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P2790 Activity of imipenem and ertapenem alone or in combination *in vitro* and in a murine model of peritonitis due to KPC-3, OXA-48 and NDM-1-producing *Escherichia coli*

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Background: Benefit from using carbapenems against carbapenemase-producing Enterobacteriaceae (CPE) is questioned. *In vitro* synergy has been shown for double-carbapenem therapies on CPE, including KPC and OXA-48 producers, but no experimental in vivo data exists. Our objective was to evaluate the activity of imipenem and ertapenem, alone or combined, *in vitro* and in a fatal murine peritonitis model, against isogenic CPE *Escherichia coli* strains, including KPC, OXA48 and NDM-1 producers.

Materials/methods: Isogenic derivatives of wild-type *E. coli* CFT073 producing KPC-3, OXA-48 and NDM-1 carbapenemases were constructed. Checkerboard dilution method and time-kill curves were used to explore *in vitro* interaction between imipenem and ertapenem. Mice with intra-abdominal infection were treated subcutaneously for 24h with imipenem 100mg/kg every 2 h, ertapenem 100mg/kg every 6 h, or both, reproducing the duration of time that the free serum concentration of these antibiotics exceeded the MIC (*f*T>MIC) in humans with standard regimens. Survival, bacterial counts in peritoneal fluid (PF), and sterilization rates were assessed at 24h.

Results: Checkerboard assays and time-kill curves did not show consistent synergy between imipenem and ertapenem against any strain. *In vivo*, combination therapy did not show any benefit compared to monotherapy, in terms of survival, reduction of bacterial counts, or sterilization rates. However, IMP and ERT alone were unexpectedly highly effective against all strains as they prevented mortality and significantly reduced bacterial counts at 24 h ($P<0.005$). Ertapenem activity could not be explained by *f*T>MIC that was equal to zero against KPC-3 and NDM-1 producing strains, suggesting protein binding may not be a limiting factor for ERT activity.

Conclusions: Lack of *in vivo* synergism between ertapenem and imipenem against CPE was due to paradoxical activity of carbapenems alone, even on NDM1 producers with very high carbapenem MIC, which are not explained by *f* T>MIC. These results are consistent with descriptions of clinical benefit from carbapenems against CPE.