Drug Metabolism & Toxicology

Shad, J Drug Metab Toxicol 2019, 9:3
DOI: 10.4172/2157-7609.1000243

Mini Review Open Access

MCR-1 Colistin Resistance in *Escherichia coli* Wildlife: A Continental Mini-review

Ahtesham Ahmad Shad*

Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan

Abstract

Antimicrobial resistance is one of the major leading problem and an issue for medical science in this era. Despite of being successful in treating bacterial infections and developing novel antibiotics, we are unfortunately going back to pre-antibiotic era. ESBLs, Cabapenemases and *MCR-1* genes are the predisposing factors together in emerging the resistance. Horizontal gene transfer makes it favorable to spread resistance mechanisms at much faster rate. Antimicrobial resistance is taken as a more significant issue, when it comes towards the resistance of bacterial strains towards our lost-resort antibiotic i.e. Colistin. Polymyxin E or colistin is an effective therapy against multi-drug resistant pathogens i.e. ESKAPE. But, the discovery of *MCR-1* gene has led to medical science to hands off at present. This mini-review aims to give a glance on *MCR-1* gene mechanism of resistance in Escherichia coli and also plasmid profile and phenotypic characteristics of wildlife strains in continents, conferring resistance to colistin. As the global transmission of resistance has accounted the wild life as one of the major culprit.

Keywords: *ESBLs*, *MCR-1*, ESKAPE, Polymyxin E

Introduction

Antimicrobial resistance is one of the notoriously leading issue and universal threat to one health in this era. WHO and US Centers for Disease Control and Prevention are clearly stating about medical science going towards pre-antibiotic era [1].The specific markers of resistance ESBLs , Carbapenemases and *mcr-1* genes are helping in prevailing resistance among bacterial strains [2].The discovery of plasmid mediated colistin resistance in the normal and routinely survey of China is devastating finding to one health [1].Then the rash of reports started globally in alarming the human and as well animals health [3].Within just three months of first discovery in November 2015,the spread of *MCR-1* gene evidently supported by medical society worldwide [4].Isolation of *MCR-1* gene from different locations and samples raised up the need to understand mechanisms underlying in spreading it globally, especially samples from Humans, animals and environment i.e. soil, river water [3,4]. As the colistin was the drug of choice or the drug of last-resort antibiotic in controlling the infections caused by multi-drug resistant pathogens in past i.e. ESKAPE [3].The deteriorating power of this powerful and effective antibiotic posing by *MCR-1* gene is a huge danger [5]. The focus of this mini-review is to highlight the basics of *MCR-1* resistance mechanism in *E. coli* and we aim to describe and provide the reader with a glance on plasmid and phenotypic characteristics in *E. coli* of wildlife origin continents.

E. coli

E. coli is a straight Gram-negative rod, most abundant facultative anaerobe in colon and feces. It has three antigens that are used to identify the organism in epidemiologic investigations: the O, or cell wall, antigen; the H, or flagellar; and the K, or capsular, antigen [6]. Because there are more than 150 O, 50 H, and 90 K antigens, the various combinations results in more than 1000 antigenic types of *E. coli* [6,7].

E. coli is the most common cause of urinary tract infection and sepsis, it is one of the two important causes of neonatal meningitis and the agent frequently associated with "traveler's diarrhea", a watery diarrhea (8).

E. coli has three major serotype classes (O, H, K), four phylotypes (A, B1, B2, D), and two broad pathotypes (Extraintestinal *E. coli* (ExPEC) and Diarrheagenic *E. coli*). The Diarrheagenic *E. coli* has six distinct classes (Enteropathogenic *E. coli* (EPEC), Enterohaemorrhagic *E. coli* (EHEC), Enterotoxigenic *E. coli* (ETEC), Enteroaggregative *E. coli* (EAEC), Enteroinvasive *E. coli* (EIEC) and Diffusely adherent *E. coli* (DAEC) (9).

MCR-1 gene discovery

The first report of plasmid mediated colistin resistance designated as *MCR-1* is from China during a routine surveillance project on antimicrobial resistance in commensal *E. coli* from food animals. *MCR-1* gene was isolated from a pig of *E. coli* strain SHP45 [8].

MCR-*1* mechanism of resistance

Previously, all reported polymyxin resistance mechanisms are chromosomally mediated, and involve modulation of two component regulatory systems (eg, pmrAB, phoPQ) [9].

