: The historical development ofcolistin, from its discovery through to the identification of plasmid-mediated *mcr* genes.

7. Colistin use in veterinary medicine

Colistin has been utilized in veterinary medicine for decades (73), primarily for medicinal and preventive use in food animals, in addition to metaphylactic and growth enhancement purposes (76, 77).

Colistin was historically regarded as an uncommon antibiotic for humans, as its use in human medicine was infrequent due to its neurotoxicity and nephrotoxicity, coupled with poor gastrointestinal absorption. Consequently, the incidence of resistance tocolistin remained low, primarily attributed to chromosomal resistance (73, 78, 79). In 2015, this perspective shifted markedly following the discovery of the plasmid-borne *mcr* gene and its globally disseminated variants, which have been largely attributed to the use ofcolistin in agriculture in China, particularly for prophylaxis and as a feed additive. Since then, the use ofcolistin in veterinary medicine has come under sustained scrutiny (74, 80). Moreover, there is a growing dependence oncolistin for the treatment of multidrug-resistant Gram-negative bacterial infections, particularly in LMICs, where alternative treatments (e.g., tigecycline) are sometimes prohibitively costly when available (81).

Due to the rising utilization ofcolistin for severe infections in various regions globally, the identification of *mcr* genes that impart transmissible resistance tocolistin, and the dissemination ofcolistin-resistant bacteria through the food chain, the WHO has determined that polymyxins, includingcolistin, should be classified as a "Highest Priority Critically Important Antimicrobial", necessitating the implementation of multiple strategies to address antimicrobial resistance (82).

The improper use ofcolistin and other antibiotics in veterinary medicine intensifies the issue of antibiotic resistance. A significant factor is the accessibility of veterinary medications without a prescription, facilitating unregulated usage (83). However, numerous initiatives undertaken in several countries have resulted in significant reductions in the sales and utilization ofcolistin in livestock production (77). The production and commerce ofcolistin, including pharmaceutical raw materials, completed pharmaceutical products, and veterinary feed additives or growth boosters, remained unchanged in several LMICs despite their consensus on the antibiotic resistance crisis (76).

8. Insights intocolistin's antibacterial activity and its possible mechanisms of action

Colistin predominantly targets the outer membrane of Gram-negative bacteria, particularly the LPS layer. The LPS comprises three domains: the innermost lipid A, the central core oligosaccharide area, and the outermost O-antigen chain (84). Lipid A is crucial for preserving the overall outer membrane structure by firmly binding to the fatty acyl chains. Cations such as calcium (Ca^{2+}) and magnesium (Mg^{2+}) promote interactions between neighboring LPS molecules, thus enhancing outer membrane stability (84). The antibacterial efficacy ofcolistin arises from electrostatic interactions between the phosphates of lipid A on the bacterial outer membrane and the cationic diaminobutyric acid (Dab) residue incolistin (85).colistin demonstrates antimicrobial effectiveness against Gram-negative bacteria via five unique methods.

8.1. The classical membrane lysis pathway

The classical mechanism of action entails the membrane lysis pathway, triggered by the electrostatic contact between negatively charged phosphate head groups on lipid A and positively charged Dab residues oncolistin within the LPS component of the outer membrane of Gram-negative bacteria. This interaction causes the displacement of divalent cations, including Ca^{2+} and Mg^{2+}, from the anionic phosphate groups of membrane lipids, thus destabilizing the LPS.colistin subsequently expands the outer membrane by infiltrating it and incorporating either the D-Leu^6-l-Leu^7 segment or its hydrophobic terminal fatty acyl chain, which increases membrane permeability and facilitates the "self-promoted uptake" ofcolistin through destabilized areas in the outer membrane created during its interaction with LPS. Ultimately, the inner membrane of the phospholipid bilayer is undermined due to membrane thinning, which weakens the bilayer's structural integrity, culminating in cell lysis (85, 86).

8.2. Vesicle–vesicle interaction pathway

An alternate mechanism that augments the antibacterial activity ofcolistin entails vesicle–vesicle contact. In this process,colistin promotes interaction between the outer leaflet of the cytoplasmic membrane and the inner leaflet of the outer membrane by binding to anionic phospholipid vesicles (87). This interaction facilitates the transfer of phospholipids between vesicles, leading to a reduction in the specificity of phospholipid composition. This ultimately disrupts osmotic equilibrium within the cell, resulting in cell lysis (85).

