of TEM-52 extended-spectrum β-lactamase in serogroup O26. *Antimicrob Agents Chemother* 2010; **54**: 4907–9.

**3** Mellmann A, Harmsen D, Cummings CA *et al*. Prospective genomic characterization of the German enterohemorrhagic *Escherichia coli* O104:H4 outbreak by rapid next generation sequencing technology. *PLoS One* 2011; **6**: e22751.

**4** Torpdahl M, Nielsen EM, Scheutz F *et al*. Detection of a Shiga toxin- and extended-spectrum-β-lactamase-producing *Escherichia coli* O157:H7 human clinical isolate. *J Antimicrob Chemother* 2013; **68**: 1203–4.

**5** Aarestrup FM, Hasman H, Agerso Y *et al*. First description of $bla_{CTX\text{-}M\text{-}1}$-carrying *Escherichia coli* isolates in Danish primary food production. *J Antimicrob Chemother* 2006; **57**: 1258–9.

**6** Dutta TK, Warjri I, Roychoudhury P *et al*. Extended-spectrum-β-lactamase-producing *Escherichia coli* isolate possessing the Shiga toxin gene ($stx_1$) belonging to the O64 serogroup associated with human disease in India. *J Clin Microbiol* 2013; **51**: 2008–9.

**7** Ishii Y, Kimura S, Alba J *et al*. Extended-spectrum β-lactamase-producing Shiga toxin gene ($stx_1$)-positive *Escherichia coli* O26:H11: a new concern. *J Clin Microbiol* 2005; **43**: 1072–5.

**8** Roest HI, Liebana E, Wannet W *et al*. [Antibiotic resistance in *Escherichia coli* O157 isolated between 1998 and 2003 in the Netherlands]. *Tijdschr Diergeneeskd* 2007; **132**: 954–8.

**9** Franck SM, Bosworth BT, Moon HW. Multiplex PCR for enterotoxigenic, attaching and effacing, and Shiga toxin-producing *Escherichia coli* strains from calves. *J Clin Microbiol* 1998; **36**: 1795–7.

**10** Karmali MA, Mascarenhas M, Shen S *et al*. Association of genomic O island 122 of *Escherichia coli* EDL 933 with verocytotoxin-producing *Escherichia coli* seropathotypes that are linked to epidemic and/or serious disease. *J Clin Microbiol* 2003; **41**: 4930–40.

**11** Tarr PI, Bilge SS, Vary JC Jr *et al*. Iha: a novel *Escherichia coli* O157:H7 adherence-conferring molecule encoded on a recently acquired chromosomal island of conserved structure. *Infect Immun* 2000; **68**: 1400–7.

**12** Ewers C, Bethe A, Semmler T *et al*. Extended-spectrum β-lactamase-producing and AmpC-producing *Escherichia coli* from livestock and companion animals, and their putative impact on public health: a global perspective. *Clin Microbiol Infect* 2012; **18**: 646–55.

*J Antimicrob Chemother* 2014
doi:10.1093/jac/dku054
Advance Access publication 26 February 2014

# The carbapenemase threat in the animal world: the wrong culprit

**Laurent Poirel[1]*, Roger Stephan[2], Vincent Perreten[3] and Patrice Nordmann[1]**

*[1]Medical and Molecular Microbiology Unit, Department of Medicine, Faculty of Science, University of Fribourg, Fribourg, Switzerland; [2]Institute for Food Safety and Hygiene, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland; [3]Institute of Veterinary Bacteriology, Vetsuisse Faculty, University of Bern, Bern, Switzerland*

*Corresponding author. E-mail: laurent.poirel@unifr.ch

**Keywords:** carbapenems, ESBLs, veterinary medicine, food chain

Sir,

We read with great interest two recent publications dealing with the same topic, i.e. the public health risk related to the occurrence of acquired carbapenemase-producing Gram-negative species in the animal world and the environment.[1,2] Woodford *et al.*[1] highlight the series of reports of carbapenemases found either in bacteria isolated from non-human sources or in *Salmonella enterica* subsp. *enterica*, a zoonotic species. This raises concern about the real spread of these threatening organisms in the food chain and other non-human sources of infection. Abraham *et al.*[2] focus on the possible role of companion animals as a source of carbapenemase-producing strains in humans, building their hypotheses on two studies reporting NDM-1-producing *Escherichia coli* isolates from dogs in the USA, and OXA-48-producing *E. coli* and *Klebsiella pneumoniae* isolates, also from dogs, in Germany. Both reports encourage public health authorities to implement measures to better evaluate the spread of carbapenemase-producing strains in animals, and reinforce efforts leading to a reduction of antibiotic consumption in veterinary practice.

