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From Pigs to Patients: Transmissible, Single Gene-mediated Resistance to *Colistin*

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Commentary

The last decade has seen a stark increase in the number of multidrug resistant Gram-negative bacterial pathogens. Of particular importance are highly carbapenem resistant *Escherichia coli* and *Klebsiella pneumoniae*, as well as fluoroquinolone resistant *Pseudomonas aeruginosa* and *Acinetobacter baumanii* [1]. Owing to the lack of new drugs entering the marketplace, physicians are increasingly revisiting older drugs that had fallen out of common use. One such drug is *colistin* and it has increasingly become the drug of last resort for these infections [2]. *Colistin* is a polymyxin type of antimicrobial lipopeptide that is produced by *Paenobacillus* species. The polymxyins were discovered 65 years ago but have limited clinical use due to their neurotoxic and nephrotoxic side effects. Despite this toxicity in humans, *colistin* is used extensively in agriculture as growth promoters and estimates of global *colistin* usage in agriculture is >12,000 tonnes per annum. A recent report in the Lancet Infectious Diseases describes the first example of a transmissible plasmid that encodes *colistin* resistance by the *mcr-1* gene. *Colistin* resistance was first detected in *Escherichia coli* isolates from pigs, but was ultimately found in meats for sale, and later in Chinese patients [3].

Clinical resistance to *colistin* is largely mediated through the modification of lipopolysaccharide via the addition of ethanolamine or 4-amino-arabinose to free phosphate moieties on the lipid A moiety. These additions reduce the negative charge and limit antimicrobial peptide binding and membrane disruption [4,5]. The emergence of clinical resistance to *colistin* is due to point mutations in regulatory proteins that control the genes responsible for these additions, PhoPQ and/or PmrAB (and MgrB in *K. pneumoniae*) and were transmitted only vertically [6-9]. These data suggest that contrary to a common argument put forward by those developing novel antimicrobial peptides, resistance to this antibiotic class is common and now transmissable as single gene determinants.

The *mcr-1* gene encodes a phosphoethanolamine transferase that adds a phosphoethanolamine to the phosphate groups of hexa-acylated lipid A, thereby blocking the negatively charged phosphates on lipid A, which otherwise serve as the binding site of cationic antimicrobial peptides [3,5]. The plasmid encoding *mcr-1* is highly transmissible by conjugation to other *E. coli* isolates, and by transformation to other Gram-negative pathogens, resulting in 8-16 fold increases in *colistin* resistance [3]. In addition, the *mcr-1* gene was active in an animal model of infection, demonstrating that it can provide a survival advantage during *colistin*-mediated chemotherapy [3]. This is the first description of plasmid-mediated *colistin* resistance and it represents a very important and worrisome development in infectious disease control.

In subsequent reports, the *mcr-1* gene was found in food isolates of *Salmonella enterica* from Portugal and France [10,11], in six healthy individuals in Laos, Algeria and Thailand [12], in the gut micro biomes of healthy and diabetic Chinese subjects [13] and in *E. coli* samples from a prospective study of Dutch patients travelling to Southeast Asia [14]. Unpublished reports have also identified the *mcr-1* gene in *S. enterica* and *E. coli* isolates in England and Wales, including at least 2 isolates from patients [15]. Perhaps most worrisome, the *mcr-1* gene was found in an *E. coli* blood-borne infection isolate from a Danish patient with recurrent UTIs [15]. While the original report demonstrated that the *mcr-1* gene was found on an IncI2 type plasmid, these short reports found the gene on IncX4 type plasmids as well showing that the gene is present in more than one plasmid type. While this is a very worrying observation, the *mcr-1* gene has not yet been linked to any documented evidence of clinical *colistin* failure in humans.

In the Liu paper, the authors used a murine thigh model to demonstrate the effect of *mcr-1* on *in vivo colistin* sensitivity [3]. Of interest, this experiment shows that in the absence of *colistin*, the *mcr-1*+ strain has a slight fitness defect [3]. Whether this is due to the *mcr-1* gene itself or other genetic elements on pHNSHP45 is unknown, but it has been well documented that regulatory changes associated with *colistin* resistance often reduce the fitness of the organism containing those mutations in the absence of selection [6,7,16,17]. This suggests that removing the use of *colistin* may have the added benefit of selecting against the long-term survival of resistant isolates because of their reduced fitness relative to sensitive strains.

In summary, the observation of plasmid-mediated *colistin* resistance offers yet more evidence that antibiotic usage in agriculture needs to be drastically curtailed if we want to continue to use antibiotics to treat people. China is one of the largest users of *colistin* in agriculture, although use is widespread in the EU as well. Surveillance data in China has already demonstrated that *colistin* resistance is widespread in animal isolates. As there is limited development of new antimicrobials, particularly those directed toward Gram-negative pathogens, we ignore this development at our peril. Although this is the first example of plasmid-mediated *colistin* resistance, it is not likely the last, as there are other single candidate genes that could also lead to *colistin* resistance. There have been previous studies describing resistance to "last resort" antibiotics, and hopefully this example of *colistin* resistance will not lead to the "apocalypse pig" [18].

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