8.3. Hydroxyl radical-induced cell death pathway

The alternative mechanism ofcolistin action involves the stimulation of rapid cell death by the formation of hydroxyl radicals resulting fromcolistin's attachment to the lipid membrane. Free radicals are produced whencolistin traverses the outer membrane and inner membrane of lipopolysaccharides. The creation of hydroxyl radicals happens through the production of reactive oxygen species, including hydroxyl radicals ($^{\cdot}OH$), superoxide (O_2^-), and hydrogen peroxide (H_2O_2), which induce oxidative stress. Superoxide is produced whencolistin penetrates and traverses the outer membrane and inner membrane, subsequently transforming O_2^- into H_2O_2 via superoxide dismutase. Subsequently, H_2O_2 oxidizes ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) while generating $^{\cdot}OH$; this process is referred to as the Fenton reaction. This process can cause oxidative damage to bacterial DNA, proteins, and lipids, resulting in cell death. This killing mechanism has been demonstrated incolistin-susceptible and MDR isolates of *A. baumannii,* but it does not occur in polymyxin-resistant bacteria (88).

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.2.1790

8.4. Respiratory enzyme inhibition pathway

Colistin has recently been recognized to possess a new mechanism of action: the suppression of essential respiratory enzymes situated in the inner membrane of Gram-negative bacteria (89). The Type II NADH oxidoreductase respiratory enzyme serves as the secondary target ofcolistin, situated in the bacterial electron transport system within the inner membrane (89). Unlike Type I NADH oxidoreductase, Type II NADH oxidoreductase, known as "alternate NADH oxidoreductase," does not facilitate the active translocation of protons across the inner membrane (90).colistin inhibits Type II NADH oxidoreductase by augmenting the respiratory chain, therefore improving its utilization of it. This inhibition impairs the bacterial electron transport chain, compromising respiratory function and threatening bacterial survival (91).

8.5. Antiendotoxin activity ofcolistin

Colistin exhibits an additional antibacterial mechanism through its significant antiendotoxin action. It targets the lipid A component of lipopolysaccharides, which serves as an endotoxin in Gram-negative bacteria, thereby inhibiting the initiation of shock via the release of cytokines such as tumor necrosis factor-alpha and interleukin 8 (72).

9. Mechanisms ofcolistin resistance

9.1. Mechanisms of intrinsic resistance in Serratia marcescens and Proteus mirabilis

Colistin resistance is inherently present in *Serratia marcescens* and *Proteus mirabilis* due to the expression of the *arnBCADTEF* and/or *eptB* genes, leading to the incorporation of phosphoethanolamine (pEtN) and 4-amino-4-deoxy-L-arabinose (L-Ara4N) cationic groups onto LPS, respectively. This modulation enhances the cationic charge on the LPS membrane, which is the primary target ofcolistin. As a result, this reducescolistin antibiotic binding, leading to inherent resistance in these bacterial species (92-94).

9.2. Mechanisms of acquired resistance in Enterobacterales

Resistance to polymyxins has been observed in various genera of the *Enterobacterales*, including *Klebsiella*, *Escherichia*, *Enterobacter*, and *Salmonella*. While for certain bacterial species the mechanisms ofcolistin resistance remain unidentified, multiple molecular processes have been elucidated. The predominant mechanism involves modification of LPS through cationic substitution, similar to that observed in bacteria with intrinsic resistance to polymyxins. To date, only a single transferable resistance mechanism, the plasmid-mediated *mcr* gene, has been identified, whereas most resistance determinants are chromosomally encoded (95).

As seen in strains that exhibit natural resistance tocolistin, the incorporation of cationic groups (L-Ara4N and pEtN) into the LPS facilitates the development ofcolistin resistance in *Enterobacterales*. A comprehensive array of genes and operons participates in the qualitative modification of LPS. These include genes and operons that encode enzymes directly involved in LPS alterations, such as those responsible for synthesizing cationic groups and/or incorporating them into LPS, for example, the *pmrC* gene, the *pmrE* gene, and the *pmrHFIJKLM* operon. Additionally, several regulatory genes play key roles, including those encoding the PmrAB and PhoPQ two-component systems, as well as regulators of these systems, such as the *mgrB* gene, which negatively modulates PhoPQ, and the *crrAB* two-component system that controls the PmrAB system. (95).

