Synergistic activity and effectiveness of a double-carbapenem regimen in pandrug-resistant *Klebsiella pneumoniae* bloodstream infections

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Sir,

Infections due to carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp) are associated with a high mortality rate.1,2 Therapeutic options are limited, especially when associated with colistin resistance.3 In this setting, a double-carbapenem regimen has been shown to be effective and safe.5,6

Herein, we evaluated through antibiotic kill studies the in vitro synergistic activity of meropenem plus ertapenem against pandrug-resistant CP-Kp isolated from three patients with bacteraemia who were successfully treated with double-carbapenem therapy.

For each patient, informed consent to participate in the study was obtained.

**Case 1**

An adult patient underwent aortic endoprosthesis placement. One year later, he developed periprosthetic infection that was treated with antimicrobial therapy and prosthesis replacement. During hospitalization, the patient had fever (39°C) and three blood cultures were positive for CP-Kp resistant to colistin (ertapenem, meropenem and colistin MICs of 128, 256 and ≥16 mg/L, respectively). Therapy with 3 g of fosfomycin every 6 h and 50 mg of tigecycline every 12 h was started without response. Therefore, 2 g of meropenem every 8 h plus 1 g of ertapenem every 24 h was given for 21 days with complete recovery.

**Case 2**

An adult patient underwent aorto-bisiliac graft placement. Four years later, the patient was hospitalized for revascularization of the left lower limb and after 2 days he developed fever (38.5°C). Three blood cultures were positive for CP-Kp resistant to colistin (ertapenem, meropenem and colistin MICs of 256, 256 and ≥16 mg/L, respectively). Meropenem (1 g) every 12 h (adjusted for creatinine clearance) plus 6 mg/kg daptomycin every 24 h was given without any clinical response. Subsequently, therapy was changed to 500 mg of ertapenem every 24 h and 1 g of meropenem every 12 h according to creatinine clearance. The patient became afebrile after 48 h of treatment and blood cultures were sterile. However, he died 2 days later due to acute heart failure.

**Case 3**

An adult patient was hospitalized because of arterial embolization due to renal haematoma. One day later, the patient had fever (39°C) and 4.5 g of piperacillin/tazobactam every 8 h was started with no clinical response. Blood cultures were positive for CP-Kp resistant to colistin (ertapenem, meropenem and colistin MICs of 256, 128 and ≥16 mg/L, respectively). Meropenem (1 g) every 8 h plus 50 mg of tigecycline every 12 h was given with partial response. Therapy was changed to 2 g of meropenem every 8 h plus 1 g of ertapenem every 24 h and administered for 24 days with complete recovery.

Phenotypic analyses showed that the three isolates were all KPC producers, in agreement with a previous report indicating that the circulating strain in our hospital is KPC-3.6,7 The activity of meropenem, alone and plus ertapenem, was investigated by time–kill studies using an initial inoculum of ~5 × 10^8 cfu/mL for all isolates. At 2, 4, 6, 8 and 24 h timepoints, the number of cfu was determined. Bactericidal activity was defined as >99.9% reduction of the initial bacterial count at each timepoint. Synergy was defined as a ≥100-fold decrease in cfu/mL between the combination and its most active constituent after 24 h.

The time–kill analysis showed that ertapenem or meropenem alone exhibited an initial reduction in log cfu/mL followed by a significant regrowth at 24 h in all the patients (Figure 1). When the double-carbapenem combination was assessed, a bactericidal and synergistic activity was achieved at 4, 6 and 8 h and maintained at 24 h at concentrations of meropenem 0.5× MIC plus ertapenem 1× MIC, meropenem 1× MIC plus ertapenem 1× MIC and meropenem 2× MIC plus ertapenem 1× MIC in all the patients (Figure 1).

In the setting of CP-Kp infections, the role of double-carbapenem regimens containing ertapenem has been recently reviewed.8,9 In fact, ertapenem, whose activity is greatly affected...
by carbapenemases, may act as a suicide substrate, thus leading the other carbapenem (meropenem or doripenem) to exert its antimicrobial activity.\textsuperscript{4,10}

To our knowledge, there are only two reports evaluating the clinical effectiveness of a double-carbapenem regimen. In the first case, a patient with ventilator-associated pneumonia due to CP-Kp was successfully cured with doripenem plus ertapenem and kill studies showed bactericidal activity of this combination.\textsuperscript{7} The other report concerning three patients successfully treated with a double-carbapenem regimen did not evaluate kill studies.\textsuperscript{5}

In our patients, ertapenem plus meropenem induced both clinical (defervescence in 48 h) and microbiological (absence of growth in blood cultures performed 48 h after therapy) responses. In the \textit{in vitro} studies, combination treatment exhibited higher bacterial killing than monotherapy, even in the presence of high carbapenem MICs. In all the isolates, the combination treatment maintained a bactericidal effect up to 24 h, thus confirming the clinical efficacy of this regimen.