We fully agree that the implementation of surveillance studies aimed to better evaluate and trace multidrug resistance in general, and carbapenem resistance in particular, is crucial in the fight against antibiotic resistance. We also agree that any effort towards a reduction of antibiotic consumption is valuable and must be sustained. However, we believe that the spread of carbapenemase-producing isolates among animals is not the main explanation for their occurrence in humans. Carbapenems are not registered for use in veterinary medicine, even though they may be used in specific circumstances in companion animals or horses when dealing with multidrug-resistant Enterobacteriaceae. This usage, at least in developed countries, remains rare.[3] The occurrence of carbapenemase-producing isolates in companion animals, as for extended-spectrum β-lactamase (ESBL) producers,[4] most probably results from contamination from the animal keeper, who is statistically more exposed to broad-spectrum antibiotics, and in particular to broad-spectrum β-lactams, than the animal itself. In this regard, an increasing and irresponsible use of carbapenems in companion animals might contribute to the selection and dissemination of carbapenem-resistant strains, and all efforts to avoid carbapenem use in veterinary practice should be pursued.[3]

The real threat related to carbapenemase resistance in humans comes from two main facts. The first corresponds to the increased consumption of carbapenems worldwide, as a consequence of an increased rate of resistance to broad-spectrum cephalosporins among human isolates. Therefore, carbapenems, although being last-resort antibiotics, are now considered to be first-line therapeutic options in certain geographical areas where multidrug resistance is endemic. The second main explanation comes from the overall increase in human population movements worldwide, including migration and tourism.[5]

In humans, carbapenemase-producing Enterobacteriaceae may be either hospital acquired (mostly *K. pneumoniae*), or community acquired (mostly *E. coli*), either as colonizers or infectious agents. Carbapenemase-producing *E. coli* are mainly the source of community-acquired infections or colonization.[5] Of note, *E. coli*, by contrast with *K. pneumoniae*, may be identified in the food chain. Numerous studies have been conducted over the past decade to evaluate the possible link between the occurrence of ESBL producers among food-producing animals on one hand, and in humans on the other. Despite the fact that the rate of colonization

of animals (poultry, pigs, cattle etc.) is high, there is still little evidence that ESBL producers are spreading mainly through the food chain.[4] Taking into account the paucity of reports of carbapenemase producers in animals, and the fact that carbapenems are not used in food-producing animals, the risk to public health remains marginal.

Nowadays, the major threat related to the spread of carbapenemase producers among humans is linked to a lack of hygiene, to contaminated drinking water and to poor control of antibiotic usage in some highly populated geographical areas.[5] As a consequence, some countries may become endemic not only for ESBL producers but also for carbapenemase producers. As examples, it is estimated that among isolates associated with intra-abdominal infections in India during 2008, 61% and 47% were ESBL-producing *E. coli* and *K. pneumoniae*, respectively.[6] In Pakistan, the faecal carriage of NDM-1-producing isolates among hospitalized patients was estimated at 15%–20%.[7]

In a country such as Switzerland, where the rate of patient colonization with ESBL-producing Enterobacteriaceae at admission has been evaluated to be 4%–5%,[8] while being 8.4% among the Swiss slaughter cattle population,[9] recent surveys have reported the lack of detection of carbapenemase-producing Enterobacteriaceae among farm animals and community patients.[10,11] The first case of colonization by a carbapenemase-producing *S. enterica* strain has recently been reported, being an OXA-48 producer recovered from a patient transferred from Libya to Switzerland.[12] Knowing that Libya is endemic for OXA-48-producing Enterobacteriaceae,[13] this case further highlights that the risk of acquisition of carbapenemase producers mainly comes from human endemic areas.