9.2.1. Genes encoding LPS-modifying enzymes

a. **The *pmrC* gene:**

The *pmrCAB* operon encodes three proteins: the pEtN phosphotransferase PmrC, the response regulator PmrA (also known as BasR), and the sensor kinase protein PmrB (often referred to as BasS) (96). The pEtN phosphotransferase PmrC attaches a pEtN group to the LPS (96).

b. **The *pmrHFIJKLM* operon and the *pmrE* gene:**

The *pmrHFIJKLM* operon (also called the *arnBCADTEF* or *pbgPE* operon) codes for a total of seven proteins (97). The *pmrE* gene and the *pmrHFIJKLM* operon are important for the biosynthesis of L-Ara4N and its attachment to lipid A (97).

c. **The *pmrA* and *pmrB* genes encoding the PmrAB two-component system:**

Environmental triggers, including macrophage phagosomes, Fe^{3+} iron, aluminum (Al^{3+}), and low pH (e.g., pH 5.5), facilitate the activation of PmrB via its periplasmic domain. The PmrAB and PhoPQ two-component systems are often active when bacteria are engulfed by macrophages,

facilitating bacterial survival (96).

PmrB is a protein exhibiting tyrosine kinase activity that phosphorylates and activates PmrA. PmrA subsequently promotes the transcription of the *pmrCAB* operon, the *pmrHFIJKLM* operon, and the *pmrE* gene, which are implicated in LPS modification (pEtN and L-Ara4N addition) (96).

Mutations in the *pmrA* and *pmrB* genes have been identified as responsible for acquiredcolistin resistance in *K. pneumoniae* (98, 99). These mutations cause the persistent activation of the PmrAB two-component system, resulting in the overexpression of the *pmrCAB* operon, the *pmrHFIJKLM* operon, and the *pmrE* gene, thereby facilitating the production of pEtN and L-Ara4N and their incorporation into lipid A (95). Specifically, the PmrC protein encoded by the *pmrCAB* operon catalyzes the addition of pEtN to the lipid A moiety, while ArnT, an integral membrane protein encoded by *pmrHFIJKLM*, transfers L-Ara4N to lipid A (100, 101).

d. **The *phoP* and *phoQ* genes encoding the PhoPQ two-component system:**

The *phoPQ* operon encodes two proteins: the regulatory protein PhoP and the sensor protein kinase PhoQ. Environmental cues, including macrophage phagosomes, low magnesium, and low pH (e.g., pH 5.5), facilitate the activation of PhoQ via its periplasmic domain (96). The PhoPQ two-component system facilitates the expression of genes responsible for magnesium transport, enzymes that alter LPS to confer resistance to cationic antimicrobial peptides, and enzymes that mitigate cellular stress induced by acidic pH or certain virulence factors. The PhoPQ two-component system enables bacterial survival in environments characterized by low magnesium levels, acidic pH, or the presence of cationic antimicrobial peptides (102, 103).

PhoQ is a protein possessing tyrosine kinase activity that stimulates PhoP by phosphorylation. PhoP subsequently promotes the transcription of the *pmrHFIJKLM* operon, which is implicated in the incorporation of L-Ara4N into the LPS. PhoP can activate the PmrA protein, either directly or indirectly through the PmrD connector protein, resulting in the addition of pEtN to the LPS (102, 103).

Polymyxin heteroresistance in *E. cloacae* has been linked to the *dedA* and *ecr* genes. Specifically, *dedA* encodes a membrane protein believed to be involved in proton motive force-dependent drug efflux, and its disruption was found to increase susceptibility towards polymyxins. While its complementation results in increased MIC (104). Moreover, the DedA protein was found to play a role in establishingcolistin resistance in many Gram-negative bacteria, including *K. pneumoniae* (105, 106). The *ecr* gene encodes a small transmembrane protein that activates the PhoPQ system, leading to the upregulation of the *pmrHFIJKLM* operon, promoting LPS modification, leading to high-levelcolistin resistance. The *ecr* gene was also found to upregulate *dedA* and *tolC*, the latter of which encodes a key component of the AcrAB-TolC efflux pump (104, 107).

Multiple mutations in the *phoP* and *phoQ* genes contribute to the development of acquired resistance to polymyxins in *K. pneumoniae* (108). These mutations cause the constitutive activation of the PhoPQ two-component system, resulting in the overexpression of the *pmrHFIJKLM* operon and consequently the production of L-Ara4N and its transfer to lipid A (95).

