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DOSE-EXPOSURE SIMULATION FOR PIPERACILLIN-TAZOBACTAM DOSING STRATEGIES IN INFANTS AND YOUNG CHILDREN

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Abstract

Background:

Extended piperacillin-tazobactam (TZP) infusions have been associated with favourable outcomes. There are currently no pediatric dosing recommendations.

Objective:

To determine appropriate TZP dosing strategies in children 2 months – 6 years according to age and different minimal inhibitory concentrations (MICs).

Methods:

Age and weight were simulated for 1000 children. *Post-hoc* pharmacokinetic parameter estimates were generated using published clearance and volume of distribution data. For different dosing regimens, we estimated the probability of target attainment (PTA) over a range of MICs from 4 to 128 mg/L. The pharmacodynamic (PD) target was defined as free piperacillin concentrations above the MIC for $\geq 50\%$ of the dosing interval. A PTA $\geq 90\%$ was defined as optimal.

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Results:

PTA decreased as MIC and age increased. In all age groups, standard dosing regimens (240-300 mg/kg/day, 0.5h infusions) failed to reach PTAs $\geq 90\%$ at MICs ≥ 16 mg/L. Standard 0.5h infusions reached PTAs $\geq 90\%$ at MICs up to 8 mg/L in infants > 2 to 6m. No 0.5h infusion reached PTAs $\geq 90\%$ for MICs ≥ 4 mg/L in children > 6m. While none of the tested regimens were optimal at MICs > 16 mg/L in children > 6m, 100 mg/kg/dose every 6h as a 3h infusion reached PD target at MICs of 32 mg/L in infants > 2 to 6m.

Conclusion:

Up to MICs of 16 mg/L, 90 mg/kg/dose every 8h as a 2h infusion in infants > 2 to 6m and 100 mg/kg/dose every 8h as a 4h infusion in children > 6m–6y achieved PTAs $\geq 90\%$.

Key Words: *modeling and simulation; pharmacokinetics; pharmacodynamics; piperacillin-tazobactam; children*

Sepsis is one of the leading causes of morbidity and mortality in children,^{1,2} with a mortality rate ranging from 4 to 14% in children from the industrialized world.²⁻⁴ In the United States, with a population-based incidence of 0.89 per 1000 children, sepsis imposes a substantial burden on healthcare costs with national estimates of \$4.8 billion annually.¹ Treatment largely depends on prompt administration of an effective antimicrobial therapy.⁵

Given its wide antimicrobial spectrum, piperacillin-tazobactam (TZP) is commonly used in children as an empiric treatment for serious infections in settings where resistance to common first-line antimicrobials has emerged.^{6,7} The most common indications for TZP in pediatrics include hospital-acquired infections, pulmonary exacerbations in children with cystic fibrosis, intra-abdominal infections, and fever with neutropenia. Similar to other beta-lactams, TZP exerts bactericidal activity in a time-dependent manner. The amount of time that free drug concentration remains above the minimum inhibitory concentration ($fT > MIC$) is the surrogate pharmacodynamic (PD) parameter that best correlates with its efficacy.^{8,9} Attainment of the PD target becomes more challenging as antimicrobial susceptibility decreases, resulting in higher MICs.^{10,11} Consequently, there is a need to find alternative therapeutic strategies in infants and children at risk of more resistant pathogens, especially with the lack of novel antibiotics approved for pediatric use. One of the proposed alternative strategies includes prolonging TZP infusion.^{12,13} In adults, TZP extended infusion increases PD target attainment

rate,^{12,14-16} and has been inconsistently associated with improved clinical outcome.¹⁶⁻²³ Extended TZP infusions studies in children are limited and mostly include dose-exposure simulations based on pharmacokinetic (PK) models developed in clinical trials with short infusions.²⁴⁻²⁷ In one recent PK study a TZP PK model was developed in 12 critically ill children who received 4-hour infusions of TZP every 8 hours.²⁸ Monte Carlo simulations based on this PK model suggest improvement of PD target attainment with longer TZP infusion times for susceptible bacteria with MICs ≥ 16 mg/L. However, due to limited data regarding the use of prolonged infusions of TZP in children, there are currently no precise pediatric dosing recommendations taking age and MIC into account. Our study aimed to determine an alternative TZP dosing strategy in infants and children > 2 months-6 years according to increasing MICs. This represents a preliminary step for a prospective population PK study aimed to determine optimal dosing regimens.