Rapid identification of carbapenemase producers by using easy-to-handle and affordable techniques will contribute to the recognition of infected and colonized patients at an early stage.[14] This will allow the rapid implementation of isolation and cohorting strategies, and the improvement of antibiotic stewardship to prevent the development of outbreaks. It may also contribute to better identification of the possible dissemination of carbapenemase producers, not only within the human population but also from a human source to animals.

## Funding

This work has been funded by the University of Fribourg, Switzerland.

## Transparency declarations

None to declare.

## References

**1** Woodford N, Wareham DW, Guerra B *et al*. Carbapenemase-producing Enterobacteriaceae and non-Enterobacteriaceae from animals and the environment: an emerging public health risk of our own making? *J Antimicrob Chemother* 2014; **69**: 287–91.

**2** Abraham S, Wong HS, Turnidge J *et al*. Carbapenemase-producing bacteria in companion animals: a public health concern on the horizon. *J Antimicrob Chemother* 2014; **69**: 1155–7.

**3** EFSA Panel on Biological Hazards (BIOHAZ). Scientific opinion on carbapenem resistance in food animal ecosystems. *EFSA J* 2013; **11**: 3501, 70 pp.

**4** EFSA Panel on Biological Hazards (BIOHAZ). Scientific opinion on the public health risks of bacterial strains producing extended-spectrum β-lactamases and/or AmpC β-lactamases in food and food-producing animals. *EFSA J* 2011; **9**: 2322, 95 pp.

**5** Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis* 2011; **17**: 1791–8.

**6** Hsueh PR, Badal RE, Hawser SP *et al*. for the 2008 Asia–Pacific SMART Group. Epidemiology and antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region: 2008 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). *Int J Antimicrob Agents* 2010; **36**: 408–14.

**7** Perry JD, Naqvi SH, Mirza IA *et al*. Prevalence of faecal carriage of Enterobacteriaceae with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media. *J Antimicrob Chemother* 2011; **66**: 2288–94.

**8** Pasricha J, Koessler T, Harbarth S *et al*. Carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae among internal medicine patients in Switzerland. *Antimicrob Resist Infect Control* 2013; **2**: 20.

**9** Reist M, Geser N, Hächler H *et al*. ESBL-producing Enterobacteriaceae: occurrence, risk factors for fecal carriage and strain traits in the Swiss slaughter cattle population younger than 2 years sampled at abattoir level. *PLoS One* 2013; **8**: e71725.

**10** Nüesch-Inderbinen M, Zurfluh K, Hächler H *et al*. No evidence so far for the dissemination of carbapenemase-producing Enterobacteriaceae in the community in Switzerland. *Antimicrob Resist Infect Control* 2013; **2**: 23.

**11** Stephan R, Sarno E, Hofer E *et al*. Lack of evidence so far for carbapenemase-producing Enterobacteriaceae in food-producing animals in Switzerland. *Schweiz Arch Tierheilkd* 2013; **155**: 417–9.

**12** Seiffert SN, Perreten V, Johannes S *et al*. OXA-48 carbapenemase producing *Salmonella enterica* Kentucky of ST198 in a patient transferred from Libya to Switzerland. *Antimicrob Agents Chemother* 2014; doi:10.1128/AAC.02417–13.

**13** Poirel L, Potron A, Nordmann P. OXA-48-like carbapenemases: the phantom menace. *J Antimicrob Chemother* 2012; **67**: 1597–606.

**14** Dortet L, Bréchard L, Cuzon G *et al*. Strategy for a rapid detection of carbapenemase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2014; doi:10.1128/AAC.01239–13.

*J Antimicrob Chemother* 2014
doi:10.1093/jac/dku075
Advance Access publication 20 March 2014

# Single- and multiple-dose pharmacokinetics and total removal of colistin in a patient with acute kidney injury undergoing extended daily dialysis

**Ann-Kathrin Strunk[1], Julius J. Schmidt[1], Eva Baroke[2], Stefanie M. Bode-Böger[3], Jens Martens-Lobenhoffer[3], Tobias Welte[2] and Jan T. Kielstein[1]**

*[1]Department of Nephrology and Hypertension, Medical School Hannover, Hannover, Germany; [2]Department of Pulmonary*