

The Global Challenge of Colistin Resistance – Recent Evidence from Romania and Elsewhere

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ABSTRACT

The increasing resistance of Gram-negative bacilli to a wide range of antibiotics has driven a return to colistin as the last resort in the treatment of severe infections. Given the stakes of colistin efficiency at both the individual level and generally, the manifestation and mechanisms of resistance to polymyxin E (also known as colistin) are now subject to careful monitoring and research. Recent findings from different parts of the world including Romania are reviewed and discussed in the light of ensuing challenges.

Keywords: Colistin; Gram-Negative Bacteria; Resistance Mechanisms and Detection

Colistin and Colistin Resistance

Colistin is a cationic polypeptide antibiotic from the polymyxin family, which includes polymyxin E (colistin) and polymyxin B. It was discovered in 1947 when it was isolated from the bacillus *Paenibacillus polymyxa* subsp. *colistinus* [1,2]. Its main activity mechanisms involve the displacement of calcium and magnesium ions from lipopolysaccharides, leading to a disruption in the permeability of the outer cellular membrane, as well as the inhibition of the type II NADH-quinone oxidoreductases, which is a crucial respiratory enzyme in the inner membrane of the Gram-negative strains [3,4]. Polymyxin E exerts a swift and strong bactericidal effect on *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and most bacilli from the *Enterobacterales* family, except for *Proteus*

spp., *Providencia* spp., *Serratia* spp., *Morganella* spp., which are naturally resistant to colistin [5]. Mutations and adaptation are the most important mechanisms of bacterial acquired resistance to polymyxin E. Because LPS is the major target of colistin it is clearly that the first mechanisms of resistance will appear at this level [5,6]. For *Klebsiella pneumoniae* strains, the modification of the *mgrB* gene is the most important mechanism of resistance to colistin [7].

Regarding *A. baumannii* strains, the alteration of the *lpxA*, *lpxC* and *lpxD* genes determine inhibition of lipid A synthesis and, as a consequence, colistin will lose the binding to bacterial cell [8]. Porin mutations and upregulation of efflux pump systems are other possible mechanisms of resistance to colistin, which results

of a combination of both [5]. Prior to 2015, resistance to colistin was explained by means of chromosomal mutations, but then new research uncovered genetic resistance that can be plasmid-mediated [9]. Over the last years, for *Escherichia coli* and *K. pneumoniae* strains have been reported plasmid mediated resistance genes, *mcr*, which encodes phosphoethanolamine transferase [10]. Traditional microbiology methods, as well as phenotyping and molecular biology techniques, are some of the ways in which resistance to colistin may be highlighted, the gold standard in this regard being the broth microdilution test. Recent evidence and epidemiologic studies have helped raise the alarm among the medical community and add a shared sense of urgency to the conversation.

Evidence of Increasing Colistin Resistance

An extended study driven in Switzerland during 2011-2015 analyzed colistin-susceptibility for 10,824 strains (9,229 isolates of *E. coli* and 1,595 isolates of *K. pneumoniae*) and the risk factors for those proved to be colistin-resistant. 53 patients had colistin-resistant strains and the major risk factor was previous carbapenem exposure [11]. Between 2013 and 2017 426 strains (18.5%) of carbapenem resistant *K. pneumoniae* were isolated from several healthcare settings from Serbia; 10.6% (a total of 45 clinical isolates) of them were colistin resistant [12]. A study conducted in South Africa in 2016-2017 revealed that colistin-resistant *A. baumannii* happened as a consequence of the clonal spread. This was the first report of this kind in that region. A possible explanation was the presence of colistin-susceptible strains that were genetically correlated in the same hospital, at the same time [13].