Based on sequence alignment, *MCR-1* should be a phosphoethanolamine transferase, a member of YhjW/YjdB/YijP superfamily ,which catalyzes the addition of phosphoethanolamine to lipid A moiety of lipopolysaccharides (LPS) and therefore confers colistin resitance to its host [10,11].

Spreading ways or routes of *MCR-1* transmission

The *MCR-1* gene may undergo evolutionary changes in the animal GI tract upon prolonged usage of colistin as growth promoter. The gene

***Corresponding author:** Ahtesham Ahmad Shad, Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan, E mail: ahtesham.ashad@yahoo.com

Received November 11, 2018; **Accepted** December 28, 2018; **Published** January 05, 2019

Citation: Shad AA (2019) *MCR-1* Colistin Resistance in *Escherichia* coli Wildlife: A Continental Mini-reviewy. J Drug Metab Toxicol 9: 243. doi:10.4172/2157-7609.1000243

is then transmitted to human through the food chain or direct human contact with animals, as well as through contamination of the fresh and seawater system, which in turn cause contamination of vegetables and seafood. The persistence of *MCR-1* in the human GI tract microflora can cause further contamination of the water systems through disposal of waste water containing human faeces. Fresh water systems outside these transmission routes remain clear of *MCR-1* contamination [12].

MCR-genes types discovered so far

Five colistin resistance genes (*MCR-1, MCR-2, MCR-3, MCR-4* and *MCR-5)* have been described, few data are available on the prevalence of *MCR*-genes other than *mcr-1* in human samples [13].Moreover, so far six different variants of the *MCR-1* gene *(MCR-1.2* to *MCR-1.7)*, which differ from each other by a single amino acid have been described in *Enterobacteriaceae* [14].

Why wildlife is so important to analyze for *MCR-1* gene?

The development of bacterial resistance is a naturally occurring evolutionary mechanism of micro-organisms, but the wide spread use and misuse of antibacterial agents in humans and animals has accelerated this process. *MCR-1* is one of the few and clear example of the animal origin of a resistance trait that may later hit the entire human health [2,15].

Since, most emerging human diseases have come from wildlife and natural environment and wildlife is considered to a "melting pot" and dissemination route of antibacterial resistance [16].

Role of wildlife in transmission of the *MCR-1* gene

The use of antimicrobials in veterinary medicine creates a selective pressure for the emergence of antimicrobial resistant bacteria, including animal human pathogens that have animal reservoirs and commensal bacteria from animals bacteria selected by this pressure can spread to humans either by direct contact with animals or food products, or indirectly *via* environmental pathways and/or non-food producing animals (Figure 1) [17].

Wildlife is a major zoonotic origin of transmission of various bacterial genes and hence the diseases among the domestic animals and human ecosystem [18].

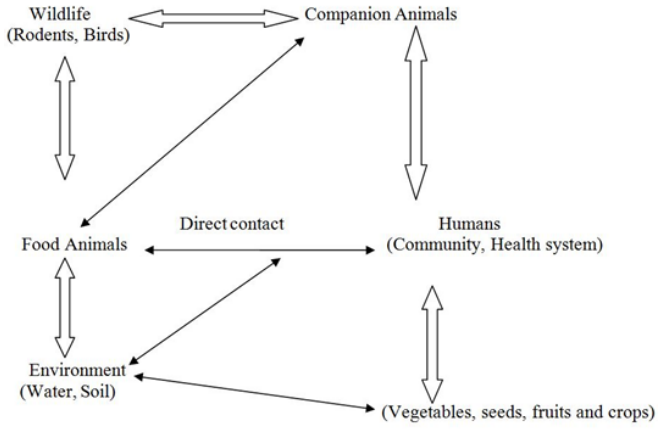

Figure 1: Interactions between groups. Antimicrobial-resistant bacteria can spread to humans either by the food supply, direct contact with food or companion animals or, more indirectly, through environmental pathways, including waterways, soils and vegetables contaminated with human or animals waste, and vectors such as rodents, insects, and birds [17].

