**Review Article**

# Colistin Resistance: critical review of the literature

Sana Yahyazadeh Jasour[1], Zahra Fekrirad[1*]

1. Department of Biology, Faculty of Basic Sciences, Shahed University, Tehran, Iran.

***Corresponding Author: Zahra Fekrirad**, Department of Biology, Faculty of Basic Sciences, Shahed University, Tehran, Iran. ORCID: https://orcid.org/0000-0003-3450-7654

**Abstract:**

**Introduction**: With the emergence of nosocomial pathogens and the emergence of multidrug resistant agents, repeated and continuous studies on changes in resistance patterns of clinic isolated bacteria seem necessary. Colistin sulfate is known to be the last line of treatment against the different range of antibiotic resistance. While recent evidences show emergence of the colistin resistance that we are going to review here.

**Methods**: A critical review of the literature.

**Results**: colistin as a member of earlier classes of antibiotics was still working against extended-spectrum beta-lactamase -producing bacteria in last decades. This feature of the colistin was affiliated with its infrequent use due to fear of its medical adverse events. Meanwhile, recent reports indicate appearance of the colistin resistance in E. Coli, Acinetobacter baumannii and Klebsiella pneumoniae isolates. Sets of different genes in relation to the colistin resistance are proposed in literature. Efflux pumps might also play important role in appearance of these resistant strains.

**Conclusion**: When any other antibiotic does not work, Colistin is use it as the last effective bead in treating patients. Because colistin is used in the last line of treatment, increasing resistance to it is a wake-up call for health systems.

**Keywords**: Colistin, antibacterial resistance, E. Coli, Acinetobacter baumannii, Klebsiella pneumoniae

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## Introduction

Antibiotics by definition contain biological and synthetic substances that will eliminate or stop the growth of microorganisms (1). The declining effectiveness of antibiotics in treating infections has accelerated in recent years (2). Overuse of antibiotics in medicine, veterinary medicine and agriculture has caused selective pressure on bacterial populations and the spread of antibiotic-resistant strains (3). This event, especially in developing countries is accompanied by an increase in the length of hospital stay in hospitals and medical centers, and an increase in the cost of treatment and economic costs (4). The presence of resistant bacteria in different wards of hospitals, especially in intensive care units and the problems that these resistant bacteria cause in the treatment of patients, indicates the need for accurate knowledge of these types of bacteria and their pattern of antibiotic resistance (5). Colistin sulfate is considered the last line of defense against a variety of antibiotic resistance. While new research suggests the establishment of colistin resistance, which we will discuss in this study.

## Antibiotic resistance history and rationale for renewing Colistin:

β-lactamases are enzymes that break down β-lactam antibiotics, which are the largest group of antibiotics. In recent years the prevalence of β-lactamases has increased rapidly and is recognized as a growing problem in the treatment of infectious diseases (6). Overuse of broad-spectrum beta-lactam antibiotics, mainly third-generation cephalosporins, has led to the production of extended spectrum beta-lactamase (ESBLs) among Gram-negative bacilli of Enterobacteriaceae families such as E. coli. and Klebsiella pneumoniae (7). ESBL enzymes break down penicillin, orido, and carboxy penicillin, the first, second, and third generations of cephalosporins and astronomers (8). Carbapenems were the only beta-lactam antibiotics that are effective against ESBL-producing bacteria; while later resistance was reported widely (9). Carbapenems are commonly used for beta-lactamase-producing bacteria, but recently the bacteria have developed simultaneous resistance to cephalosporins and carbapenems by producing different beta-lactamases (9,10). Because it is difficult to identify the type of beta-lactamase, doctors are unable to prescribe appropriate antibiotics for treatment, resulting in increased antibiotic use and bacterial resistance to many antibiotics. The genes encoding ESBLs are commonly found in plasmids and are transmitted between different bacteria in plasmids or other transmissible DNA (11), but colistin was still working against ESBL-producing bacteria (12). This feature of the colistin was affiliated with its infrequent use due to fear of nephrotoxicity (13). Meanwhile, recent reports indicate appearance of the colistin resistance plasmids (mcr) that led to colistin resistance in E. Coli. (14-16). Aguirre et al. found set of genes, etpA, arnT, ccrB, pmrB in relation to the colistin resistance in E. Coli. (17).

