Colistin

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Colistin, also known as polymyxin E, is an antibacterial cationic polypeptide that binds to the negatively charged lipid A of Gram-negative outer membrane lipopolysaccharide. Colistin is a last resort antibiotic medication for the treatment of infections caused by carbapenem-resistant Klebsiella pneumoniae.

colistin resistance | Klebsiella pneumoniae | chromosomal mediated resistance | plasmid-borne resistance

1. Introduction

Bacterial resistance to chemotherapeutic antibiotics has become a global public health threat. The current annual death rate associated with infections caused by drug-resistant microorganisms is estimated at 700,000 and might increase to 10 million by 2050 if urgent action is not taken [1]. In 2017, the WHO global priority list classified drug-resistant pathogens into three tiers, with carbapenem-resistant *Enterobacteriaceae* as critical and requiring immediate attention [2]. The increased prevalence of resistance to carbapenems associated with the expression of specific virulence factors and the spread of new clones, limits treatment options for infections caused by multidrug-resistant *Enterobacteriaceae* such as *Klebsiella pneumoniae* [3][4]. This has led to the reintroduction of polymyxins which were previously discontinued for use in humans [5]. Colistin, also known as polymyxin E, is an antibacterial cationic polypeptide that binds to the negatively charged lipid A of Gram-negative outer membrane lipopolysaccharide. The antibacterial agent competitively displaces membrane-stabilizing divalent cations (Ca^{2+} and Mg^{2+}) from the lipopolysaccharide, resulting in cell membrane disruption and cell death [6]. Gram-negative bacteria are known to be intrinsically susceptible to colistin except for bacteria of the genera Proteus, Providencia, Morganella, Serratia, Edwardsiella, and Burkholderia [6]. Colistin is a last-resort antibiotic therapy against multidrug-resistant infections caused by Gram-negative carbapenem-resistant bacteria; however, the overuse of colistin has resulted in the acquisition of resistance by several bacterial genera.

The emergence of colistin-resistant *Enterobacteriaceae* poses a severe challenge to the continued reliance on antibiotics chemotherapy. The spread of carbapenemase-producing colistin-resistant *K. pneumoniae* has been reported by researchers from different regions of the world, including Africa [7][8][9], Asia [10][11][12], Australia [13], Europe [14][15], North America [16], and South America [17]. Recently, a 71.3% prevalence was reported for colistin resistance among Escherichia coli, and *K. pneumoniae* isolates from Thailand [18]. Up to 2015, colistin resistance was related to chromosomal mutations resulting in the alteration of Gram-negative outer membrane lipopolysaccharide, which reduces the negative charge of the lipid A component and affinity for colistin. However, in

2016 the emergence of a plasmid-borne *mcr*-1 gene, a gene of the phosphoethanolamine transferase enzyme family was first reported [19][20][21][22]. This has raised concerns due to the potential rapid dissemination of resistant mediating plasmid between strains and subsequent selection pressure.

Colistin resistance in *K. pneumoniae* is mediated by several factors, including alterations of capsular polysaccharide and capsular type, efflux pumps, outer-membrane alterations, and alterations in lipid A and lipopolysaccharides. The inactivation of the mgrB gene, by products of the pmr operon encoding a negative feedback regulator of PhoQ-PhoP signaling system, is majorly responsible for acquired chromosomal related colistin resistance. Upregulation of PhoQ-PhoP activates the Pmr system responsible for lipopolysaccharide modification [23][24]. Alterations in the *mgrB* gene coupled with the disruption of pmrH operon, mutation in *phoQ*, elevated expression of *phoPQ*, and mutations of the crrAB two-component regulatory system with elevated expression of *pmrCAB* were reported in colistin-resistant *K. pneumoniae*. In addition, genes involved in cation transport and maintenance of membrane integrity were upregulated [25]. Studies have shown that the interruption of transcripts and amino acid mutation in mgrB are major mechanisms contributing to colistin resistance [26]. Amino acid substitutions in *K. pneumoniae* CrrB protein were associated with resistance to colistin [27]. A hospital outbreak of colistin-resistant carbapenemase-producing *K. pneumoniae* was traceable to the clonal expansion of an mgrB deletion mutant of a ST512 strain [28]. Furthermore, the presence of insertion sequences and nonsense/missense mutations on the cell chromosomal components were responsible for the inactivation of the mgrB gene [29]. Insertion sequences in the mgrB gene or surrounding region of *crrCAB* disrupted the regulatory function of the gene [30]. An IS-like element at the nucleotide position 75 of the mgrB and substitutions in PhoQ were identified as mechanisms of resistance [31]. In addition, an epidemiological investigation of colistin-resistant *K. pneumoniae* strains revealed that capsular type K64 and ST11 are the prevalent capsular and sequence types amongst colistin-resistant strains [26]. Atomic force microscopy revealed an altered capsule in a susceptible strain and intact capsules in a resistant strain suggesting that capsular polysaccharides influenced the response of *K. pneumoniae* to colistin [32]. Similarly, the presence of an efflux pump attributed to mutations in the two-component systems induced a high resistance to colistin in sequence type ST147 *K. pneumoniae* [33].

