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Global Dissemination of the *mcr-1* gene

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Abstract

Antimicrobial resistance is one of the most severe threats to human health. The first report of plasmid-mediated colistin resistance in *Escherichia coli* from animals, food, and humans was in 2015 from China. The current increasing trend of resistance is extremely troubling because polymyxins are the last-resort antibiotics for treating infections with carbapenem-resistant *Enterobacteriaceae*.

Keywords: Colistin, Antibiotic Resistance, Enterobacteriaceae, Plasmid, *Mcr-1*

1. Introduction

Antimicrobial resistance is one of the most severe threats to human health in the 21st century (1-3). Colistin belongs to the family of polymyxins and is active against a broad range of Gram-negative bacteria, including most members of Enterobacteriaceae. Some *Enterobacteriaceae* members (such as *Proteus*, *Providentia*, *Morganella*, and *Serratia marcescens*) are intrinsically resistant to colistin and polymyxin (4). The two polymyxins that are currently used in the clinical context are polymyxin B and polymyxin E (colistin). These antibiotics have similar biological activity, differing from each other by only one amino acid. Polymyxin resistance may develop through modification of lipid A, which results in reduction of polymyxin affinity. As of now, all reported mechanisms of polymyxin resistance are chromosomally mediated and involve modulation of two component regulatory systems (e.g., *pmrAB*, *phoPQ*, and its negative regulator *mgrB* in the case of *Klebsiella pneumoniae*), which leads to lipid A modification with parts such as phosphoethanolamine or 4-amino-4-arabinose, or in unusual instances, total loss of the lipopolysaccharide (1).

2. Arguments

In *The lancet infectious diseases*, Yi-Yun Liu and coworkers (cited in Du et al.) reported the detection of *mcr-1* a plasmid-mediated gene that confers colistin resistance in *Escherichia coli* and *Klebsiella pneumoniae* strains isolated from animals and human patients in China (5). In the case of plasmid-encoded resistance, resistance elements can be easily transmitted to human beings through horizontal gene transfer from livestock, where colistin is used to treat infected animals. Transfer of the resistance to multidrug resistant Enterobacteriaceae would seriously limit our current treatment options (6). This increased resistance has exacerbated the situation because polymyxins are the last-resort antibiotics for treating infections with carbapenem-resistant Enterobacteriaceae (7). Subsequent findings report that *mcr-1* has spread to South Asia, South America, Europe, and Africa and also to other members of Enterobacteriaceae. These reports confirm that the *mcr-1* gene is a plasmid-encoded gene that has spread to different Enterobacteriaceae species. Of great concern is the unavoidable spread of plasmids carrying the *mcr-1* gene into a carbapenem-resistant Enterobacteriaceae, which could result in a multidrug-resistant strain that would eventually become pandrug resistant (5). Since the first report on the plasmid mediated colistin resistance gene (*mcr-1*), strains formerly collected in countries such as Denmark, Laos, the Netherlands, Thailand, Nigeria, France, and the UK have been found to carry *mcr-1* (Table 1). Furthermore, the sequences in GenBank show that *mcr-1* might also be circulating in Portugal and Malaysia. Colistin has been used in animals as a therapeutic drug or food supplement. In addition, recent studies indicate that *mcr-1* has been spread from animals to human beings (8). In order to monitor isolates for the presence of *mcr-1* by PCR, the following primers are used: CLR5-F (5'-CGGTCAGTCCGTTTGTTC-3') and CLR5-R (5'-CTTGGTCGGTCTGTA GGG-3'). To confirm the results of PCR, amplicons should subsequently be sequenced (1). In addition, techniques for the detection of susceptibility to polymyxins include disc diffusion, broth microdilution, and E-testing (CLSI 2014).

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Table 1. Dissemination of the *mcr-1* Gene

Organism	Country	No	Reference
Klebsiella pneumoniae	Suzhou-China	2	(5)
Escherichia coli	Suzhou-China	2	(5)
Escherichia coli	Belgium	13	(9)
Escherichia coli	China	104	(8)
Escherichia coli	Canada	2	(10)
Escherichia coli	Vietnam	9	(11)
Escherichia coli	Japan	2	(12)
Escherichia coli	Cambodia	1	(13)
Escherichia coli	Germany	4	(6)
Escherichia coli	Switzerland	1	(7)
Escherichia coli	Laos	9	(14)
Escherichia coli	Thailand	2	(14)
Escherichia coli	Algeria	1	(14)
Escherichia coli	Denmark	6	(15)
Escherichia coli	Italy	1	(16)

New-Delhi metallo-beta-lactamase (NDM-1) producing bacteria are resistant to nearly all antibiotics, including carbapenem antibiotics, which are also known as antibiotics of last resort. Such bacteria are usually susceptible only to colistin (17). In the case of coexistence of *mcr-1* and NDM-5 resistance, a pandrug resistant phenotype will result, for which the use of colistin and the combination of a ß-lactam–ß-lactamase inhibitor and ceftazidime–avibactam is no longer effective (5). An *E. coli* strain co-producing MCR-1, NDM-9, and FosA3 isolated from chicken was unexpected and is concerning because carbapenems and fosfomycin are not approved for use in food for animals. Keeping in mind that the resistance genes responsible for antimicrobial resistance are found on conjugative plasmids and that carbapenem and colistin-resistant *E.coli* may be found in retail meat, if such strains colonize the human intestinal tract, they can transfer the resistance plasmids to other Gram-negative pathogens, resulting in untreatable infections (17).

3. Conclusions

These findings highlight the need for screening studies and an active plan for surveillance of colistin in the treatment of human beings and animals, as well as the current situation of colistin resistance. There is urgent need for delicate infection control to restrict further dissemination of colistin resistance.

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Footnote

Authors' Contribution: All the authors contributed in writing this article.

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