Previous studies have described the risks associated with antibiotic resistance induced by ESBL production. Comparison of sepsis caused by ESBL-producing bacteria against E. coli and Klebsiella that did not produce ESBL showed that these bacteria were five times more resistant to proper antibiotic treatment (18) and their mortality is almost four times higher (18) and the length of hospital stay of patients with ESBL-producing bacteria is significantly longer (18,19). The first ESBLs to be discovered in the 1980s were derivatives of the β-lactamases produced by SHV and TEM genes, which inhibited the activity of beta-lactam antibiotics, including third-generation cephalosporins (20). Since then, more than 200 TEM enzyme β-lactamases and nearly 200 SHV enzymes have been discovered; About half of these molecules have ESBL activity (21). CTX-M is the newest member of the ESBLs encoded by plasmids,

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and more than 160 molecules derived from this group have been shown to have ESBL activity. CTX-M derivatives have been expanding rapidly over the past decade (21-23). But colistin was showing great efficacy and low resistance rate in CTX-M ESBLs producing microorganisms (22); while later, colistin-resistant E. coli was reported for the first time in the cockroaches in 2022 (23).

The widespread utilization carbapenems to combat multidrug-resistant (MDR) Gram-negative bacterial infections has aided the spread of carbapenem-resistant Enterobacteriaceae over the world. In some regions, serine and metallo—lactamases (MBLs) have grown common, requiring the usage of earlier classes of antibiotics like colistin (24).

**Colistin sulfate resistance in carbapenemase-producing Klebsiella pneumoniae**

Colistin resistance is becoming more common among Klebsiella pneumoniae isolates that produce carbapenemase and it was reported in SHV-5-produning strains (25). Medical care centers should be able to detect broad-spectrum beta-lactamase-producing bacteria and carbapenemaze, and if they see broad-spectrum beta-lactamase-producing bacteria and carbapenemase, use a combination of beta-lactamase inhibitors and beta-lactam antibiotics. A set of recent studies have investigated synergism of Colistin and meropenem for treatment of the carbapenemase-producing Klebsiella pneumoniae. Nutman et al. found such synergism in-vitro; but clinical efficacy of Colistin and meropenem combination was not satisfying (26). A randomized clinical trial in 2018 showed that Colistin monotherapy was as effective as colistin plus meropenem in carbapenemase producing microorganisms (27).

**Colistin sulfate resistance in Acinetobacter**

Multidrug resistance in Acinetobacter baumannii is the main cause of treatment failure for nosocomial infections Acinetobacter baumannii strains due to inherent resistance and acceptance of genetic elements carrying resistance genes to most Antibiotics, and multidrug-resistant strains have emerged. Colistin sulfate is known to be an effective antibiotic especially for the treatment of nosocomial infections with multiple antibiotic resistance, although cases of resistance to Colistin is recently reported in Acinetobacter that has raised concerns on the global deterioration of the situation (28). From the first reports of the Colistin resistance, scientists have tended developing new generations of Colistin, like Wang et al. study recommending the phage therapy (28).

While Colistin was still working on carbapenem-resistant Acinetobacter baumannii (CRAB), emerging evidences are opposing in some endemic regions. Adams et al. suggested PmrAB gene as the mechanism of antibacterial resistance in Acinetobacter baumannii (29). Another study reported lpsB, dnaK, and blsA genes to be associated with colistin resistance Acinetobacter baumannii (30).

**Efflux pumps and colistin resistance:**

Today, active efflux pumps as one of the most important mechanisms of intrinsic and acquired resistance of antibiotics have been reported in bacteria (31). Antibiotic effusion pumps in bacteria belong to five large families in terms of phylogeny. Among them are pumps of Resistance-Nodulation-Division and Multidrug and Toxic compound Extrusion of Acinetobacter baumannii pump (32). Influx pumps not only increase the minimum concentration of inhibitory growth of antibiotic bacteria, but also reduce Intracellular drug concentrations lead to the development of antibiotic-resistant mutant strains in bacteria. Many efflux pumps, such as KpnEF and the AcrAB–TolC complex, have been discovered as lowering colistin sensitivity (33).

**Conclusion:**

In the last few decades, colistin, a member of an older family of antibiotics, was nevertheless

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effective against extended-spectrum beta-lactamase-producing bacteria. This property of colistin was linked to its uncommon usage due to concerns about its medical side effects. Meanwhile, findings suggest that colistin resistance has emerged in E. coli, Acinetobacter baumannii, and Klebsiella pneumoniae isolates. Literature has hypothesized a number of alternative gene sets in relation to colistin resistance. Efflux pumps might also play important role in the appearance of these resistant strains.

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