The spread of plasmid-mediated colistin resistance presents a critical threat. The carriage of resistant mediating genes on self-transmissible broad-host-range plasmid accentuates the potential to spread to a wider range of pathogens. Although the *mcr* plasmid that mediates colistin resistance was first reported between 2015–2016, recent research findings suggest a wide range of spread amongst *Enterobacteriaceae*, including *K. pneumoniae* and *E. coli* with the emergence of several variants. The *mcr*-2 to *mcr*-9, share 81%, 32.5%, 34%, 36%, 83%, 35%, 31% and 36% identical amino acid sequences with *mcr*-1, respectively [34][35][36]. In addition, minor variants have been reported for *mcr*-2, -4, -5, -6, -7, -8 and -9; however, a greater number of minor variants were identified for *mcr*-1 and *mcr*-3 with 18 and 28 variants, respectively [37].

2. Colistin Resistance in Klebsiella pneumoniae

The revitalization of colistin as the re-emerging choice drug for the management of infections caused by carbapenem-resistant Gram-negative bacteria faced a sudden setback following the emergence of resistance in

Enterobacteriaceae. This has left the health sector vulnerable to assault from carbapenem-resistant bacterial isolates, leading to increased morbidity and mortality. *K. pneumoniae*, an opportunistic bacterial species associated with mild to severe infections is a potential threat due to the recent emergence and spread of hypervirulent strains that havebroadened the number of people susceptible to infections, including both healthy and immunosufficient individuals [38]. Currently, researchers are overwhelmed in the search for alternative effective options, with synergistic combination therapies serving as an interim option [39].

Preceding articles published between 2005 and 2006 presented colistin as the re-emerging antibiotic of choice for the management of drug-resistant Gram-negatives including *K. pneumoniae*. Although colistin is effective against Gram-negative carbapenemase-producing *Enterobacteriaceae*, the re-emergence and revitalization of colistin were met with the sudden development of resistance following the first detection of carbapenem-resistant *Enterobacteriaceae*. Analysis of research output relating to colistin-resistant *K. pneumoniae* indicates a progressive increase beginning in 2009. However, 50.19% of all the retrieved documents were published within the last three years (2017–2019). This is due to the surge in cases of colistin resistance resulting from the extensive use and misuse of colistin in chemotherapy, and veterinaries, leading to an increased severity of colistin resistance as well as the heightened interest prompted by the categorization of antimicrobial resistance and prioritization of carbapenem-resistant *Enterobacteriaceae* in the critical class of the WHO global priority pathogens list [2]. In addition, the steep rise over the last three years stems from the elevated interest due to the emergence and rapid spread of colistin resistance arising from the emergence of the transferrable plasmid-mediated *mcr*-genes first reported in 2016, and its variants. Moreover, the acquisition of resistance in environmental isolates and reports of resistant mediating genes in both food and water might have widened the horizon of researchers interested in the topic, thus contributing to the rapid growth of research output. In addition, our results further suggested poor research outputs from the Eastern Mediterranean, Southeast Asia, and Africa, which calls for improved investment and surveillance on antimicrobial resistance. The available data on the prevalence of antimicrobial resistance across the globe indicated high levels in Africa and Asia. The yearly death attributable to AMR by 2050 according to the review on antimicrobial resistance estimates 4,150,000 and 4,730,000 annual deaths for Africa and Asia respectively [40]. The low research output on antimicrobial resistance suggests that irrespective of the World Health Assembly global and national action plan on AMR, there might be a lack of awareness and intervention policies within countries in the regions. Global AMR maps viewed at resistancebank.org indicated a high rate of resistance in Asia and Africa, with colistin resistance hotspots in Asia, and Latin America. Furthermore, resistance maps reveal the absence of major colistin resistance hotspots in Africa, and this probably suggests low surveillance and research activities regarding resistance. A recent work on the global trends in antimicrobial resistance in animals in low- and middle-income countries identified Asia as possessing the largest hotspot of AMR [41]. Similar to the findings of Sweileh and Moh'd Mansour [42], the results of the present study indicated that the United States and China dominated the research on colistin resistance in *K. pneumoniae*. In this study, China and India which are hotspots of AMR ranked 2nd and 4th in research output. The high rate of AMR in China has been linked to the unregulated usage of antimicrobial drugs in food-producing animals [43]. This might likewise be applicable in neighbouring countries such as India and other Asian countries.

3. Conclusions

As antimicrobial resistance spreads, it has become essential to monitor the trends, patterns, and prevalence of resistance emergence and spread across the globe. This will provide reliable information and will enable proper surveillance.

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