9.2.2. Regulators of the PmrAB and PhoPQ two-component systems

a. **The *mgrB* gene:**

MgrB, also known as YobG, is a diminutive transmembrane protein comprising 47 amino acids (109). Activation of PhoP results in the upregulation of the *mgrB* gene. The MgrB protein subsequently inhibits the expression of the PhoQ-encoding gene, resulting in negative regulation of the PhoPQ two-component system (110). The inactivation of the *mgrB* gene, which negatively regulates the PhoPQ two-component system, results in the overexpression of the *phoPQ* operon, subsequently activating the *pmrHFIJKLM* operon and facilitating the formation of L-Ara4N, responsible forcolistin resistance acquisition (95).

Research indicates that transcript interruption and amino acid mutations in *mgrB* are significant factors behindcolistin resistance (111). A recent study highlighted the significance of *mgrB*-related mutations in *K. pneumoniae*, reporting that these mutations account for more than 80% of the resistance-associated genetic alterations detected globally in *K. pneumoniae* isolates (98). Alarmingly, recent reports indicate that the transposition of genes encoding ESBLs or carbapenemases, resulting in the disruption of the chromosomal *mgrB* gene, serves as a source of resistance tocolistin (112, 113).

b. **The *crrAB* operon:**

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.2.1790

The *crrAB* operon encodes two proteins: the regulatory protein CrrA and the sensor kinase CrrB. Induced mutations of the *crrB* gene result in the overexpression of the *pmrCAB* operon, which activates the *pmrHFIJKLM* operon, *pmrC* and *pmrE* genes, ultimately leading to the synthesis of L-Ara4N and pEtN, both of which confercolistin resistance. Inactivation of the CrrB protein may alter lipid A via the activation of a glycosyltransferase-like protein (95). Additionally, the CrrAB and PmrAB two-component systems are indirectly linked through the modulator protein, CrrC. Mutations in the *crrB* gene lead to elevated expression of *crrC*. Specific amino acid substitutions in the CrrB protein enhance its autophosphorylation activity, which contributes to increased resistance tocolistin (101, 114). While the *crrAB* operon was found to regulate polymyxin resistance and affect virulence, its physiological function in the absence of antibiotic pressure remains incompletely understood (115).

9.2.3. The intrinsic regulator RamA

RamA, the intrinsic regulator of *K. pneumoniae*, is recognized for its substantial role in the comprehensive response to antimicrobials. It modulates genes associated with permeability barriers and may thus contribute to diminished susceptibility to antibiotics. Findings indicate that elevated levels of this regulator resulted in modifications to LPS, hence diminishing vulnerability to polymyxins (116).

9.3. Mechanisms of acquired resistance in Pseudomonas aeruginosa and Acinetobacter baumannii

In *P. aeruginosa*,colistin resistance is primarily mediated by five two-component regulatory systems: PmrAB, PhoPQ, ParRS, ColRS, and CprRS (95). Mutations in PmrAB and PhoPQ lead to constitutive activation of the *pmrHFIJKLM* operon, resulting in the addition of L-Ara4N to lipid A, which reducescolistin binding and confers resistance (117). Unlike what is observed in *K. pneumoniae*, PhoPQ-mediated resistance in *P. aeruginosa* does not depend on the PmrAB system (95). The ParRS system contributes to adaptive resistance, also activating the *pmrHFIJKLM* operon (118). In contrast, the roles of ColRS and CprRS are less clearly defined; although their mutations have been associated with high-level polymyxin resistance, particularly when occurring alongside *phoQ* mutations (119).

In *A. baumannii*, resistance occurs via two major mechanisms: (1) qualitative modification of LPS through PmrAB mutations that activate the *pmrCAB* operon, leading to pEtN addition, and (2) quantitative loss of LPS production due to inactivating mutations in lipid A biosynthesis genes (*lpxA*, *lpxC*, and *lpxD*) (95).

9.4. Emergence of plasmid-mediated mcr genes

Resistance acquired from plasmid DNA, encoded by transposable genetic elements on plasmids containing *mcr-1* and its variants, was initially reported in *E. coli* from China. Subsequently, plasmid-mediated *mcr-1* and its variants have been identified in other Gram-negative bacterial isolates (120, 121). The resistance pattern involves encoding the *mcr-1* protein pEtN transferase. It was suggested that *mcr* genes originated from inherently resistant environmental bacteria, such as *Paenibacillus species*, yet *mcr* genes spread globally via a highly transmissible plasmid. Epidemiological and molecular studies have identified the presence of *mcr-1* within the diverse *Enterobacterales* family, which includes *K. pneumoniae, E. aerogenes, Shigella sonnei, E. cloacae, Salmonella, Kluyvera species, Cronobacter sakazakii, Citrobacter species, and Raoultella ornithinolytica.* Furthermore, bacterial isolates containing *mcr-1* demonstrated intricate reservoirs encompassing human-associated settings and natural ecosystems' food supplies (1). The LPS is altered by *mcr-1* expression through the addition of cationic pEtN transferase (71). Nonetheless, novel variations of *mcr-1* (*mcr-1.0* to *mcr-1.30*) have been documented, exhibiting expression through modifications of the LPS membrane.

