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P0262 Imipenem kills Pseudomonas aeruginosa (PA) substantially faster than meropenem and doripenem most likely due to more rapid outer-membrane (OM) penetration

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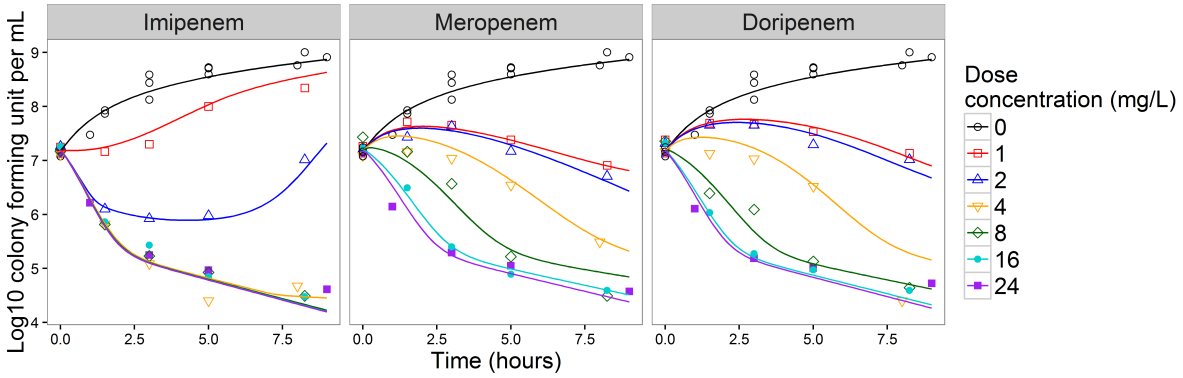
Background: Rapid initial bacterial killing may be life-saving in severe infections which are commonly caused by PA in immune-compromised patients. Carbapenems can kill PA rapidly at low and high (>10^7 CFU/mL) bacterial densities and very few studies showed that carbapenems penetrated the OM of PA more rapidly than other beta-lactams. We aimed to compare the rate of initial killing of PA by imipenem, meropenem and doripenem and estimate the rate of OM penetration via mechanism-based PK/PD models (MBM). These three carbapenems are known to have very similar IC50s for PBPs 1a, 1b, 2, 3 and 4 in PA.

Materials/methods: *In vitro* static concentration time-kill studies over 8 h used a growth control and six carbapenem concentrations between 1 and 24 mg/L all in duplicate against wild-type PAO1 PA (inoculum: $10^{7.2}$ CFU/mL). Viable counts, carbapenem concentrations (via LC-MS/MS) and AmpC beta-lactamase activity were determined over time for each carbapenem. MBM were developed in the S-ADAPT software.

Results: Imipenem at 2, 4 and 8 mg/L killed PA substantially faster during the first 5 hours than doripenem and meropenem (Figure). At 16 mg/L, all three carbapenems achieved near identical maximum rates of killing. Imipenem up-regulated AmpC beta-lactamase more extensively than doripenem and meropenem; this caused considerable degradation of imipenem at 1, 2 and 4 mg/L starting at 2 to 4 h; degradation was minimal for meropenem and doripenem. The new MBM provided excellent population fits for all three carbapenems (Figure).



Conclusions: Imipenem achieved much faster initial killing of PA than doripenem and meropenem at low to intermediate, clinically relevant concentrations despite near-identical PBP IC50s among these carbapenems. Imipenem also up-regulated AmpC beta-lactamase fastest. This strongly suggested

that imipenem penetrated the OM more rapidly than doripenem and meropenem in PA (to be confirmed by penetration assays). Animal infection model studies are warranted to show the benefit of rapid initial killing by imipenem on mortality of severe infections.