Polymyxins: old antibiotics are back

Parchuri and colleagues recently reported a patient receiving chronic ambulatory peritoneal dialysis who developed peritonitis and bacteraemia due to an extended-spectrum β-lactamase-producing strain of *Klebsiella pneumoniae*. The infection was not controlled despite removal of the dialysis catheter and treatment for a week with intravenous amikacin and meropenem, although the isolate was intermittently sensitive to these antibiotics. Fortunately, the patient was cured with intravenous administration of polymyxin B. All symptoms, including abdominal pain, improved within 36 h of start of polymyxin B treatment, and the patient became completely asymptomatic 12 h later. This case highlights the renaissance of polymyxins as salvage antibiotics for patients with infections due to multidrug-resistant gram-negative bacteria.1

Polymyxins belong to a class of antibiotics that were discovered about 60 years ago. They are decapeptide antibiotics with an antimicrobial spectrum that includes gram-negative bacteria, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *K pneumoniae*. Although there are five main polymyxins (*A, B, C, D, and E*), only two—polymyxin B and colistin (polymyxin E)—have been used in clinical practice. Systemic administration of polymyxins was used to treat patients with infections at various body sites by gram-negative bacteria for about two decades (1960s and 1970s). However, these antibiotics were gradually abandoned in most parts of the world around 1980 because of reports of serious toxic effects, mainly to the kidney and nervous system.3,4 An exception to this practice has been for patients with cystic fibrosis, to whom polymyxins have been administered intravenously and via the respiratory tract for prevention and treatment of respiratory tract infections.3,5 Furthermore, polymyxins have been used for several decades in topical formulations for eye and ear infections and in regimens for selective bowel decontamination.

The growing epidemic of infections due to gram-negative bacteria such as *A baumannii*, *P aeruginosa*, and *K pneumoniae*, which are resistant to most classes of antimicrobial drugs, including carbapenems, has led to use of intravenous polymyxins in several parts of the world. Reassuringly, data from several studies suggest...
that these antibiotics are not less effective or more toxic than other classes of antimicrobials. For example, in a small comparative study of intravenous colistin versus imipenem/cilastatin for multidrug-resistant gram-negative bacterial infections, the effectiveness and safety of the studied antibiotics did not differ. Moreover, from several case series of patients who received intravenous colistin or polymyxin B for multidrug-resistant gram-negative bacterial infections (mainly *A baumannii* and *P aeruginosa*), polymyxins should be regarded as an acceptable treatment option when isolates are not susceptible to other antibiotics. However, these salvage antibiotics were not available in the market in some countries for the treatment of patients with infections due to (inappropriately called) pandrug-resistant gram-negative bacteria, since isolates were susceptible to polymyxins. Many questions remain unanswered about polymyxins, partly because most of the scientific knowledge about these antibiotics was accumulated before 1980. Polymyxins were developed in an era when molecular microbiological methods had not been fully established and randomised trials were not widely used. Thus further work is urgently needed to better understand the pharmacology and therapeutic use of polymyxins. Future research efforts should define the best dosing strategies for polymyxins, including mode of administration, total daily dose, dose intervals, and duration of treatment. Studies are needed to clarify mechanisms of resistance of bacteria to polymyxins, because reports are already available of *P aeruginosa* clinical isolates that are truly pandrug-resistant—ie, resistant to all classes of antimicrobial drugs, including polymyxins. Also, randomised trials are needed to compare the effectiveness and safety of polymyxin monotherapy with combinations of polymyxins and various antimicrobial drugs in well-defined populations and settings. Finally, the effectiveness and safety of polymyxins needs further investigation when administered via the respiratory tract for prevention and treatment of pneumonia caused by bacteria susceptible to this class of antimicrobial drugs.

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We declare that we have no conflict of interest.