Further *mcr* variations have been documented, including *mcr-2* (*mcr-2.1* to *mcr-2.7*) (122). Phylogenetic analyses revealed a novel variation of *mcr-1* exhibiting 80% identity. Subsequently, three more plasmid-mediated *mcr*-like gene variations were identified in *E. coli* and *Salmonella*: *mcr-3* (*mcr-3.1* to *mcr-3.41*), *mcr-4* (*mcr-4.1* to *mcr-4.6*), and *mcr-5* (*mcr-5.1* to *mcr-5.4*). Phylogenetic research indicated that *mcr-3*, *mcr-4*, and *mcr-5* are derived genes of *mcr-1*/*mcr-2*. In 2018, novel *mcr* gene variants, *mcr-6* (*mcr-6.1*), *mcr-7* (*mcr-7.1*), and *mcr-8* (*mcr-8.1-mcr-8.5*), were discovered, resulting in an expanded range ofcolistin resistance (123-125). Carrol et al. identified a new *mcr* homolog, designated *mcr-9* (*mcr-9.1* to *mcr-9.3*), in multidrug-resistantcolistin-susceptible *Salmonella enterica* (*S. enterica*) *serovar Typhimurium* isolates (126). Unexpectedly, the *S. enterica serovar Typhimurium* strain exhibited phenotypic sensitivity tocolistin, with an MIC of 2 µg/ml, in accordance with European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations. Comparative research

indicated that the protein structures of all nine *mcr* homologs (*mcr-1* to *mcr-9*) demonstrated significant structural similarity among *mcr-3, mcr-4, mcr-7,* and *mcr-9* genes (126).

The *mcr-10* (*mcr-10.1*) variation has recently been found on an *Inc*FIA plasmid in a clinical strain of *Enterobacter roggenkampii*. This *mcr* variation has the highest nucleotide identity (79.69%) with *mcr-9* and yields Mcr-10, which shares 82.93% amino acid identity with Mcr-9 (127).

Given the rapid, global emergence of plasmid-mediatedcolistin resistance genes (*mcr-1* through *mcr-10*) across diverse bacterial species and environments, including human, animal, and environmental samples, the potential for widespread horizontal dissemination is a significant public health concern (128). Identifying *mcr* genes is crucial for monitoring plasmid-mediated resistance and tracking the global dissemination ofcolistin resistance among Gram-negative pathogens (129-131). Notably, *mcr* genes are often located on mobile plasmids (e.g., IncI2, IncX4, IncHI2) that frequently co-harbor other resistance determinants, such as ESBLs (bla_{CTX-M}) and carbapenemases (bla_{KPC}, bla_{OXA-48}, bla_{NDM}). This co-localization facilitates the horizontal transfer of resistance to multiple antimicrobial classes, accelerating the emergence and spread of multidrug- and extensively drug-resistant strains across bacterial species and ecological settings (80).

10. The role of β-lactam/β-lactamase inhibitor combinations and cefiderocol in antibiotic resistance

The continuous rise of carbapenem-resistant Gram-negative bacteria has driven the development of new β-lactam/β-lactamase inhibitor combinations to combat these formidable pathogens (132). These new agents offer advantages over revived agents such ascolistin, primarily due to the latter's unfavorable toxicity profile, suboptimal pharmacokinetics, and increasing resistance rates, all of which complicate therapeutic decision-making and adversely affect patient outcomes (133). These agents include carbapenem-based combinations, such as meropenem/vaborbactam and imipenem/cilastatin/relebactam; cephalosporin-based combinations, including ceftazidime/avibactam and the siderophore cephalosporin cefiderocol. Furthermore, two β-lactam/β-lactamase inhibitor combinations approved in the past two years, namely aztreonam/avibactam, a monobactam paired with a β-lactamase inhibitor, and sulbactam/durlobactam, a combination of β-lactamase inhibitors (134).

