EDITORIAL

Using carbapenems for carbapenem-resistant *Klebsiella pneumoniae*-Are we flogging a dead (work)horse antibiotic?

Russell E. Lewis

Department of Medical Sciences and Surgery, Infectious Diseases, U.O. Infectious Diseases, S. Orsola, Malpighi Hospital, University of Bologna, Bologna, Italy

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KPC-carbapenemase producing *Klebsiella pneumoniae* (KPC-Kp) have spread worldwide and are endemic in Southern Europe where more than one-third of isolates in Italy and two-thirds of isolates in Greece are resistant to carbapenems.1 The high mortality rate reported in patients with KPC-Kp bloodstream infection (25–70%) is attributed, in part, to the limited effectiveness of remaining treatments- colistin, tigecycline, gentamicin, or fosfomycin.2 These “last-line antibiotics” are prone to the rapid emergence of resistance when used as monotherapy, are often more toxic, or have significant pharmacokinetic limitations for treating KPC-Kp infections in the urine, bloodstream, or lung.3

To overcome these weaknesses, many physicians have adopted a strategy of treating KPC-Kp infections using a combination of these last-line antibiotics with high-dose, extended infusions of meropenem. The hope is that synergy between meropenem and these other antibiotics will achieve a bactericidal effect and overcome pharmacokinetic limitations of the single agents.3-5 Other investigators have proposed treating KPC-Kp with a dual carbapenem regimen, based on a hypothesis that a less-enzymatically stable carbapenem such as ertapenem can spare the hydrolysis of a second, more stable agent such as doripenem or meropenem.5,6

Although it seems counterintuitive, several case-control studies have in fact found that patients with KPC-Kp bloodstream infections are more likely to survive if they received a carbapenem as part of a combination treatment regimen.7,8,9,10 However, the benefits of including a carbapenem were only evident for strains with a meropenem MIC ≤ 8 mg/L.7,8 With many circulating KPC-Kp strains now harboring higher levels of carbapenem resistance and cross-resistance to colistin, tigecycline, and gentamicin, the question of which combination to use, and whether to continue including a carbapenem, is even less certain.

In this issue of Virulence, Del Bono and colleagues11 explored the pharmacokinetic/pharmacodynamic impact of including meropenem as part of a combination regimen for KPC-Kp bloodstream infection in 19 critically-ill patients. They first examined serum concentration profiles of meropenem in their patients to determine if any subject achieved the minimal carbapenem PK/PD dosing target (40% time above MIC). The answer was predictably “no” given the high MICs of the isolates recovered from patients (256–1024 mg/L). However, meropenem exposures would have been sufficient in nearly all of their patients at an MIC of 8 mg/L, and in more than half of their patients at a MIC of 16 mg/L.

Next, the authors used time kill-curve studies to explore whether the meropenem concentrations achieved in their patients would exhibit synergistic interactions with a single, clinically-relevant concentration of colistin, tigecycline, or gentamicin against the patient’s infecting isolate. In the end, they did not find any evidence of synergy with any antibiotic combination, even though some 2-drug combinations (colistin plus tigecycline, meropenem plus gentamicin) showed trends of greater colony forming unit reduction.

On the surface, it seems Del Bono and colleagues have made a strong case for the futility of continuing to use carbapenems for KPC-Kp strains with high meropenem MICs. Nevertheless, several factors may have limited their ability to detect synergy with meropenem. First, only single concentration (ratio) of each drug was tested in the time-kill studies. Therefore, the authors could not assess how the dose-effect curve of each antibiotic was changed when...
tested in combination—an important requirement for pharmacodynamic analysis of combination therapy.\(^{12,13}\) Put another way; we do not know if the results from testing a single concentration by time-kill studies are representative of the interactions that occur across the entire range of the dose-response curve in vitro or in vivo. A second limitation acknowledged by the investigators is that they did not measure tigecycline, colistin or serum gentamicin concentrations in their patients. We are unsure if the concentrations tested in vitro were really representative of exposures in vivo. Finally, the high rates of colistin resistance (68%) in their isolates raises questions of whether synergy would be more prevalent at lower colistin resistance rates.

Finally, while the analysis if Del Bono and colleagues provide a clear picture of possible PK/PD target attainment for a single antibiotic, understanding the probability of PK/PD target attainment for a combination of antibiotics will require much more complex semi-mechanistic PK/PD models. Ideally, these models would consider MIC distributions, population pharmacokinetics in critically ill patients, and robust data on pharmacodynamic interactions drawn from in vivo studies.

Despite these limitations, Del Bono and colleagues’ work provides useful insight into the limits of meropenem treatment for KPC-Kp infection. A looming question is whether meropenem could still have clinically-useful synergy with newer antibiotics that inhibit carbapenemases (cefazidime-avibactam) or other new drugs on the horizon (ceftaroline-avibactam, plazomicin, eravacycline, meropenem-vaborbactam). The authors’ work also highlights the critical need for better scientific guidance and application of PK/PD principles in the treatment of multidrug resistant Gram negative pathogens with combination therapy. Without better knowledge of how combination therapy optimally works, we risk shortening the lifespan of not only current, but also future workhorse antibiotics against Enterobacteriaceae.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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