Piperacillin-Tazobactam Extended Infusion Education

The efficacy of antibiotics can be predicted by pharmacokinetic-pharmacodynamic (PK-PD) parameters such as:

- **T>MIC**: the amount of time (T) serum concentration exceeds the minimum inhibitory concentrations (MIC) of an antibiotic against a strain of bacteria during a dosing interval. Antibiotics such as β-lactams (penicillins, cephalosporins, carbapenems) fall into this category.
- **C_{max}/MIC**: the ratio of maximum serum concentration (C_{max}) of an antibiotic to MIC. Efficacy of aminoglycosides can be predicted based on this ratio.
- **AUC/MIC**: the ratio of area under the concentration-time curve (AUC) to MIC. Efficacy of vancomycin, fluoroquinolones, and macrolides can be predicted based on this ratio.

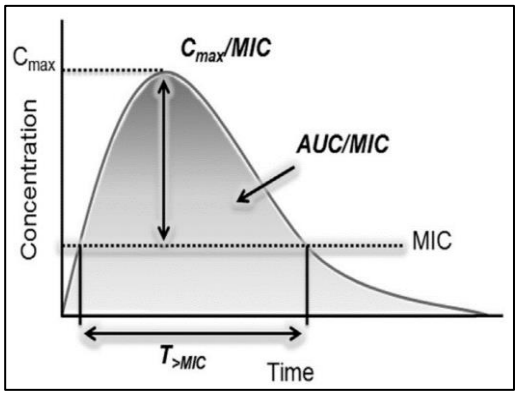

Figure 1. PK-PD parameters for prediction of antibiotic efficacy[1]

Table 1. Representative PK-PD category, target values that predict efficacy for selected antibiotic-pathogen combinations[1-3]

PK-PD Parameter Predictor	Antibiotic-Pathogen Combination	Target Value
T>MIC	Penicillins--Gram positive organisms	30 – 40%
	Penicillins--Gram negative organisms	50 – 60%
	Cephalosporins—Gram positive organisms	40 – 50%
	Cephalosporins—Gram negative organisms	60 – 70%
	Carbapenems—Gram positive organisms	20 – 30%
	Carbapenems—Gram negative organisms	40 – 50%
C_{max}/MIC	Aminoglycosides—Gram negative organisms	≥10
AUC/MIC	Vancomycin—*Staphylococcus aureus* (in pneumonia)	≥400
	Ciprofloxacin—Gram negative organisms (in pneumonia)	≥125
	Levofloxacin—Gram negative organisms (in pneumonia)	≥87

Traditionally, β-lactams, including piperacillin-tazobactam, are administered using short infusions over 30 to 60 minutes. With better understanding of antibiotic PK-PD, β-lactams are being administered over longer duration of 3-4 hours. The rationale of this practice is to maximize T>MIC, allowing a given dosing regimen to target pathogen with higher MIC. Figure 2 illustrates an example in which both short and extended infusions of a penicillin was able to reach the T>MIC target of 50-60% for Gram negative bacilli (GNB) 2. However, with a higher MIC, only the extended infusion regimen was able to reach that target for GNB 1.

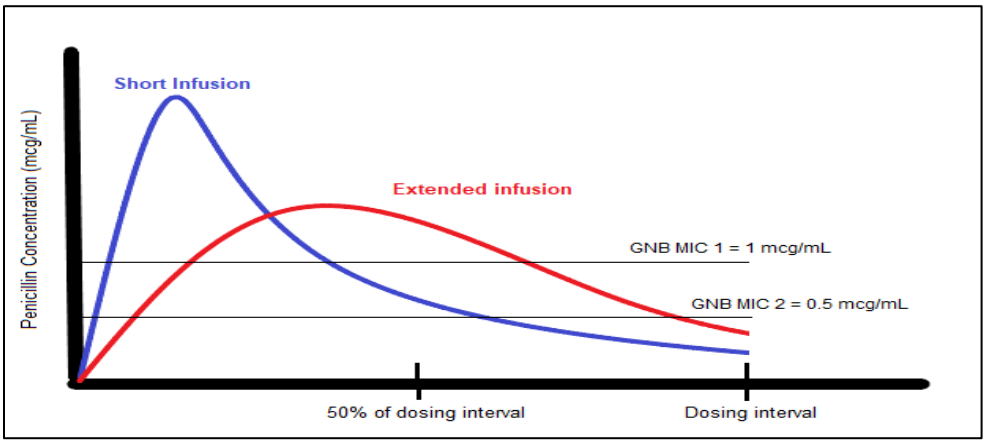

Figure 2. Differences in serum concentration relative to MIC with short and extended antibiotic infusions