While some agents, such as ceftazidime/avibactam, are now commercially available in Egypt (135), others have yet to receive local regulatory approval, though ongoing studies are evaluating their potential clinical role.

Table 1 summarizes the core features of new agents against carbapenem-resistant Gram-negative bacteria, including their approved indications, the Ambler β-lactamase classes they inhibit, and their key mechanisms and target organisms.

Table 1: Summary of clinical use, β-Lactamase coverage, and mechanism of action of novel β- Lactam/ β-Lactamase inhibitor combinations and cefiderocol

Agent	Key Approvals & Indications	Target β-Lactamase	Mechanism of action & target organism	References
Carbapenem-based combinations				
Meropenem/ Vaborbactam	**FDA:** cUTI. **EMA:** cUTI, cIAI, HAP, VAP.	Serine carbapenemases, specifically KPC enzymes.	**MOA:** Vaborbactam (a cyclic boronic-acid inhibitor) inhibits serine carbapenemases, mainly KPC, preventing meropenem degradation. **Target organism:** Strong first-line option for severe KPC-CRE infections.	(132, 136, 137, 138)

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.2.1790

Imipenem/ Cilastatin/ Relebactam	**United States & European Union:** Nosocomial pneumonia, cUTIs, cIAIs, and other infections by CRE and carbapenem-resistant *Pseudomonas*	Class A (including KPC) and Class C β-lactamases.	**MOA:** Relebactam (a DBO derivative) inhibits class A (KPC) and class C β-lactamases. **Target organism:** Effective against CRE strains. Retains some activity against non-MBL-producing carbapenem-resistant *P. aeruginosa* strains.	(136, 139)
Cephalosporin-based combinations and siderophore cephalosporin				
Ceftazidime/ Avibactam	**FDA & EMA:** cIAI, cUTI, HAP, VAP.	Class A (e.g., KPC), Class C (AmpC), and selected Class D (OXA-48-like) β-lactamases	**MOA:** Avibactam (a non-β-lactam DBO inhibitor) exhibits potent inhibition of class A, C, and selected class D, protecting ceftazidime (a third-generation cephalosporin) from degradation **Target organism:** Active against CRE and carbapenem-resistant *P. aeruginosa* (non-MBL producers). **Note:** Co-administration with Aztreonam overcomes MBL limitation (viable for MBL-producing *Enterobacterales*).	(16, 136, 139, 140)
Cefiderocol	**FDA:** cUTI, HAP, VAP.	Active against all Ambler classes: Class A (KPC) and ESBLs (CTX-type, SHV-type, TEM-type), Class B (NDM, IMP, VIM), Class C (AmpC), Class D (OXA, OXA-24, OXA-48, OXA-48-like).	**MOA:** "Trojan horse" mechanism: Catechol-type siderophore cephalosporin that binds to iron, entering bacterial cell via active iron transporters. Circumvents resistance mechanisms like decreased permeability, efflux pump upregulation, and carbapenemase inactivation. **Target organism:** Effective against aerobic fermentative and non-fermentative MDR Gram-negative bacilli Reserved for patients with few or no alternative therapeutic options.	(136, 141, 142, 143, 144, 145)
Other β-lactam/β-lactamase inhibitor combinations				
Aztreonam/ Avibactam	**EMA & FDA:** cIAI, **EMA:** HAP, VAP, cUTI, and infections by aerobic Gram-negative bacteria (hindered/scarce therapeutic alternatives).	The combination covers Class A (including KPC, ESBLs), Class C (AmpC), Class D (OXA-48), and Class B MBLs (specifically VIM or NDM-type).	**MOA:** The combination works because Avibactam protects Aztreonam (a monobactam) from being destroyed by the concurrent serine β-lactamases (Classes A, C, and D) often co-expressed alongside MBLs in resistant bacteria. This safeguard ensures that the intact Aztreonam is free to act, as it is already safe from the MBLs themselves. **Target organism:** Robust efficacy against MBL-producing carbapenem-resistant Gram-negative bacteria, especially those that produce a diverse set of β-lactamases (Serine β-lactamases and MBLs together)	(132, 137, 139, 146)
Sulbactam/ Durlobactam	**FDA:** HAP, VAP.	Serine β-lactamases, predominantly OXAs (produced by the *A. baumannii–calcoaceticus* complex).	**MOA:** Durlobactam (a non-β-lactam β-lactamase inhibitor) protects sulbactam, which has inherent mild antibacterial activity. **Target organism:** Specifically approved for *A. baumannii-calcoaceticus* complex infections.	(134, 147, 148)