Continents	Country	Species	ST-type	Plasmid	Year
1 - South America	Argentina	*Larus dominicanus*	1. ST101, 2. ST744	IncI2	2016
2- Europe	Lithuania	*Larus argentatus*	-	SHP45	2016
3- Asia	Pakistan	*Fulica atra*	ST354	IncI2	2016

Table: 1 *MCR-1* in wildlife of Subcontinents.

Global distribution of *E. coli* harboring *MCR-1* gene

Wild birds and animals are the potential reservoirs and vectors for the global distribution of *MCR-1*, it has been identified on *Enterobacteriaceae* isolates from food-producing animals, companion animal, food products, the environment and humans worldwide [2,19].

The gene has been found primarily in *E. coli* but has also been identified in other members of the *Enterobacteriaceae* in human, animal, food, and environmental samples on every continent [20]. The *MCR-1* gene has been rapidly detected in several European, Asian, South-East Asian, South American, Northern American and African countries. Retrospective studies led to establishing the presence of the *MCR-1* gene in China as early as the 1980s and in Europe since 2005 [21]. The global distribution of *MCR-1* over at least five continents is well documented, but little is known about its origin, acquisition, emergence, and spread [22].

A plasmid-mediated (horizontally transferable) colistin resistance (*MCR-1*) gene was recently reported in China ,and subsequently detected in Asia (Vietnam, Laos, Thailand, Cambodia, Malaysia, Singapore, Taiwan and Japan), Europe (The Netherlands, Germany, Belgium, Switzerland, France, Denmark, United Kingdom, Spain, Italy, Sweden and Portugal), Africa (Algeria, Egypt, South Africa and Tunisia), and America (Canada, Argentina and Brazil) [23].

Continental plasmid profile and phenotypic characteristics of *E. coli* harbouring *MCR-1* gene of wildlife origin

A brief summary is given below in Table 1, Continents in which the *MCR-1* harboring colistin resistance gene has been reported from *E. coli* of only wildlife origin so far:

The first report of the dissemination of the *MCR-1* gene in Kelp gulls is from ushuaia, Argentina. The fact that gull species migrate, sometimes even between continents, indicates that they may play a role in the global dissemination of these clinically relevant bacteria. The association of the *MCR-1* gene with conjugative IncI2 plasmids also among gulls illustrates a successful plasmid–gene combination, resulting in the emergence spread of this gene [24]. The first known occurrence of the *MCR-1* gene in *E. coli* carried by a wild migratory bird-the European herring gull (*Larus argentatus*) [25]. The first detection of *MCR-1* in colistin-resistant extended spectrum β-lactamase-producing *E. coli* (*ESBL-E. coli)* isolated from wild transboundary migratory waterfowl species *Fulica atra* from Pakistan, Asia[26].

Conclusion

No doubts, a set of data has been reported so far from wildlife [24-26].But it is not sufficient to estimate and account for *MCR-1* gene distribution in *E. coli* wildlife globally. There is an urgent need and we emphasize to look for *MCR-1* gene, not only in birds but also in animals. Although birds can travel and disseminate more than animals, but we cannot neglect the impact of interaction between domestic and wildlife animals, as indicated from wild animals in Poland [16]. Also, we suggest investigating *MCR-1* gene presence in other continents of

wildlife, so that a more comprehensive picture can be established in accounting *MCR-1* gene.

