P. aeruginosa, where neither CI nor SI of ceftazidime had an impact on resistance development regardless of the dosing regimen.[38] With doripenem, $fT > 6.2$ times the MIC has been found to be correlated with suppression of resistance in *P. aeruginosa* HFIM experiments, and achievement of this target was maximized with EI.[18] This finding might indirectly support the use of PI as these administration modes increase the time above this threshold compared to SI, assuming the same daily dose is used. However, another study identified different PK/PD targets for SI and CI regimens in *P. aeruginosa* HFIM experiments to suppress the emergence of resistance – C_{min}/MIC of 3.4 with SI and C_{min}/MIC of 10.4 with CI,[28] suggesting different targets may exist. Finally, cefepime showed similar antibacterial effects during the first 12 h of experiments mimicking cefepime 1 g every 12 h SI versus 1 g bolus dose followed by 2 g daily as a CI.[35] Regrowth was observed during experiments with SI but not with CI, which may be partly the result of a higher total dose during the first 24 h of experiments. No resistance development was observed in the study.

Very few preclinical studies investigated the emergence of resistance with β-lactam infusions in combination with other agents. PK profiles representing augmented renal clearance (creatinine clearance [CrCl] 250 mL/min) were simulated in an HFIM for meropenem (1–2 g every 8 h over 30 min or 3–6 g daily CI) and tobramycin (7 mg/kg every 24 h over 30 min) over a 7-day total duration of therapy. Two carbapenem-resistant *P. aeruginosa* isolates were studied with an initial inoculum of ~10^7 CFU/mL and MICs 8 mg/L and 32 mg/L. The only regimen that suppressed the regrowth of resistant subpopulation was meropenem 6 g/day CI with tobramycin in the isolates with MIC 8 mg/L. In the less susceptible population (MIC 32 mg/L), no regimen suppressed the growth of resistant bacterial population.[43] A similar study investigated imipenem–tobramycin combination against *A. baumannii* (MICs 0.25, 4, and 32 mg/L) and initial inoculum of ~10^7 CFU/mL. The investigators combined the mechanism-based combination PD model with the published PK models of tobramycin and imipenem in critically ill patients, and simulated imipenem (1 g every 6–8 h over 1 h and 1 g loading dose followed by 3–4 g/day CI) and tobramycin (5–7 mg/kg every 24 h over 30 min) regimens. The regimen with the highest probability of success for eradication of *A. baumannii*-resistant isolates (MIC 32 mg/L) was imipenem 4 g/day CI plus tobramycin 7 mg/kg/day.[44] The PD of meropenem and polymyxin B combination against *A. baumannii* (MIC 16 mg/L and initial inoculum 10^8 CFU/mL) has been evaluated. The comparative approach identified a preference for meropenem regimens which improve the $fT_{>MIC}$ by prolonging the infusion time or shortening the dosing interval. The best-simulated regimen was meropenem 19.6 g/day as a 2-h infusion every 5 h plus polymyxin B 5.17 mg/kg/day every 6 h to eradicate *A. baumannii* from initial inoculum of 10^8 CFU/mL to zero.[45]

3.3.3 | Future research needs

Additional preclinical studies are needed to better understand if differences exist between SI and PI schemes. Greater diversity of bacterial species and baseline resistance profiles encompassing a heterogeneity of phenotypic and genotypic differences are needed. Starting inocula should mimic bacterial loads from the intended infection types.

3.4 | Background question IV

Is there a role for TDM of PI β-lactams?

3.4.1 | Background consensus statement 4

We suggest that β-lactam TDM and personalized dosing may be considered on a patient-by-patient, indication-by-indication, drug-by-drug basis until further evidence is available. We cannot recommend for or against routine TDM for PI β-lactams at this time. (Consensus recommendation).

3.4.2 | Evidence summary

Three randomized controlled studies have evaluated the impact of β-lactam TDM on PK/PD exposure and clinical outcomes (Table S4).[46-48] Adverse effects and resistance development were not reported in any of these studies. A single-center, open-label RCT in critically ill adults ($n = 41$) who received meropenem or piperacillin–tazobactam by EI were randomized to daily TDM or standard of care.[46] The primary outcome was the proportion of patients achieving the PK/PD target of 100% $fT > 4$ times the MIC at 72 h. At baseline, only 21% of patients receiving piperacillin–tazobactam and 0% of those receiving meropenem reached this exposure threshold. At 72 h, 58% and 16% of patients in the TDM and standard-of-care groups, respectively, achieved 100% $fT > 4$ times the MIC ($p = 0.007$). There was no difference between groups in mortality, treatment failure, or bacterial persistence.

A second single-center, open-label RCT enrolled patients with febrile neutropenia receiving piperacillin–tazobactam and randomized them to TDM or standard of care.[48] All patients ($n = 32$) initially received piperacillin–tazobactam by SI; EIs could be used as a strategy to increase exposure in those randomized to TDM. The primary outcome was the proportion of patients achieving the PK/PD target of 100% $fT_{>MIC}$ on day 3. Overall, only 22% of patients reached the target at baseline. On day 3, 69% of patients in the TDM group compared with 19% of those in the standard-of-care group achieved 100% $fT_{>MIC}$ ($p = 0.012$). There was no difference in the duration of fever or time to recovery from neutropenia.

The third single-center, open-label RCT focused on critically ill burn patients ($n = 38$).[47] Patients were allocated to groups where they received alternate β-lactams; all were administered by SI during the first 3 years of the study and by EI during the final 2 years. PK/PD targets varied by the agent but, in general, were close to 100% $fT_{>MIC}$. Less than 60% of patients reached the targets at baseline. There was no difference between groups in the primary outcome of time