International Journal of Infectious Diseases 54 (2017) 77–84

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals?

Jaffar A. Al-Tawfiq [a,b,*], Ramanan Laxminarayan [c,d], Marc Mendelson [e]

[a] Johns Hopkins Aramco Healthcare, PO Box 76, Room A-428-2, Building 61, Dhahran Health Center, Dhahran 31311, Kingdom of Saudi Arabia
[b] Indiana University School of Medicine, Indianapolis, Indiana, USA
[c] Center for Disease Dynamics, Economics, and Policy, Washington, DC, USA
[d] Princeton University, Princeton, New Jersey, USA
[e] Division of Infectious Diseases and HIV Medicine, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

ARTICLE INFO

Article history:
Received 2 September 2016
Received in revised form 8 November 2016
Accepted 22 November 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Plasmid-mediated colistin
Colistin resistance
Multi-drug resistant bacteria

SUMMARY

Objective: The widespread use of antibiotics in humans and animals has contributed to growing rates of antibiotic resistance. Previously treatable bacterial infections now require the last line of antibiotics or are untreatable. The current antibiotic of last resort for carbapenem-resistant Gram-negative bacterial infections is often colistin. Evidence for the shifting pattern of colistin resistance and how the international community should respond are discussed in this review.
Methods: The literature on colistin resistance was reviewed.
Results: Plasmid-mediated colistin resistance encoded by *mcr-1* was first documented in China during the routine surveillance of food animals. This has been followed by similar reports across a wide geographic area, in humans, animals, and the environment. The *mcr-1* gene has been reported among human isolates in 29 countries, related to environmental samples in four countries, and in food animals and other animals in 28 countries. More recently, a second gene encoding resistance, *mcr-2*, has been isolated from porcine and bovine *Escherichia coli*.
Conclusion: The emergence and horizontal transmission of colistin resistance highlights the need for heightened stewardship efforts across the One Health platform for this antibiotic of last resort, and indeed for all antibiotics used in animals and humans.

1. Introduction

Over the 74 years since the introduction of penicillin, our use and misuse of antibiotics in humans and animals has led to rising antibiotic resistance – to such an extent, that once commonly treatable bacteria are now either untreatable or require the last line of antibiotics.[1,2] The movement of resistance genes between different bacterial species through plasmid-mediated horizontal gene transfer increases the variety of bacterial populations possessing multidrug-resistant (MDR) potential, and the intense selection pressure exerted by antibiotics selects out antibiotic-resistant bacteria capable of causing infection in humans and animals.[3]

The recent identification of new plasmid-mediated resistance genes conferring colistin resistance in bacterial isolates from food animals has re-ignited the debate concerning the contribution of antibiotic consumption in animals to levels of resistance in humans.[4] Although pertinent to all antibiotics, resistance to colistin is of particular concern as it plays the role of 'antibiotic of last resort' against common Gram-negative bacterial infections that are now increasingly MDR.[5] The shift in patterns of colistin resistance and how we should respond are examined and discussed in this review.

2. Colistin resistance

2.1. Measuring colistin resistance

Measurements of in vitro colistin resistance by disk diffusion, Etest, and agar dilution have a number of important limitations, chief amongst which are high error rates, low reproducibility, and

* Corresponding author. Tel.: +966 13 877 3524; fax: +966 13 877 3790.
E-mail addresses: jaffar.tawfiq@aramco.com, jaltawfi@yahoo.com (J.A. Al-Tawfiq).

http://dx.doi.org/10.1016/j.ijid.2016.11.415

the time they take to perform.[6–13] Broth microdilution is considered the reference standard for polymyxin susceptibility testing. The Etest, agar dilution, and broth microdilution assays are generally concordant, although discordance of Etest and agar dilution with broth microdilution has been reported.[14,15] Automated antimicrobial susceptibility testing includes Vitek 2 (Vitek 2 XL; bioMérieux, Hazelwood, MO, USA), MicroScan (MicroScan WalkAway 96 Plus; Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA), and Etest (Etest; bioMérieux SA, Marcy l'Etoile, France) assays. Compared to agar dilution, Vitek 2 and Etest show excellent agreement for the testing of colistin resistance in Acinetobacter.[16] Definite breakpoints for colistin susceptibility have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[17] The Clinical and Laboratory Standards Institute (CLSI) has also provided susceptibility criteria for Pseudomonas and Acinetobacter.[18]

2.2. Chromosomally mediated colistin resistance

The recent identification of plasmid-mediated colistin resistance mechanisms has extended our understanding of colistin resistance that has been chromosomally mediated, with vertical transmission and slow evolution.[19–21] Colistin resistance is thought to relate to lipopolysaccharide modification via changes in the *mcrB* gene and upregulation of PhoP/PhoQ.[4,22–24] The worldwide prevalence of resistance to polymyxins is about 10% among Gram-negative bacteria and is highest in Mediterranean countries and Southeast Asia.[25]

