

Carbapenemase-producing bacteria in companion animals: a public health concern on the horizon

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Clinical infections attributed to carbapenemase-producing bacteria are a pressing public health concern owing to limited therapeutic options and linked antimicrobial resistance. In recent years, studies have reported the emergence and spread of carbapenemase-producing Enterobacteriaceae and their public health impact. This has been closely followed by the global dissemination of highly resistant and virulent zoonothonotic extraintestinal pathogenic *Escherichia coli* (ExPEC) ST131 clones. It has also been hypothesized that companion animals may act as a reservoir for Gram-negative multidrug-resistant pathogens in the community. Two recent reports have documented the emergence of carbapenemase-producing bacteria in companion animals. This phenomenon is of great concern because of the close contact between humans and their pets, and the potential for cross-species transmission. This scenario suggests a role for multifaceted control of Gram-negative multidrug-resistant infections in companion animals. This short article addresses this issue and identifies steps that could facilitate this process.

Keywords: *Escherichia coli*, urinary tract infections, UTIs, antibiotic resistance, NDM-1, OXA-48, ST131

Introduction

Clinical infections attributed to carbapenemase-producing bacteria are a pressing public health concern owing to limited therapeutic options and linked antimicrobial resistance to almost all classes of antimicrobials. In recent years, studies have reported on the emergence and spread of carbapenemase-producing Enterobacteriaceae and their impact on public health.^{1,2} One classic example is the global dissemination of almost pan-resistant NDM-1-producing Gram-negative bacteria.^{1,2} In addition to NDM-1, carbapenemases of the KPC, VIM, IMP and OXA-48-like types are also responsible for carbapenem resistance in Enterobacteriaceae.³ Thus far, carbapenemase-producing bacteria have been isolated predominantly from humans and environmental samples.^{1,2,4} A recent review by Woodford *et al.*⁴ has highlighted the global emergence of carbapenem resistance in livestock^{4–8} and, more recently, companion animals.^{9,10} Two studies have demonstrated the detection of carbapenemase-producing *Escherichia coli* (NDM-1 and OXA-48) and *Klebsiella pneumoniae* (OXA-48) from clinical infections in companion animals.^{9,10}

Furthermore, this problem may already be much larger than has been documented to date. In companion animals, carbapenemase-producing Enterobacteriaceae may go undetected because most veterinary diagnostic laboratories would not be testing clinical isolates, since carbapenems are not

registered for use in animals. Moreover, even if such testing were done, laboratories would have to default to using (probably inappropriate) human breakpoints, which are known not to (and are not designed to) detect all carbapenemase producers. Thus, considering the close contact between humans and their pets, and the potential for cross-species transmission, the emergence of carbapenem resistance in companion animals is a worrying trend.

Zoonothonotic nature of *E. coli* from companion animals

The emergence of carbapenemase-producing Enterobacteriaceae has followed closely behind the rapid global dissemination of extraintestinal pathogenic *E. coli* (ExPEC) ST131 clones, which are highly virulent and can exhibit resistance to critically important antimicrobials, including fluoroquinolones,^{11,12} extended-spectrum cephalosporins⁴ and, most recently, carbapenems.¹³ ExPEC from companion animals are becoming increasingly resistant to a wide range of critically important antimicrobials, such as extended-spectrum cephalosporins, fluoroquinolones and aminoglycosides.^{14,15} Our previous studies have shown that fluoroquinolone-resistant ExPEC have zoonothonotic potential.^{14–18} Significantly, fluoroquinolone-resistant ST131 isolates from companion animals and humans are genetically closely related, with the majority belonging to a single globally disseminated PFGE

type (pulsotype 968).^{12,14,17} It is also well established that dogs may carry fluoroquinolone-resistant ExPEC strains, including ST131, in their faecal microbiota,¹⁸ and that interspecies transmission occurs readily between humans and companion animals within the same household.^{18–20} The emergence of carbapenemase-producing Gram-negative pathogens from companion animals provides further evidence that companion animals are a previously overlooked reservoir for multidrug-resistant Gram-negative bacteria in the community.¹⁰

