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.
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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
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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

Table 1
Countries reporting plasmid-mediated colistin resistance encoded by *mcr-1*

Country	Reference	Year of sample/publication	Ref.
Food animals and other animals			
Algeria	Chicken	2012	93
Argentina	Kelp gulls	2012	103
Belgium	Porcine and bovine (diarrhea)	2011–12	56
Belgium	Porcine and bovine (diarrhea)	2011–12	21
Brazil	Poultry and swine	2000–16	27, 45
Canada	Ground beef	2010	104
China	Swine	2011–14	20
China	Chicken	1980–2014	26
China	Chicken	2014	109
China	Cats and dogs	2015	90
Denmark	Imported chicken meat	2012–14	97
Egypt	Bovine (subclinical mastitis)	2014	51
England and Wales	Poultry meat	2012–15	43
England	Swine	2014–15	101
Estonia	Pig slurry	2016	66
European collection	Bovine and swine digestive infections	2004–14	61
France	Live stock (swine, broiler, turkey)	2007–14	35
France	Veal calves	2005–14	98
France	Poultry, sausage	2013	99
Germany	Swine (R253, V163, 112065)	2010	37
Germany	Poultry	2016	63
Germany	Livestock	2010–15	80
Japan	Cattle (mastitis) and swine (septicemia)	2007–14	47, 48
Laos	Swine	2012	93
Lithuania	European herring gull	2016	102
Malaysia	Swine, chicken,	2013	94, 84, 50
Netherlands	Retail chicken meat (at supermarkets)	2009–14	28, 29
Portugal	Retail meat	2011–12	42
Portugal	Food samples	2011	84
South Africa	Poultry	2016	38–40
South Korea	Livestock	2013 and 2015	69
Spain	Poultry and swine	2016	32
Switzerland	Poultry	2016	79
Taiwan	Humans and retail meats	2016	49
Taiwan	Retail meat (beef, chicken, pork)	2012–13, 2015	49
Tunisia	Chicken farms	2016	53
USA	Swine	2016	62
Venezuela	Swine	2015	54
Vietnam	Swine	2014–15	95
Vietnam	Swine and chicken	2013–14	100
Humans			
Argentina	Human	2016	46
Bahrain	Bed sore and urine	2015	70
Cambodia	Feces of a child	2012	92
Canada	Urine from a returning traveler	2016	73
Canada	Gastrostomy tube	2011	104
China	Hospitalized patients	2011–14	20
China	Stool	2011–12	77
China	Human microbiome	2011	84, 86, 89
China	Blood, urine, peritoneal fluid	2014–15	85
China	Respiratory isolates	2015	87
China	Human samples	2014	88
China	Urine and blood	2015	90
China	Human isolates	2016	91
Denmark	Blood	2015	97
Ecuador	Peritoneal fluid	2016	64
Egypt	Clinical isolate	2016	52
England and Wales	Humans	2012–15	43
Germany	Single wound infection	2010	37
Hong Kong	Urine, blood, and stool samples	2015–16	74
India	Travelers	2015	55
Italy	Hospitalized patients	2012–15	33
Italy	Surveillance rectal swab of a leukemic child	2012–15	34
Laos	Human	2012	93
Malaysia	Poultry meat; swine; human (urine)	2013	50
Netherlands	Fecal samples of healthy travelers	2010–12	71
Netherlands	Hospitalized patients	2016	30
Nigeria	Patient	2012	93
Poland	Hospitalized patient	2015	41
Saudi Arabia	Pilgrims		60
Saudi Arabia	Blood	2012	70
Singapore	Urine	2016	75
South Africa	Hospitalized and community patients	2014–16	25, 40
Spain	Clinical isolates	2012–15	31
Switzerland	Urinary isolates	2016	72

Table 1 (*Continued*)

Country	Reference	Year of sample/publication	Ref.
Switzerland	Blood	2016	82
Switzerland	Blood	2016	83
Taiwan	Humans	2010, 2012, 2014	49
Thailand	Human	2012	93
United Arab Emirates	Blood	2013	70
USA	Urine	2016	44
USA	Stool of pediatric patient	2016	58
USA	Urine	2016	59
USA	Urine	2014	65
Venezuela	Human isolates	2015	54
Vietnam	Stool	2008	96
Environment			
Switzerland	River water and imported vegetable samples	2016	36
China	Hospital sewage	2016	57
Malaysia	Water		50
France	Boot swab from broiler farm	2013	99

promotion of uniform practices of infection prevention and control in healthcare establishments to prevent healthcare-associated infections and the transmission of bacteria between patients through poor hand hygiene.

