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Plasmid-mediated colistin resistance: an additional antibiotic resistance menace

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Background

The increasing trend in antibiotic resistance continues to threaten global health due to the limited pipeline of new antibiotics. Multidrug resistance in Gram-negative bacteria is of special concern because it may associate resistance to the three main classes of antibiotics in single isolates. These three classes are: (i) the β-lactams with plasmid-encoded extended-spectrum β-lactamases (ESBLs) hydrolysing cephalosporins and with carbapenemases hydrolysing additionally carbapenems, (ii) the aminoglycosides with 16S rRNA methylases modifying their cellular target and conferring pan-aminoglycoside resistance, and (iii) the fluoroquinolones mostly with topoisomerase mutations. Due to the paucity of remaining antibiotics for treating infections, polymyxins (colistin, polymyxin B) have become the last resort, in particular for treating infections due to carbapenem-resistant *Enterobacteriaceae*. Polymyxins, although introduced to the antibiotic armamentarium in the 1950s, have been considered until recently to be too nephrotoxic and too neurotoxic for their regular use for treating infections in humans [1]. Their large usage was restricted to animals.

Now, plasmid-encoded colistin resistance mediated by the mobile colistin resistance-1 (MCR-1) protein has been identified from human, animal and environmental isolates from China, as published in November 2015 [2]. MCR-1 is a phosphoethanolamine transferase that catalyses the addition of a phosphoethanolamine group to lipid A, leading to a decreased affinity of colistin for the lipopolysaccharide [2]. Resistance to colistin is not new; numerous bacterial species are intrinsically resistant to colistin and acquired resistance has been selected on chromosomal mutations [1]. What is new here is the plasmid location of the colistin resistance trait and hence its interspecies transferability. Soon after the pioneering Chinese work had led to the identification of MCR-1, the same *mcr-1* gene was identified on all continents, in animals, human isolates, food and environmental samples, mostly in *Escherichia coli* [3–7]. Several pieces of evidence suggest that the reservoir of the *mcr-1* gene is in animals as follows: (i) the heavy usage of polymyxins in animals as growth promoter, prophylaxis and metaphylaxis, and their curative usage mostly in pigs, chickens and cattle that constitute a driving force for selection of MCR-1-producers [1,2]; (ii) the identification so far of the *mcr-1* gene being mostly from animal isolates (20% among animal isolates, compared with 1% among human isolates in China from 2011 to 2014) [1]; (iii) the identification of the florfenicol resistance gene, *floR*, in MCR-1 producers when florfenicol is given only to animals [3]; (iv) the genetic association of the *mcr-1* gene with insertion sequence IS*Apl1* originating from *Pasteurella multocida*, a common pathogen for animals [3]; and (v) the association of MCR-1 with plasmid-mediated cephalosporinase, CMY-2, which is known to be widespread in animal isolates [4].

How Worried Should We Be About MCR-1?

The pessimistic viewpoint of this issue can be summarized as follows. Transfer of the *mcr-1* gene to carbapenemase producers in nosocomial settings may ensure the apocalypse of antibiotics. Indeed, a community-acquired *E. coli* isolate producing MCR-1 and the carbapenemase Verona imipenemase-1 (VIM-1) [3], an *E. coli* isolate expressing MCR-1 and *Klebsiella pneumoniae* carbapenemase-2 (KPC-2) [4], and a *Klebsiella pneumoniae* isolate producing MCR-1 and New Delhi metallo enzyme-5 (NDM-5) [5] have already been identified. The *mcr-1* gene may be identified in bacteria responsible for severe infections such as bacteraemia as evidenced recently in Switzerland [6]. The spread of MCR-1 has already occurred on a large scale with its simultaneous identifi-