Monte Carlo simulation, a predictive analytical technique, has been used to predict the efficacy of antibiotic regimens with different doses, frequencies and administration times against pathogens with different MICs. In one particular study, Lodise, *et al*. predicted that a dosing regimen of piperacillin-tazobactam 3.375g q8h infused over 4 hours has a higher probability of reaching the T>MIC target of 50% against *Pseudomonas aeruginosa* isolates with MIC of 16 mcg/mL (the current susceptibility breakpoint) compared to a regimen of 3.375g q6h infused over 0.5 hour (0% vs. ~90%).[4]

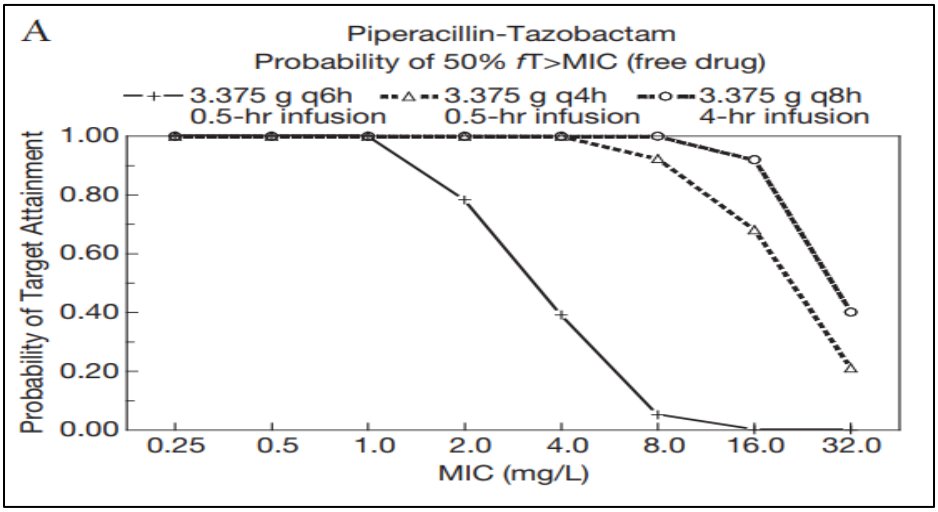

Figure 3. Probability of reaching the target of T>MIC 50% (or target attainment) using different piperacillin-tazobactam regimens against *P aeruginosa* with different MIC.

A retrospective cohort study comparing the clinical outcomes of patients with *P aeruginosa* infections treated with short (0.5-hour) or extended (4-hour) infusions of piperacillin-tazobactam found improved outcomes with the latter administration strategy.[5] For patients with APACHE score ≥17, lower 14-day mortality (12.2% vs. 31.6%, *p*=0.04) and shorter median length of stay (21 vs. 38 days, *p*=0.02) were associated with the extended infusion regimen. These clinical outcomes, however, were similar between different infusion regimens for patients with APACHE score <17. A meta-analysis that included 6 studies also found lower mortality risk with extended infusion of piperacillin-tazobactam compared to the short infusion (risk ratio 0.55, 95% CI 0.34-0.89) strategy.[6]

Taken together, these data suggest that the use of extended infusion of piperacillin-tazobactam is associated with shorter hospital stay and/or lower mortality.

Extended Infusion Piperacillin-Tazobactam Dosing Regimen for Adults

Creatinine Clearance (mL/min)	Dosing Regimen*
≥20	4.5g IV q8h infused over 4 hours
<20, HD, or CAPD	4.5g IV q12h infused over 4 hours

Abbreviations: HD = hemodialysis; CAPD = continuous ambulatory peritoneal dialysis

* A loading dose of 4.5g infused over 30 minutes can be given

References

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4. Lodise TP, Lomaestro BM, Drusano GL. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on β-lactam antibiotics. Pharmacotherapy 2006;26:1320-32.
5. Lodise TP, Lomaestro, Drusano. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. Clin Infection Dis 2007;44:357-63.
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