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Opinion

Building a Framework to Curb the Rising Colistin Resistance Among Gram-Negative Bacteria from Wastewater

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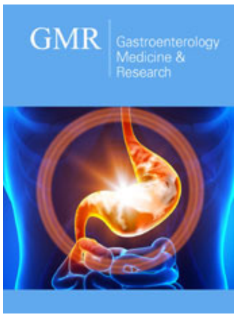

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Abstract

Wastewater from various sources, households, hospitals, veterinary and animal husbandry as well as pharmaceutical factories is a reservoir of an array of antimicrobial compounds and multi-resistant bacteria (MDR). The global increase of MDR and Extra-Drug Resistant (XDR) Gram-negative bacteria especially Enterobacterales in human medicine has led to the reintroduction of colistin as last-resort antibiotic. Colistin is the only salvage therapy especially in case of carbapenemase-producing strains among multi-resistant Gram-negative bacterial species. Although there is no available data in the recent past on the content of colistin residues in wastewater, there exists numerous scientific reports on colistin resistance among Gram-negative bacteria, more so among the members of the order Enterobacterales. At first, mechanisms attributed to colistin resistance were associated with mutations in genes domiciled on the chromosome. However, the presence of mobilizable colistin resistance genes on transferrable plasmids among Gram-negative bacteria continue to be documented in wastewater in different regions after the initial discovery of *mcr-1* gene in China in 2016.

Colistin Mechanism of Action

In Gram-negative bacteria where colistin (polymyxin E) exhibits its bactericidal effect, it acts as a membrane disruptor by interacting with Lipopolysaccharide (LPS) and phospholipids in the outer cell membrane. Both cell membranes are damaged due to the competitive displacement of divalent cations Mg^{2+} and Ca^{2+} from the phosphate groups of membrane lipids [1], leading to intracellular content leakage and eventual bacterial mortality. Most members belonging to the order *Enterobacterales*, including *Salmonella, Klebsiella*, *Shigella*, *E. coli* and *Enterobacter*, as well as other medically significant Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* can be controlled using polymyxins. This class of antibiotics on the other hand, has no known effect against Gram-positive and Gram-negative cocci. Similarly, polymyxins show no activity against Gram-positive *bacilli*. Furthermore, these drugs are non-efficacious against intrinsically resistant bacteria such as *Neisseria*, *Providencia*, *Serratia*, *Stenotrophomonas* and *Proteus* spp., *Morganella morganii*, *Burkholderia, pseudomallei*, and *Edwardsiella tarda*, as well as anaerobic bacteria [2,3].

Burden of Resistance

Colistin products are provided to a wide range of animal species in Europe, including poultry, pigs, cattle, sheep, goats, rabbits and laying hens as well as to milk-producing species such as cattle, sheep and goats to treat gastrointestinal illnesses resulting from Gram-negative bacteria such as diarrhea in pigs caused by *E. coli* and *Salmonella* spp. as well as colibacillosis prevalent in poultry [4]. This practice increases the possibility of the presence of colistin in wastewater from livestock sources. The high prevalence of colistin-resistant Gram-negative bacteria in livestock feces, process waters and wastewater from slaughterhouses and eventually wastewater treatment plants implies that these sites represent potential reservoirs with the possibility of contributing to the resistance progressing to other natural environments, especially surface water [5]. The rising prevalence of colistin-resistant isolates from wastewater points to possible selection pressure by colistin residues in the wastewaters, since colistin has been continuously and extensively used in the global livestock enterprise for preventive, medicinal, and even growth enhancement, which has been already prohibited in Europe from 2006 [6].

For the last decades, the use of colistin in animal production has been extensive [7]. Additionally, it was often used as a feed additive in low doses until the prohibition of antimicrobial growth promoters in the European Union (EU) in 2006 [8]. Inspite of its adverse effects relating to nephrotoxicity and neurotoxicity, colistin was re-introduced into human therapy to control ailments resulting from multidrug-resistant *A. baumannii* and *P. aeruginosa* or *carbapenemase*-Producing *Enterobacterales* (CPE) [9]. Following its significant impact, the World Health Organization (WHO) categorized colistin among the "highest priority critically important antimicrobials" for human medicine [10], alongside other premium antibiotics including amikacin, tigecycline and the newly produced combinations of ceftazidime-avibactam and ceftozolane-tazobactam. Earlier on in 2016, colistin had also been recognized and classified as a highly critical antimicrobial (VHIA) in the field of veterinary medicine by the World Organization for Animal Health [11].

Colistin resistance among multi-resistant Gram-negative bacteria from wastewater is undoubtedly in the upward trend considering the recent research reports and critical reviews. Recently, bacteria and associated genes that confer resistance to colistin were detected at the Los Angeles county's two largest wastewater plants, marking the first time traces of this particular antibiotic resistance in Los Angeles has been detected [12]. Mutations in chromosomal genes were primarily linked to colistin resistance initially. However, the discovery of the first plasmid-encoded, mobilizable colistin resistance gene (*mcr-1*) in *E. coli* from Chinese livestock and locally supplied meat, as well as clinical *Klebsiella pneumoniae* isolates from China [13,14], drew the attention of public health stakeholders as a major concern following the emergence of colistin-resistant bacteria. Further research into the genetic basis of colistin-resistant bacteria resulted in the identification of nine more *mcr* genes (*mcr-2* to *mcr-10*). Furthermore, the detection of the mobile colistin resistance gene, (*mcr-10)* in *K. quasipneumoniae* in Italy following wastewater-based surveillance suggests an increasing colistin resistance trend among Gram-negative bacteria facilitated by mobile genetic elements [15]. The *mcr-1* variant remains the most widespread globally [16].

Future Perspectives

A. Colistin is only used in clinical situations where no other treatments are available. Currently, the use of colistin in livestock in certain European countries like in the case of Hungary is restricted and only allowed for clinical use as a last resort antibiotic. As a result, very limited residues of this antibiotic if any, may be detected in wastewater or other environmental matrices. This ban would be of great value if extended to other regions.

B. In a concerted effort to promote the achievement of the One Health paradigm, it is imperative for the global regions to formulate and adopt a universal regulatory framework on the use of this salvage antibiotic in order to minimize its presence in environmental matrices as a strategy of reducing its exposure to microbes with the aim of minimizing the development of its resistance among bacteria associated with human and animal hosts.

C. At present, there is hardly any documented data investigating colistin residues in wastewater from slaughterhouses, poultry or pig farming process wastewater despite its enormous usage in animal production globally. A focus on the load of colistin residues in wastewater would be useful to correlate its presence in the environment to the development of its resistance among environmental bacteria associated with human infections.

D. There is a handful of research reports on colistin resistance in Gram-negative bacteria from wastewater with numerous articles focusing mainly on Enterobacterales and centered on clinical setting, thus the need to extend research to focus on additional multiple drug resistant Gram-negative bacteria of medical importance either transient or domiciled in the environment.

E. Besides monitoring what happens at the point-of-care, it is important to continuously monitor or "characterize" wastewater from anthropogenic activity and the immediate microbial community. This can be coupled with tracking the use of byproducts of wastewater from human and animal sources such as biosolids which supply nutrients for agricultural crops to establish the developing resistance trends which would provide useful insights.

F. There is need for all the stakeholders to remain loyal to "One Health" approach so that our focus on resistance development illuminates human hosts, animals and the environment as well as any other reservoirs. Additionally, frequent testing of more environmental sites would be valuable.

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