2.3. Plasmid-mediated colistin resistance

Plasmid-mediated colistin resistance encoded by *mcr-1*, a gene of the phosphoethanolamine transferase enzyme family, was first documented in China during the routine surveillance of food animals.[20] A retrospective analysis of 1611 isolates of *Escherichia coli* from chicken farms showed that the earliest *mcr-1*-harboring isolate was from the 1980s when colistin was first used for livestock in China.[26] Since then, *mcr-1* has been identified in isolates from humans, animals, and the environment in an increasing number of countries (Table 1).[20,21,26–104] In keeping with other resistance mechanisms, *mcr-1* is capable of travelling with its human host; 10% of 38 travelers from India were found to harbor *mcr-1* resistant *E. coli* in stool.[55] The identification of *mcr-1*-mediated colistin resistance in *E. coli* and *Klebsiella pneumoniae* in pilgrims attending the annual Hajj indicates a risk for acquisition in those attending mass gatherings.[60]

The initial description of *mcr-1* was in 21% of healthy swine at slaughter, 15% of marketed pork and chicken meat, and 1% of hospitalized patients in China.[20] The first human isolate was detected in *E. coli* in Latin America.[46] In the SENTRY program, 5% of clinical isolates of *E. coli* and *K. pneumoniae* were found to carry *mcr-1* resistance.[105] *K. pneumoniae* with variant *mcr-1* resistance was also isolated from a rectal swab of an Italian child.[34] Lastly, resistant isolates carrying *mcr-1* were described in 11 Salmonella from clinical samples, food, and water in Portugal,[106] and in *Shigella sonnei* from Vietnam.[96]

Recently, *mcr-2*, another phosphoethanolamine transferase plasmid-mediated colistin resistance gene, which shares 76.7% nucleotide sequence homology to *mcr-1*, was isolated from porcine and bovine *E. coli*.[21] *mcr*-2 was identified in 21% of porcine colistin-resistant *E. coli* in Belgium compared with 13% with *mcr-1*.[21]

The co-localization of *mcr-1* with other resistance mechanisms highlights the fact that discussions regarding the stewardship of antibiotics across the One Health platform are not only pertinent to antibiotics of last resort such as colistin, but also to more commonly used antibiotics. There have been a number of reports of co-localization of *mcr-1* with carbapenemases and/or extended-spectrum β-lactamase (ESBL); *mcr-1* and $bla_{\text{NDM-5}}$, a metallo-β-lactamase, were transferred by an IncX3-X4 hybrid plasmid.[54] A similar finding was reported from a patient with a urinary tract infection in the USA.[65] *mcr-1* has also been found to be associated with ESBL-producing isolates bearing $bla_{\text{CTX-M-1}}$ and a human isolate with a $bla_{\text{KPC-2}}$ carbapenemase gene.[37,81,92,98] In addition, the *mcr-1* gene co-localizes with multiple plasmid replicon types: IncI2, IncHI2, IncP, IncFIP, and IncX4.[43,81,107] These plasmids are associated with resistance to quinolones and may acquire genes conferring resistance to cephalosporin ($bla_{\text{CTX-M-14}}$) and fosfomycin (*fosA3*).[108]

The coexistence of *mcr-1* with other resistance genes indicates the existence of different pathways for the horizontal transmission of colistin resistance.[37] One isolate had $bla_{\text{NDM-9}}$, *fosA3*, *rmtB*, $bla_{\text{CTX-M-65}}$, and *floR* thus confirming resistance to carbapenems, fosfomycin, aminoglycoside, cephalosporin, and florfenicol, respectively.[109] Resistant *mcr-1* isolates to colistin, polymyxin B, cephalosporin, gentamicin, and ciprofloxacin are thought to have been transmitted from animals to humans.[90] The coexistence of these genes with high potential of spread is of great concern. It is also important to keep in mind that these genes may be present in strains that are relatively susceptible to other antibiotics, but as they are reported as susceptible, colistin resistance is unlikely to be routinely tested for.

3. Avoiding the blame game

Due to the status of colistin as the 'antibiotic of last resort' for Gram-negative bacteria in humans, its use across the One Health platform has come under intense scrutiny, and a climate of blame has been generated, mainly directed towards farmers and veterinarians.[110,111] It is assumed that plasmid-mediated colistin resistance moved from animals to humans, based on the fact that *mcr-1* and *mcr-2* predominate in animals and were first described in animals, which as a group, consume the largest volume of that antibiotic.[28]

However, the intense overuse and misuse of antibiotics such as colistin across the One Health platform is driving selection pressure, and it is therefore a collective, unified reduction in total antibiotic use that must be focused upon.[112] The human consumption of colistin is itself a marker of overuse and misuse of all antibiotics, which have systematically been rendered ineffective by stepwise selection out of increasingly resistant bacteria, resulting in the need to use 'the last man standing', i.e., colistin.

In livestock, colistin (and the vast majority of total antibiotic use) has historically spoken to a simple need: an expanding global population that requires food security in terms of animal protein.[113] To ensure this, sub-therapeutic concentrations of antibiotics have been used for decades to promote animal growth, and treatment doses are used for large-scale prophylaxis (metaphylaxis) to protect healthy feed animals from infection. In contrast, much smaller volumes are used for the individual treatment of sick animals.[114] Approximately 12 000 tons of colistin is estimated to be used per year in 2015 in food production, with consumption expected to rise to 16 500 tons by 2021.[20] These volumes may be underestimates because surveillance data are lacking for many countries.

The key to unlocking this conundrum is preventing infection in humans and animals to reverse the continued reliance on antibiotics to perform the task that tackling the social determinants of infection would achieve. In human public health, this relates to the provision of clean water and sanitation to reduce diarrheal diseases, ensuring global access to immunization against bacterial and viral illnesses that drive the use of antibiotics, and the