References

1. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, et al. (2015) Emergence of plasmid-mediated colistin resistance mechanism *MCR-1* in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 16: 161-168.
2. Wang J, Ma ZB, Zeng ZL, Yang XW, Huang Y, et al. (2017) The role of wildlife (wild birds) in the global transmission of antimicrobial resistance genes. Zool Res 38: 55-80.
3. Castanheira M, Griffin MA, Deshpande LM, Mendes RE, Jones RN, et al. (2016) Detection of *mcr-1* among Escherichia coli clinical isolates collected worldwide as part of the SENTRY Antimicrobial Surveillance Program. Antimicrob Agents Chemother 60: 5623-5624.
4. Skov RL, Monnet DL (2016) Plasmid-mediated colistin resistance (*mcr-1* gene): three months later, the story unfolds. Euro Surveill 21: 30155.
5. Schwarz S, Johnson AP (2016) Transferable resistance to colistin: a new but old threat. J Antimicrob Chemother 71: 2066-2070.
6. Taj MK, Zohra S, Ji Xiu, Imran (2014) Escherichia coli as a model organism. Int J Engg Res Sci & Tech 3: 1-8.
7. Wirth T, Falush D, Lan R, Colles F, Mensa P, et al. (2006) Sex and virulence in Escherichia coli: an evolutionary Perspective. Mol Microbiol 60: 1136-1151.
8. Jafari A, Aslani MM, Bouzari S (2012) Escherichia coli: a brief review of diarrheagenic pathotypes and their role in diarrheal diseases in Iran. Iran J Microbiol 4: 102.
9. Tahir H (2015) An introduction to the serotypes, pathotypes and phylotypes of Escherichia coli" Int J Microbiol Allied Sci 2: 9-16.
10. Guixing Ma, Zhu Y, Yu Z, Ahmad A, Zhang H (2016) High resolution crystal structure of the catalytic domain of MCR1. Scientific Reports 6: 39540.
11. Sun J, Zhang H, Liu YH, Feng Y (2018) Towards understanding MCR-like colistin resistance. Trends Microbiol 26.9:794-808.
12. Chen K, Chan EW, Xie M, Ye L, Dong N, et al. (2017) Widespread distribution of *mcr-1*-bearing bacteria in the Ecosystem. Euro Surveill 22: 39
13. Zhang J, Chen L, Wang J, Butaye P , Huang K, et al. (2018) Molecular detection of colistin resistance genes (*mcr-1* to mcr-5) in human vaginal swabs. BMC Research Notes 11: 143.
14. Yanat B, Machuca J, Yahia RD, Touati A, Rodriguez M, et al. (2016) First report of the plasmid-mediated colistin resistance gene *mcr-1* in a clinical Escherichia coli isolate in Algeria. Int J Antimicrob Agents 48.6:760.
15. Laurent P, Patrice N (2016) Emerging plasmid-encoded colistin resistance: the animal world as the culprit? J Antimicrob Chemother 71: 2326–2327.
16. Wasyl D, Magdalena Z, Anna L, Magdalena S (2017) Antimicrobial resistance in Escherichia coli isolated from wild animals in Poland. Microbial Drug Resistanc 24: 0184.
17. Argudín MA, Deplano A, Meghraoui A, Dodemont M, Heinrichs A, et al. (2017) Bacteria from animals as a pool of antimicrobial resistance genes. Antibiotics 6: 12.
18. Kruse H, Anne MK, Kjell H (2004) Wildlife as source of zoonotic infections. Emerg infect dis 10: 2067.
19. Huang X, Linfeng YU, Xiaojie C, Chanping Z, XU Y, et al.2017 High prevalence of colistin resistance and *mcr-1* gene in Escherichia coli isolated from food animals in China. Front Microbiol 8: 562.
20. McGann P, Snesrud E, Maybank R, Corey B, Ong AC, et al. (2016) Escherichia coli harboring *mcr-1* and blaCTX-M on a novel IncF plasmid: first report of *mcr-1* in the United States. Antimicrob Agents Chemother 60: 4420-4421.
21. Lepelletier D.2018. "Emergence of plasmid-mediated colistin resistance (*mcr-1*) among Enterobacteriaceae strains: Laboratory detection of resistance and measures to control its dissemination." Medecine maladies infectieuses 48.4: 250-255
22. Wang R, Lucy V, Liam P, Phelim B, Qi W,et al. (2018) The global distribution and spread of the mobilized colistin resistance gene *mcr-1*. Nature communications 9: 1179
23. Kwang P, Jung HL, Moonhee P, Kwan SK, Sang HL (2017) How many *mcr-1*-harbouring bacteria were spreading geographically?. Biomedical Research 28.
24. Liakopoulos A, Dik JM, Bjorn O, Jonas b (2016) The colistin resistance *mcr-1* gene is going wild." Journal of Antimicrobial Chemotherapy 71: 2335-2336
25. Ruzauskas M, Lina V (2016) Detection of the *mcr-1* gene in Escherichia coli prevalent in the migratory bird species Larus argentatus. J Antimicrob Chemother 71: 2333-2334.
26. Mohsin M, Raza S, Roschanski N, Schaulfler K, Guenther S.2016 "First description of plasmid-mediated colistin-resistant extended-spectrum β-lactamase-producing Escherichia coli in a wild migratory bird from Asia. Int J Antimicrob Agents 48: 463-464.