Experience from the European Union since the ban on animal growth promoters (AGP) in 2006 suggests that improving biosecurity, biosafety, and the diet of livestock could render the need for AGPs obsolete and significantly reduce the need for metaphylaxis, reserving it for the protection of healthy animals only when others in the group become sick.[114] Furthermore, cleaning and disinfection between meat production cycles is an important public health intervention in food production to limit the spread and accumulation of resistance genes in the following cycles.[115–117] Lastly, the companion animal–human axis should not be ignored. A study by Zhang et al. has recently highlighted the transmission of *E. coli* carrying *mcr-1* between companion animals and humans.[90]

4. How should we respond?

According to the US Centers for Disease Control and Prevention (CDC), "the One Health concept recognizes that the health of humans is connected to the health of animals and the environment".[118] Another definition is "the collaborative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals and our environment".[119] The One Health program relies on three pillars: human health, livestock or aquaculture, and environmental health.[120] Understanding the relative importance of the contribution of each component is important in tackling antimicrobial resistance.[120]

A One Health approach to decrease the consumption of all antibiotics is the goal.[121,122] To protect food security, phasing out antibiotic use for AGP and metaphylaxis in favor of heightened infection prevention and nutrition interventions will take time. However, critical antibiotics required for human use, such as colistin, should be protected by an immediate cessation of use in livestock, as has been announced by the Responsible Use of Medicines in Agriculture (RUMA) alliance[123] and China.[124] This must be done in concert with restrictions in human use: restricting colistin for definitive treatment based on susceptibility testing, or to empirical use in clearly defined circumstances, coupled with attention to pharmacokinetics and pharmacodynamics to ensure optimal dosing, must be part of every country's national action plan. Ambitious targets should be set by each country to reduce overall consumption.[125]

In terms of dosing, high doses of up to 720 mg (9 million IU) per day are employed,[126,127] and the need for a loading dose has been highlighted.[128,129] Under-dosing colistin in patients with critical illness, burns, renal failure, and obesity risks the emergence of resistance.[130] Resistant strains have been reported in burn patients,[130] and critically ill patients on continuous venovenous hemodiafiltration require higher doses.[131] There have been no prospective studies evaluating the optimal dosing of colistin to limit side effects and provide the best bactericidal effect. It is feared that doses that result in sub-optimal bactericidal colistin concentrations may lead to the selection of resistant bacteria.[132,133] In a retrospective observational study of 72 patients with MDR Gram-negative pneumonia, the clinical cure rate was 55% in those receiving a regular dosing regimen compared to 67% in those receiving a loading dose and high-dose maintenance regimen.[134]

As with other antibiotics, prior use of colistin is itself a risk factor for the development of resistance.[135] In a study of 20 patients, both colistin-susceptible and colistin-resistant Acinetobacter from the same patients were found to be highly related by pulsed-field gel electrophoresis (PFGE), indicating the development of resistance during colistin treatment.[136] In a further study of 41 colistin-resistant isolates, colistin was the only independent risk factor for such resistance.[137] The enteral use of colistin for selective gastrointestinal decontamination has been associated with the emergence of colistin resistance.[138] However, this resistance is thought to be secondary to sub-therapeutic colistin doses.[139,140]

Ultimately, the action we take to protect human health, which relies just as much on food security as it does on antibiotics to treat serious bacterial infections, must be translatable to all antibiotics (and indeed all antimicrobials), including the new antibiotics to come. The proposed global stewardship framework, which will lay out how we steward a new antibiotic to ensure equity of access and define the working parameters for how it should be used, must be enforceable and countries must be accountable for their protection. A United Nations-led coordinating mechanism, as agreed at the UN General Assembly in September 2016, provides an opportunity to define a true One Health approach to antibiotic consumption and to set up monitoring and evaluation mechanisms to ensure countries comply.[141] This will be essential if we are to conserve colistin pending the development of new antibiotics to treat MDR Gram-negative bacteria.

Funding: RL's time was supported by the Global Antibiotic Resistance Partnership which is funded by the Bill & Melinda Gates Foundation.

Conflict of interest: None.

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