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Review

Resistance to colistin: what is the fate for this antibiotic in pig production?

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ABSTRACT

Colistin, a cationic polypeptide antibiotic, has reappeared in human medicine as a last-line treatment option for multidrug-resistant Gram-negative bacteria (MDR-GNB). Colistin is widely used in veterinary medicine for the treatment of gastrointestinal infections caused by Enterobacteriaceae. GNB resistant to colistin owing to chromosomal mutations have already been reported both in human and veterinary medicine, however several recent studies have just identified a plasmid-mediated *mcr-1* gene encoding for colistin resistance in *Escherichia coli* colistin resistance. The discovery of a non-chromosomal mechanism of colistin resistance in *E. coli* has led to strong reactions in the scientific community and to concern among physicians and veterinarians. Colistin use in food animals and particularly in pig production has been singled out as responsible for the emergence of colistin resistance. The present review will focus mainly on the possible link between colistin use in pigs and the spread of colistin resistance in Enterobacteriaceae. First we demonstrate a possible link between Enterobacteriaceae resistance emergence and oral colistin pharmacokinetics/pharmacodynamics and its administration modalities in pigs. We then discuss the potential impact of colistin use in pigs on public health with respect to resistance. We believe that colistin use in pig production should be re-evaluated and its dosing and usage optimised. Moreover, the search for competitive alternatives to using colistin with swine is of paramount importance to preserve the effectiveness of this antibiotic for the treatment of MDR-GNB infections in human medicine.

1. Introduction

Colistin is an antibiotic from the polymyxin family, a group of cationic polypeptide antibiotics consisting of five chemically different compounds (polymyxins A–E). Only polymyxin E (colistin) and polymyxin B are currently available on the market [1]. Two forms of colistin (polymyxin E) are used for the treatment of infections caused by Gram-negative bacteria (GNB) in humans: colistin sulphate (CS) for oral and topical use; and colistin methanesulphonate sodium (CMS) for parenteral use [2]. Among the two commercially available forms, CS is the only approved product in pig production in some countries to control pig intestinal infections caused by Enterobacteriaceae [3–5].

The mechanism of antibacterial action of colistin is essentially based on the electrostatic interaction between positively charged amino groups of colistin and the negatively charged phosphate groups of lipid A subunits present in the structure of lipopolysaccharide (LPS) [2,6,7]. Colistin alters the structure of LPS and leads to increased permeability of the cell membrane, resulting in leakage of the cell contents and bacterial death [8,9].

The lack of new antibacterial chemical entities commercialised over the last several years as well as the rapid development of resistance in GNB to current antibiotics has led to an overuse of colistin both in human and veterinary medicine [10,11]. During the last decade, research on colistin experienced a very significant increase (Fig. 1). Despite its high toxicity, colistin has replaced aminoglycosides in humans for the treatment of multidrug-resistant (MDR) GNB and it is considered a last-line treatment option for carbapenemase-producing Enterobacteriaceae [2]. Given the importance this antibiotic has taken on since 2012, the *World Health Organization (WHO)* has reclassified colistin as critically important for human medicine [12].

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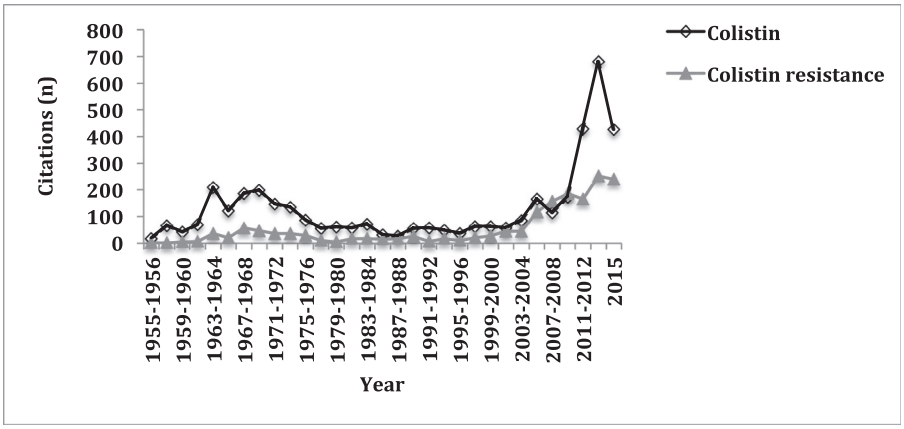

Fig. 1. Number of citations found in the PubMed database from 1955 to 2015 using either the search phrase 'colistin' or 'colistin resistance'.