Risks of carbapenem use in companion animals

The discovery of carbapenem resistance in ExPEC isolates from companion animals could possibly be linked to carbapenem use in veterinary practice, which has significant public health ramifications.²¹ Even though carbapenems are not registered for use in animals in any major jurisdiction, off-label veterinary use of this critical ‘last-line’ antimicrobial class has been reported in dogs for the treatment of urinary tract infection (UTI) and post-operative infection caused by multidrug-resistant *E. coli*.²¹ In our opinion, veterinary use of last-line therapies such as carbapenems must be prevented or at least severely restricted, owing to the obvious risk of increasing selection pressure for the maintenance of carbapenemase-producing ExPEC in the faecal microbiota of companion animals and their potential transfer to humans.

The promiscuous mobile genetic elements containing *bla*_{NDM-1} and *bla*_{OXA-48}, such as *InCA/C* plasmids and their *ISCR* insertion elements, may transfer readily between unrelated bacterial strains in the gut of companion animals.^{1,2,22,23} This has been a major factor contributing to the rapid global dissemination of NDM-1-producing bacteria among humans. The carbapenemase-encoding plasmids also encode resistance to other β -lactams, such as cephalosporins (via *bla*_{CMY-2}).²² Therefore, once carbapenemase-producing bacteria emerge in companion animals, the selection pressure resulting from the use of other β -lactams may select and maintain these highly resistant Gram-negative bacteria within the companion-animal population.

Recommendations for future control

This new scenario confirms the need for immediate control of multidrug-resistant Gram-negative infections in companion animals. Antimicrobial stewardship programmes similar to those being implemented widely in the Western world in human medicine must be developed rapidly for companion animal veterinary practice, from which they currently are essentially absent. Optimal use of currently available antimicrobial classes through the judicious application of pharmacokinetic/pharmacodynamic dosing principles must also be explored. The development of new classes of antimicrobial agents that could be uniquely applied to animals would also be a major step forward, especially if accompanied by an international agreement that such classes would not be developed for human use.

One way of managing resistant bacterial infections in companion animals is to routinely perform culture and antimicrobial susceptibility testing for all UTIs in companion animals, coupled with MIC testing of isolates from chronic and recurrent infections to determine the most favourable pharmacokinetic/pharmacodynamic parameters. Other creative solutions should be explored,

such as competitive exclusion, for example by the administration of asymptomatic bacteriuria strains such as *E. coli* 83972. This strain has recently been shown to colonize the urinary tract of healthy dogs without causing infection, and may prevent colonization by more virulent, antimicrobial-resistant uropathogenic *E. coli*.^{24,25}

Globally, resistance to carbapenems has been reported infrequently in Gram-negative pathogens such as *E. coli* from companion animals.⁴ To sustain this favourable status quo, prudent use of critically important antimicrobials such as fluoroquinolones and third-generation cephalosporins, combined with severe restriction or elimination of carbapenem use, must be extended to veterinary practice. We therefore propose the following recommendations:

- (1) Development of antimicrobial stewardship programmes in companion animal veterinary practice to ensure that carbapenems are used only in the very few cases that lack other suitable alternatives on the basis of culture and susceptibility testing.
- (2) Surveillance for antimicrobial-resistant zoonotic pathogens, as done in livestock, should be extended to include antimicrobial-resistant ExPEC in companion animals, and should include screening for carbapenemase production.
- (3) An evidence-based approach to diagnosing and treating infectious diseases in companion animals should be developed and promulgated, with culture and antimicrobial susceptibility testing used for all UTIs in companion animals, along with MIC-based susceptibility testing for chronic or recurrent UTI, to guide therapeutic options for multidrug-resistant pathogens.
- (4) Surveillance and monitoring of antimicrobial resistance in companion animals should include tracking the movement of mobile genetic elements that encode resistance to critical antimicrobials, such as plasmids encoding NDM, OXA-48, VIM, IMP and CTX-M β -lactamases.

Urgent action is required to prevent or reduce the threat to public health posed by the development of carbapenem resistance in Gram-negative pathogens in companion animals.

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