In summary, this report suggests that meropenem plus ertapenem might be considered a promising option in CP-Kp infections, especially in patients for whom colistin treatment is inappropriate due to resistance or toxicity. A prospective evaluation of this therapeutic approach together with systematic \textit{in vitro} kill studies should be encouraged in order to better define the role of double-carbapenem regimens in the clinical practice.

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**Transparency declarations**

None to declare.

**References**


Association between fluoroquinolone resistance and resistance to other antimicrobial agents among *Escherichia coli* urinary isolates in the outpatient setting: a national cross-sectional study

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Sir,

Fluoroquinolones are among the most widely prescribed antibiotics.¹ Recent reports show that quinolones are prescribed in nearly half of all outpatient urinary tract infection (UTI) visits in the USA,² although current guidelines recommend against their use as first-line treatment for uncomplicated UTIs.³ As a result, the prevalence of quinolone-resistant pathogens, particularly Gram-negative bacteria, is on the rise globally.⁴ Horizontally transferable genes (*qnr*) borne by plasmids encode low-level quinolone resistance in *Escherichia coli*. Previous studies have found that plasmid-mediated resistance to low concentrations of ciprofloxacin increases the selection of higher ciprofloxacin resistance, by allowing the bacterial population to survive and grow to a level at which secondary mutations to higher resistance can occur.⁵ This low-level resistance, conferred by multiresistance plasmids, would not be detected by the usual breakpoints for susceptibility used in microbiology laboratories. By prescribing a quinolone to patients infected with these apparently susceptible isolates, physicians may inadvertently facilitate the selection of higher-level resistance. There are important clinical and public health implications. First, the treatment of infections caused by Gram-negative bacteria containing these resistance elements may be less effective than the treatment of infections caused by bacteria lacking these genes.⁶ Second, the biological linking of quinolone resistance with other resistance types that can be carried by plasmids means that over-prescribing of quinolones and other antibiotics is likely to further fuel the dissemination of multidrug-resistant bacteria, for which there are limited available treatment options.⁶

To inform the practice of evidence-based prescribing, we aimed in the present study to ascertain whether there was an association between fluoroquinolone resistance among urinary *E. coli* isolates and resistance to other antimicrobial agents. We conducted a cross-sectional analysis of antimicrobial surveillance data from a nationally representative network of microbiological laboratories (The Surveillance Network Database—USA) described in detail elsewhere.¹ The results of all routine susceptibility tests were reported based on CLSI criteria adopted by the facility at the time of testing. Aminoglycoside (gentamicin) susceptibility was chosen as a marker because resistance to it in *E. coli* is almost always plasmid mediated and plasmids containing *qnr* and other quinolone resistance genes (such as *qepA*) commonly contain genes for aminoglycoside resistance.⁷ Since clinicians may be more likely to prescribe a quinolone if an isolate is non-susceptible to other treatment options, we included only isolates that were also susceptible to at least trimethoprim/sulfamethoxazole, ampicillin or nitrofurantoin, which are commonly used for treatment of UTIs. Multivariable Poisson regression with robust error variances was used to estimate the relative risk (RR) of fluoroquinolone non-susceptibility.⁸ Statistical analyses were performed using Stata v.12.0, with *P* values <0.05 considered significant. The study was exempt from Institutional Review Board review at Harvard University.

The study included 16 515 066 outpatient urine *E. coli* isolates tested for fluoroquinolone (ciprofloxacin or levofloxacin) and aminoglycoside (gentamicin) susceptibility between 2000 and 2010 (Table S1, available as Supplementary data at JAC Online). The majority of isolates in the sample were from female patients (89.5%) and the mean age was 46 years. Fluoroquinolone and gentamicin resistance increased significantly over the sample period, from 3.2% in 2000 to 18.2% in 2010 (*P* < 0.001) and from 2.3% to 7.4% (*P* < 0.001), respectively. After controlling for age, sex, region and year, isolates that were non-susceptible to gentamicin were seven times more likely to be fluoroquinolone resistant than gentamicin-susceptible isolates (adjusted RR: 7.0; 95% CI: 6.5 – 7.5; *P* < 0.001) (Table 1) that were also susceptible to