By 2017, up to 8.5% of strains were found to be colistin-resistant (2.4% for *K. pneumoniae*), the highest reported incidence being in Greece and Italy [14]. One year later, the World Health Organization elevated polymyxins to the level of critically-important antimicrobial agents, recommending that colistin be used only in the treatment of infections with Gram-negative bacilli already multidrug-resistant [15]. During 2011-2018, Macesic, et al. [16] identified 665 patients with carbapenem-resistant and 106 patients with colistin-resistant *K. pneumoniae* strains. In 48% patients the first *K. pneumoniae* polymyxin-resistant isolate was linked to an infection of the respiratory tract. Consecutively to the detection of colistin-resistant *K. pneumoniae* the 7-day and 30-day all-cause mortality rates raised from 13% and 32%, respectively, to 15% and 38%, respectively. The mechanisms of polymyxin resistance were heterogenous, leading to the conclusion that, in most occasions, polymyxin-resistant strains emerge after colistin treatment rather than clonal dissemination.

According to a recent study, no fewer than 590 strains of colistin-resistant *K. pneumoniae* were identified in six countries: 438 in Turkey, 86 in Iran, 24 in Saudi Arabia, 31 in the United

Arab Emirates, 5 in Kuwait, 3 in Israel, and another 3 in Lebanon, between 2013 and 2018. The *mcrB* gene was found to be involved in the resistance mechanism [17]. In another study from 2020, in Turkey, from a total of 150 strains of *Enterobacterales* isolated in pediatric patients suffering from infections, 41% were resistant to carbapenems and 15% to colistin. The reported risk factors for colistin resistance in these cases were mechanical ventilation, urinary catheterization, and the associated pathology of necrotizing enterocolitis [18]. The presence of the gene *mcr-1* and colistin resistance were monitored over a 5-year period (2014-2019) in patients infected with carbapenem-resistant *Enterobacterales* strains, who were administered colistin as part of their treatment. At the beginning, the incidence of strains carrying the *mcr-1* gene was low (0.41%), but then it began to rise (1.38%), especially once colistin was introduced. This pointed to the hypothesis that polymyxin E was responsible for triggering the *mcr-1* gene. The fact that the colistin minimal inhibitory concentration increased from <2 mg/L in 80% of the strains to 2 mg/L in 100% of the strains in a relatively short amount of time was yet another reason of concern [19].

In India, by 2020, 2499 strains of *Klebsiella* spp. were isolated from urine, sputum, broncho-alveolar lavage, blood culture and pus, in patients hospitalized in intensive care unit; 8.75% of colistin-resistant *Klebsiella* spp. were isolated from blood specimens, 4.26% from urine samples and 4.4% from sputum [20]. Another recent study highlighted the risk factors for patients with colistin-resistant *Enterobacterales* and identified some particular mutations associated with some of the strains isolated. From a total number of 16,373 isolates, 103 were colistin-resistant *Enterobacterales* strains. The main risk factors associated were: age >55 years and prescription of an antibiotic for no longer than 90 days. The main mutations that were identified from 33 strains, 8 were from *E. coli* isolates (*mcr-1/mcr-1.1* and *pmrA/B* mutations) and 8 from *K. pneumoniae* (*mcrB* and *pmrA* mutations). Regarding *Enterobacter* species the mutations were not related to colistin resistant phenotype [21].

Colistin Resistance in Romania

In Romania, in 2015, the presence of four colistin-resistant *K. pneumoniae* strains with identical PFGE profiles (Pulse-field Gel Electrophoresis) was reported in the cardiac intensive care unit at a university hospital in North-Eastern Romania. Fortunately, they did not produce carbapenemases [22]. However, in a recent study on patients with urinary tract infections, approximately 30% of *K. pneumoniae* isolates were found to be colistin-resistant and to produce wide-spectrum beta-lactamases [23]. Close monitoring and additional studies are needed in order to attain a more comprehensive understanding of the phenomenon and plan accordingly before the problem aggravates.

Conclusion

The increasing prevalence of multidrug-resistant strains has substantial, far-reaching negative implications for the entire world. The still excessive use of antibiotics and their diminishing effectiveness can limit treatment options to colistin, which we now know is not invulnerable. Invasive medical procedures and prolonged hospitalization can further contribute to the risk of developing resistance to this life-saving medication. In countries like Romania, where data is still scarce but sufficiently concerning, more research and communication need to be conducted with an adequate sense of urgency.

Conflict of Interest

The authors declare no conflict of interest.

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