Abbreviations: *cIAI: Complicated intra-abdominal infections, CRE: Carbapenem-resistant Enterobacterales, cUTI: Complicated urinary tract infections, DBO: Diazabicyclooctane, EMA: European medicines agency, FDA: Food and Drug Administration, HAP: Hospital-acquired pneumonia, MBLs: Metallo-beta-lactamases, MOA: Mechanism of action, VAP: Ventilator-associated pneumonia*

10.1. Carbapenem-based combinations

10.1.1. Meropenem/vaborbactam

Meropenem/vaborbactam is the combination of meropenem with the new-generation beta-lactamase inhibitor vaborbactam. This combination was initially approved by the FDA in 2017 for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis. In 2018, meropenem/vaborbactam was also approved by the European Medicines Agency (EMA) for treatment of cUTI, complicated intra-abdominal infections (cIAI), and hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (136).

Vaborbactam, a cyclic boronic-acid inhibitor, is specifically designed for potent inhibition of serine carbapenemases, especially KPC enzymes, but lacks activity against MBLs and shows no efficacy against *A. baumannii* or *P. aeruginosa* (132, 137).

Given its activity against ceftazidime/avibactam-resistant KPC variants and its favorable pharmacokinetics/pharmacodynamics properties, meropenem/vaborbactam emerges as a strong first-line option for treating severe KPC-CRE infections (138).

10.1.2. Imipenem/cilastatin/relebactam

Imipenem/cilastatin/relebactam is approved in the US as well as in the European Union, in adults for the treatment of nosocomial pneumonia, cUTIs, cIAIs, and other infections by CRE and carbapenem-resistant *Pseudomonas* strains in the case of limited or no alternative treatment options (136).

Relebactam, a diazabicyclooctane (DBO) derivative structurally related to avibactam, effectively inhibits class A (including KPC) and class C β-lactamases but demonstrates no activity against class D carbapenemases and no efficacy against MBLs. Similar to vaborbactam, relebactam is ineffective against *A. baumannii*, although it retains some activity against non-MBL-producing carbapenem-resistant *P. aeruginosa* strains (139).

10.2. Cephalosporin-based combinations and siderophore cephalosporin

10.2.1. Ceftazidime/avibactam

Ceftazidime/avibactam is a ß-lactam/ß-lactamase inhibitor combination authorized by the FDA and the EMA for the management of cIAI, cUTI, HAP, and VAP. Ceftazidime is a third-generation cephalosporin exhibiting a wide range of efficacy against Gram-negative bacilli, including *P. aeruginosa* (136).

Avibactam, a non-β-lactam DBO inhibitor, exhibits potent inhibition of class A (e.g., KPC), class C (AmpC), and selected class D (OXA-48-like) β-lactamases, particularly those associated with *K. pneumoniae*, protecting ceftazidime against hydrolysis. However, it has no effect on MBL producers. It also has no activity against *A. baumannii* but has demonstrated activity against *P. aeruginosa* isolates that are resistant to carbapenems but do not produce MBLs (139).

Although the ceftazidime/avibactam combination is ineffective against MBL producers, co-administration with Aztreonam has been shown to overcome this limitation (16). The combination of ceftazidime/avibactam and Aztreonam has emerged as a viable therapeutic option for BSIs caused by MBL-producing *Enterobacterales*, particularly NDM and VIM producers. In a prospective study involving 343 patients from 2019 to 2022, the combination of ceftazidime/avibactam and Aztreonam was the predominant regimen for treating infections caused by MBL-producing *Enterobacterales*, utilized in 62.7% of patients. In comparison tocolistin-based regimens, the combination of ceftazidime/avibactam and Aztreonam was independently linked to a notable decrease in 30-day mortality, with synergy between ceftazidime/avibactam and Aztreonam observed in 99.7% of evaluated isolates. Patients administeredcolistin experienced significantly elevated incidence of adverse events, notably acute renal injury, in comparison to those treated with ceftazidime/avibactam combined with Aztreonam (140).

10.2.2. Cefiderocol

Cefiderocol is a siderophore-cephalosporin that was approved by the FDA for the treatment of urinary tract infections and nosocomial pneumonia, including both HAP and VAP. It exhibits *in vitro* activity against aerobic fermentative and non-fermentative MDR Gram-negative bacilli (136).