Concurrent with the excessive use of colistin over the last few years both in human and veterinary medicine worldwide is a reported increase in resistance to colistin of bacteria that were normally susceptible to this antibiotic [11,13]. The most documented mechanism of colistin resistance in *Salmonella* and *Escherichia coli* involves mutation in the two-component systems PhoP–PhoQ and/or PmrA–PmrB that result in structural modifications of the lipid A subunit, which affects the LPS negative charge and leads to less electrostatic interaction with the positive charges of colistin [13,14]. However, the mechanisms of colistin resistance are multifaceted and do not involve just one molecular origin [13]; despite the fact that this mutation is an important cause of colistin resistance in *E. coli*, it appears that it is not the exclusive resistance mechanism [15–17].

The study by Liu et al published in *The Lancet Infectious Diseases* was the first to show the involvement of a stable plasmid-mediated *mcr-1* gene encoding a phosphoethanolamine transferase conferring resistance to colistin in *E. coli* [17]. This study contributed to our understanding of other potential *E. coli* resistance mechanisms to colistin and described for the first time an *mcr-1* gene on a mobile genetic element involved in colistin resistance dissemination between animals and humans. In addition, because of the high rate of colistin-resistant *E. coli* carrying the *mcr-1* gene isolated from food animals compared with humans [17], livestock production was pinpointed as the greatest cause of colistin resistance amplification and spread. It has been reported in several studies that the *E. coli* colistin resistance rate was higher in swine compared with other animal productions [18–22]. We conducted the following literature review to determine a possible link between colistin use in pig production and the emergence of colistin resistance in Enterobacteriaceae and to discuss its potential impact on public health with respect to resistance.

2. Colistin sulphate use in pig production and the Enterobacteriaceae resistance rate

Among the two forms of colistin commercially available, the only approved product in pig production is CS, which is used for the control of pig intestinal infections caused by *E. coli* and *Salmonella* [3,23,24]. Indeed, CS is used therapeutically, prophylactically and even as a growth promoter in pig industries in some countries [25–29].

In human medicine, use of colistin was abandoned in the 1970s mainly because of its ability to cause human nephrotoxicity [30–32]. However, in *the late 1990s* the development of resistance of GNB to aminoglycosides led to a resurgence of the clinical use of colistin [6,30]. Nowhere in the literature is there an indication that colistin usage was also interrupted in pig production when it was withdrawn in human medicine between 1970 and 2000. Furthermore, colistin is used orally in pigs and is characterised by low oral bioavailability [24,33], therefore the risk of side effects associated with CS systemic exposure in pigs is negligible.

Colistin is used in massive quantities in pig production worldwide [17,28,29]. In France, 90% of farms in the pig industry reported using colistin during the post-weaning period, 48% used it to treat sows during gestation and lactation, and 19% used it at the finishing level [11]. In Belgium, more than 30% of prophylactic and metaphylactic oral treatment in 50 randomly chosen fattening pig farms was based on colistin use [23]. In Spain, Casal et al reported that colistin was the most frequently used antibiotic for metaphylactic intestinal disease control in 107 pigs farms and that there was a high rate of prophylactic use of this antibiotic without a defined diagnosis [26]. In Austria, a study of 49 pig farrow-to-finish farms chosen for antibiotic monitoring showed that 34.4% of the farms used colistin for metaphylactic/prophylactic purposes [27]. In 60 Swedish farrow-to-finish pig herds, Sjolund et al reported that the use of colistin accounted for 18% of all antibiotic treatments in weaned piglets [34]. In Germany, Van Rennings et al reported that in 495 pig farms, colistin was among the most used antibiotics in piglets [35], and of the 20,373.6 kg of antimicrobial agents used on these farms in 2011, polypeptides (colistin) represented 4.2% of all antibiotics used [35]. In the Red River Delta region of Vietnam, Kim et al reported that 210 pig husbandry entities representing three different systems (farm household, semi-industrial and industrial) have been using colistin for several purposes [29]. Indeed, in 78 entities colistin was used for growth promotion, in 12 for disease prevention and in 56 for therapy [29]. In The Netherlands, Bos et al reported that colistin has been little used in piglets and sows compared with its use in starter calves [36]. In an Australian national survey of antimicrobial use in the pig industry conducted in 2006, Jordan et al did not report any colistin use in pig production during that period [37].

China remains the largest user worldwide of colistin in agriculture, with 11,942 tonnes per year by the end of 2015. Given the expansion and intensification of animal husbandry and a 4.75% average annual increase of colistin use in this country, the annual quantity used will be 16,500 tonnes by 2021 [17]. Furthermore, CS in pig production in some countries outside North America and the European Union (EU) was used as a feed additive for growth promotion [25,29,38]. In 2015, the EU and North America imported 480 tonnes and 700 tonnes of colistin from China, respectively [17]. However, CS is an unapproved antibiotic in veterinary medicine in some countries, including Canada, and it is used under the veterinarian liability (dose, withdrawal period) for the treatment of Enterobacteriaceae infections in pigs [33]. It should be stressed here