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# Double-Carbapenem Therapy Not Proven To Be More Active than Carbapenem Monotherapy against KPC-Positive *Klebsiella pneumoniae*

Hopes of a new option for therapy of KPC-associated infections may have been raised by the report of Bulik and Nicolau that double-carbapenem therapy comprising ertapenem and doripenem can be more active than either drug alone (3). While not discounting the possibility that carbapenem combinations may confer therapeutic advantages, there is an experimental concern that raises doubt about this report.

Two studies were described, an *in vitro* chemostat model and an *in vivo* immunocompetent murine thigh infection model, both utilizing a single KPC-3-positive *Klebsiella pneumoniae* isolate. In the chemostat model, doripenem and ertapenem, alone and in combination, rapidly reduced bacterial counts, with regrowth being delayed in the presence of the combination. In the murine thigh infection model, doripenem plus ertapenem "achieved a statistically significant reduction in bacterial density" compared to doripenem alone. Taken together, the data were concluded to indicate that the carbapenem combination had enhanced efficacy compared to that of carbapenem monotherapy.

The experimental flaw was that the mice were dosed with doripenem an hour after receiving a dose of ertapenem. This was designed "to maximize ertapenem's hypothesized use as a suicide substrate, and in turn maximizing the high affinity of carbapenemase for this agent." Since ertapenem alone was shown to be rapidly bactericidal in the chemostat experiment, with counts decreasing approximately two logs in 1 h, it is likely that when the mice on combination therapy were given doripenem an hour after receiving ertapenem, the inoculum had been substantially reduced. It is well known that carbapenem activity against KPC producers is markedly enhanced by a reduction in inoculum density (2). Therefore, it is unsurprising that doripenem was more active when given an hour after the inoculum had been reduced to a lower level by ertapenem.

In short, an alternative explanation for the greater *in vivo* killing by the combination is that there was an initial reduction in inoculum density due to pretreatment with ertapenem rather than the effect being due to a suicide substrate effect of ertapenem. Confirmation of a therapeutic advantage based on a suicide substrate effect due to carbapenemase affinity for ertapenem remains elusive, both in the reported experiments and also in the reference to which this effect was purportedly attributed (1).

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## REFERENCES

1. **Anderson KF, et al.** 2007. Evaluation of methods to identify the *Klebsiella pneumoniae* carbapenemase in *Enterobacteriaceae*. J. Clin. Microbiol. **45**: 2723–2725.
2. **Bratu S, et al.** 2005. Emergence of KPC-possessing *Klebsiella pneumoniae* in Brooklyn, New York: epidemiology and recommendations for detection. Antimicrob. Agents Chemother. **49**:3018–3020.
3. **Bulik CC, Nicolau DP.** 2011. Double-carbapenem therapy for carbapenemase-producing *Klebsiella pneumoniae*. Antimicrob. Agents Chemother. **55**:3002–3004.

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