Cefiderocol is a synthetic compound consisting of a cephalosporin moiety and a catechol-type siderophore, which binds to iron and enables bacterial cell entrance through active iron transporters, employing a "Trojan horse" mechanism (141). Upon entering the periplasmic region, it dissociates from iron, and the cephalosporin moiety mostly binds to PBP3, thereby inhibiting bacterial cell wall

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.2.1790

formation (142). Cefiderocol's capacity for active transport within the cell enables it to circumvent resistance mechanisms caused by diminished bacterial membrane permeability, which arises from decreased expression or mutation of porin channels, upregulation of efflux pumps, and inactivation by carbapenemases (141, 143, 144). Cefiderocol exhibits efficacy against ESBLs in CRE, including CTX-type, SHV-type, and TEM-type, as well as all Ambler classes of β-lactamases: class A (KPC), class B (NDM, IMP, and VIM), class C (AmpC), and class D (OXA, OXA-24, OXA-48, and OXA-48-like) (145). Cefiderocol's broad spectrum of activity against all carbapenemases renders it reserved for patients with few or no alternative therapeutic alternatives, hence mitigating the risk of widespread resistance or serving as empirical treatment in high-resistance environments (141).

10.3. Other β-lactam/β-lactamase inhibitor combinations

10.3.1. Aztreonam/avibactam

Aztreonam/avibactam is an antibiotic authorized by the EMA for the management of cIAI, HAP, including VAP, cUTI, including pyelonephritis, and infections attributable to aerobic Gram-negative bacteria in patients with hindered therapeutic alternatives. The FDA has similarly authorized aztreonam/avibactam for the treatment of individuals with cIAI when therapeutic alternatives are scarce or nonexistent (139).

Avibactam proficiently inhibits class A and C β-lactamases, along with certain class D enzymes. Nevertheless, it does not impede MBLs. The combination of avibactam with the monobactam aztreonam exhibits robust efficacy against MBL-producing carbapenem-resistant Gram-negative bacteria. This effectiveness arises from the inability of MBLs to hydrolyze Aztreonam, which stays structurally unaltered. Moreover, avibactam augments the efficacy of Aztreonam by safeguarding it from degradation by concurrent serine β-lactamases, commonly found in carbapenem-resistant Gram-negative bacteria. Therefore, for *Enterobacterales* strains demonstrating diverse resistance mechanisms that include VIM or NDM-type MBL alongside co-expression of ESBLs, KPC, OXA-48, or AmpC β-lactamases, the combination therapy of aztreonam/avibactam is a successful treatment strategy (132, 137, 146).

10.3.2. Sulbactam/durlobactam

Sulbactam is a β-lactamase inhibitor that contains a β-lactam ring (147). The β-lactam ring imparts sulbactam with inherent mild antibacterial activity, unlike other β-lactamase inhibitors that require binding to the β-lactam to demonstrate their antibacterial efficacy (147).

Durlobactam is a non-β-lactam β-lactamase inhibitor that, when paired with sulbactam, safeguards the latter from degradation by certain serine β-lactamases, predominantly OXAs, produced by the *A. baumannii–calcoaceticus* complex (134). Durlobactam is a chemical derivative of avibactam (148).

Sulbactam/durlobactam was approved by the FDA in May 2023 for use in adult patients with HAP and VAP due to *A. baumannii–calcoaceticus* complex (134).

11. Conclusion and Future Perspectives in the Egyptian Context

The emergence of carbapenem-resistant Gram-negative bacteria is a major global public-health threat, and Egypt is no exception. This rise has created a critical gap in effective therapy, prompting the re-use ofcolistin, an older polymyxin largely abandoned because of nephrotoxicity and neurotoxicity, as a last-resort option. Alarmingly,colistin resistance is increasing, driven in large part by uncontrolled veterinary use and the dissemination of mobilizedcolistin resistance (*mcr*) genes; a recent systematic review reportedcolistin resistance in roughly 9% of Gram-negative isolates and nearly 31% of carbapenem-resistant strains in Egypt. These findings highlight the urgent need for robust antibiotic stewardship and strengthened national surveillance to curb antimicrobial resistance. Novel β-lactam and β-lactam/β-lactamase-inhibitor combinations offer promising, safer alternatives, but access and affordability remain major barriers in LMICs; although ceftazidime-avibactam is now commercially available in Egypt, several other agents lack local approval and continue to be evaluated in clinical studies.

Data Availability
This study did not generate or analyze any new data.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Funding
Not Applicable.

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