of animals (poultry, pigs, cattle etc.) is high, there is still little evidence that ESBL producers are spreading mainly through the food chain. 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. 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. In Pakistan, the faecal carriage of NDM-1-producing isolates among hospitalized patients was estimated at 15%–20%.

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%, while being 8.4% among the Swiss slaughter cattle population, recent surveys have reported the lack of detection of carbapenemase-producing Enterobacteriaceae among farm animals and community patients. 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. Knowing that Libya is endemic for OXA-48-producing Enterobacteriaceae, 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. 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.

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

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2008
Sir,

The emergence of multidrug-resistant bacteria has recently renewed interest in colistin, which was first introduced in 1959. For intravenous administration, not colistin itself, but its inactive prodrug colistin methanesulfonate (CMS) is administered. As ≈70% of CMS is excreted unchanged in the urine, its $t_1/2$ increases with a decline in glomerular filtration rate (GFR) to up to 14 h in patients with a GFR of <15 mL/min. Additionally, a larger fraction of the CMS dose is converted into colistin with decreasing renal function. Thus, dose reduction is recommended with decreasing GFR. Data from 1968 on four patients treated with twice-weekly dialysis for 11–16 h using a cuprophane membrane are the foundation for current dosing regimens in chronic haemodialysis. In these patients a dose of 1 million units every 48 h is recommended. Data on dosing in critically ill patients undergoing extended dialysis are missing. Written informed consent was obtained from the patient’s mother for publication of this study. Ethical approval for reporting this case was obtained from the Medical School Hannover.

A patient aged between 30 and 40 years (height 163 cm, weight 53 kg) was admitted to our intensive care unit (ICU) for rapidly progressive respiratory failure. The patient had undergone lung transplantation for pulmonary hypertension 10 months earlier. The patient’s post-transplant course had been complicated by acute rejection and an Aspergillus fumigatus infection. On admission, the patient required non-invasive ventilation. Bronchoalveolar lavage revealed a multiresistant Klebsiella pneumoniae in addition to the previously known Aspergillus. Endotracheal intubation was required owing to worsening respiratory failure. Extended dialysis for acute kidney injury was started. As the K. pneumoniae was only susceptible to colistin, we initiated treatment with 3 million units every 8 h after an initial dose of 6 million units. Blood samples were taken at regular intervals on day 1 and day 9 of treatment. Colistin and CMS concentrations were determined separately by HPLC combined with tandem mass spectrometry, as recently used in its modified form. The average dialysis time between day 1 and day 9 was 552 min; mean blood and dialysate flow were 191 mL/min and 121 mL/min, respectively. After a loading dose of 6 million units, peak levels of colistin and CMS were 10.01 mg/mL and 24.76 mg/mL, respectively. The lowest plasma concentrations on day 1 were 3.83 mg/mL for colistin and 0.1 mg/mL for CMS. Extended dialysis with the above-mentioned specifications led to a reduction of peak colistin levels (Figure 1). After 9 days of treatment with 3 million units every 8 h there was neither an accumulation of colistin (peak level day 9: 8.96 µg/mL, trough level 2.13 µg/mL) nor an accumulation of CMS (peak level day 9: 11.83 µg/mL, trough level <0.1 µg/mL). Depending on the blood and dialysate flow, the dialyser clearance of colistin ranged between 54 and 71 mL/min and the CMS clearance between 25 and 62 mL/min. The amount of colistin in the total collected dialysate was 245 mg on day 1 and 191 mg on day 9. Although the patient responded well to this antibiotic therapy, subsequent cerebral aspergillosis could not...
be treated, leading to the death of the patient after 5 weeks of treatment in the ICU. There are scarce data on the dosing of antibiotics in patients undergoing renal replacement therapy.7 Our data suggest that extended dialysis eliminates colistin effectively and to a larger extent than regular intermittent outpatient haemodialysis. This is in line with recent data on two critically ill patients undergoing a modern type of intermittent dialysis (1.6 m² polymethylacrylate membrane, blood/dialysate flow 300/500 mL/min, duration 4 h), in whom a CMS dialyser clearance of 90 mL/min was reported.8 Li et al.9 described a dialyser clearance of 11.9 mL/min for colistin and 11.2 mL/min for CMS in one critically ill patient undergoing continuous venovenous haemodiafiltration, which due to its continuous mode would remove approximately the same amount of the drug. Lastly, dialyser clearance in five patients receiving continuous venovenous haemodiafiltration was recently reported to be 72 mL/min for colistin and 32 mL/min for CMS.10

Thus, dosing colistin as recommended during regular haemodialysis is inadequate and would result in a significant under-dosing, which could be associated with a substantial risk, especially in critically ill patients in the ICU. A dose of 3 million units every 8 h seems to be adequate for patients undergoing daily extended dialysis for ~9 h a day with a high flux 1.3 m² dialyser. This dose of 9 million units per day did not lead to accumulation of the drug.

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Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study

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Sir, β-Lactam agents have been the main antibacterial agents used for the treatment of infective endocarditis since the discovery of penicillin more than 70 years ago. Indeed, due to their bactericidal activity and a safety profile that allows the use of high doses, this class represents the backbone of most first-line regimens in this indication.1 However, no β-lactam effective against methicillin-resistant staphylococci was available until recently, and the use of antibacterial agents recommended in these settings (mostly vancomycin and daptomycin) may be limited by dose-dependent toxicity and/or the emergence of resistance. Ceftaroline is a new cephalosporin agent with in vitro and in vivo activity against methicillin-resistant staphylococci, with MIC90s of 0.5 and 1 mg/L for methicillin-resistant coagulase-negative