cation worldwide in the environment, community-acquired and hospital-acquired pathogens and animals. The animal reservoir may already be important. This animal, and possible environmental, reservoir will be difficult to control compared with any emerging hospital-acquired resistance determinant. Worringly, *E. coli* being the main host of MCR-1, is one of the bacterial species that is the most widely distributed and exchanged between the environment, animals and humans. Spread of the MCR-1 determinant may follow the same trend as that observed for ESBLs of the CTX-M type two decades ago, first located in *E. coli* then in nosocomial species such as in *K. pneumoniae* as a source of multiple outbreaks. The identification of the *mcr-1* gene on several plasmid backbones suggests that its spread corresponds to multiple genetic events that have occurred independently in distantly related geographical areas. Several genetic analyses have already indicated that the *mcr-1* gene is located on transferable plasmids increasing the variety of potential transmission vectors. Detection of MCR-1 producers may be difficult because MCR-1 confers a low level of resistance to colistin [2–7] (4–16 mg/L with a breakpoint value of 2 mg/L according to the EUCAST guidelines) and colistin susceptibility remains difficult to determine in routine microbiology [1].

In contrast, the optimistic point of view may be summarized as follows. The MCR-1 determinant seems to be so far mostly located in animal isolates and not in human isolates. The true prevalence of MCR-1-producing isolates is difficult to estimate and may be very low in geographical areas such as the USA where polymyxin is not used in animals. It is not a true emerging resistance trait because MCR-1-producing isolates collected as early as 2005 have already been identified [7]. Many of the MCR-1 producers still remain susceptible to antibiotics such as cephalosporins and carbapenems, leaving many treatment options [2–7]. *Escherichia coli*, as the main target of MCR-1, is not responsible for hospital-based outbreaks compared with *K. pneumoniae* (see the example of ESBL-producing *K. pneumoniae*). The very low amounts of polymyxins used in human medicine will not be a driving force for spreading the *mcr-1* gene in human isolates. The fitness cost of MCR-1-mediated modification of the lipopolysaccharide may be as high as shown for strains expressing chromosome-encoded modifications of the lipopolysaccharide [1]. Therefore, MCR-1 producers may be eliminated rapidly from the gut flora in the absence of selection pressure with polymyxins. The stability and transferability of the *mcr-1*-bearing plasmids may be low and those plasmids do not harbour many other antibiotic resistance genes (P. Nordmann, unpublished data). Finally, many MCR-1 producers exhibit low levels of resistance to polymyxins. Therefore, it is possible that polymyxins might retain some *in vivo* activity for treating infections due to MCR-1-producing isolates, either alone or in association with other antibiotic molecules.

What Should Be Done Now?

Taking into account the massive use of polymyxins in animals (as they are cheap antibiotics), polymyxins should be banned as growth promoters worldwide, as was done in Europe as early as 2005. Restricted use of polymyxins in prophylaxis and metaphylaxis in animals should also be promoted in a coordinated effort at the international level. Selective digestive decontamination in humans by using colistin-containing mixtures should be revised urgently.

Detection of colistin-resistant bacteria should be encouraged by promoting the development of reliable techniques for susceptibility testing such as the broth dilution technique and rapid diagnostic tests for polymyxin resistance. A precise determination of susceptibility to polymyxins should be performed at least for all carbapenemase-producing enterobacterial isolates and for enterobacterial species that are known to be the source of nosocomial outbreaks (*K. pneumoniae*, *Enterobacter* spp.). Once MCR-1 producers are detected, the issue of isolation of infected/carriers will be raised. We believe that patients carrying isolates that produced MCR-1 in association with carbapenemases should be strictly isolated whatever the bacterial species and whatever the cost for the hospital community. Isolation of carriers of isolates producing MCR-1 only is debatable. While waiting for the results of further clinical studies, we may suggest not isolating patients carrying MCR-1-producing *E. coli* but isolating patients carrying MCR-1-producing *K. pneumoniae* and *Enterobacter* sp. This recommendation is based on the fact that ESBL-producing *E. coli* are not responsible for nosocomial outbreaks in acute settings whereas ESBL-producing *K. pneumoniae* and *Enterobacter* spp. are.

Conclusion

Finally, the identification of plasmid-mediated colistin resistance is certainly bad news. However, if adequate measures are rapidly taken, both in veterinary and human medicines, it is possible that the spread of this resistance trait may remain under control to prevent its further dissemination to bacteria in immunocompromised patients in hospitals. The preservation of the efficacy of polymyxins is of utmost importance for those immunocompromised patients who are already infected by other multidrug-resistant bacteria.

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Transparency Declaration

The authors have no conflicts of interest to declare.

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