METHODS**Study Design**

A virtual pediatric population was created by simulating weight and age distributions by sex. Simulations were based on hypothetical pediatric populations generated using the distribution of body weight reported in the WHO growth charts²⁹ and generalized additive models for location scale and shape (GAMLSS). Two age groups were defined (> 2–6m, > 6m–6y).

TABLE 1 Published Piperacillin Pharmacokinetic Parameters in Infants and Children Aged 2 Months to 6 Years.

| | 2 to 5 months (Mean (\pm SD)) N=12 | 6 months to 5 years (Mean (\pm SD)) N=24 |
|-------------|---|---|
| CL (L/h/kg) | 0.20 (0.05) | 0.31 (0.1) |
| V (L/kg) | 0.37 (0.1) | 0.36 (0.1) |

Adapted from Reed et al.³⁰

Pharmacokinetic Simulation Analysis

PK parameters were estimated for each virtual child based on published clearance (CL) and volume of distribution (V) data, with a set inter-individual variability of 50% for both CL and V (30) (Table 1). Data used for the > 6m–6y age group were calculated by combining published data in infants 6–23m and 2–5y, because there was no significant difference in CL and V between those 2 age groups.³⁰ Piperacillin concentrations were analyzed by applying a one-compartment model using non-linear mixed effect (Phoenix-NLME® and Trial Simulator®).²⁶ Based on

individual CL and V, steady-state plasma piperacillin concentrations were then predicted every 15 minutes over the dosing interval, for 30 simulated TZP dosing regimens ranging from 240 to 400 mg/kg/day given every 4 to 8 hours as 0.5, 2, 3, and 4 hour infusions (i.e., half of the dosing interval) (Table 2). A maximum daily dose of 400 mg/kg/day was used based on the recommended standard dosing range.³¹

Given that TZP dosing recommendations are based on the piperacillin component, we defined our surrogate PD efficacy target as $fT > MIC \geq 50\%$ of the dosing interval, for the steady-state free piperacillin concentration.^{9,32} Additionally, we also used $fT > MIC = 100\%$ of the dosing interval as a secondary PD target. Free piperacillin concentration was calculated as 70% of total predicted concentration.³³ $fT > MIC$ was estimated over a range of MICs from 4 to 128 mg/L. An a priori probability of target attainment (PTA) of 90% was considered optimal. The suggested regimens were selected according to their capacity to reach PTAs $\geq 90\%$ for susceptible bacteria (i.e., strains with piperacillin MICs ≤ 16 mg/L)³⁴ using minimal doses and infusion time.

Our study population included 1000 virtual infants and children (Table 3). For each age group,

TABLE 2 Simulated Piperacillin-Tazobactam Dosing Regimens

| Dosing (mg/kg/dose) | Daily dosing (mg/kg/day) | Dosing Interval (hours) | Duration of Infusion (hours) |
|---------------------|--------------------------|-------------------------|------------------------------|
| 80 | 240 | 8 | 0.5, 2, 3, 4 |
| 90 | 270 | 8 | 0.5, 2, 3, 4 |
| 50 | 300 | 4 | 0.5, 2 |
| 75 | 300 | 6 | 0.5, 2, 3 |
| 100 | 300 | 8 | 0.5, 2, 3, 4 |
| 80 | 320 | 6 | 0.5, 2, 3 |
| 90 | 360 | 6 | 0.5, 2, 3 |
| 130 | 390 | 8 | 0.5, 2, 3, 4 |
| 100 | 400 | 6 | 0.5, 2, 3 |

TABLE 3 Baseline Characteristics of Simulated Cohorts*

| | > 2 to 6 months (N=300) | > 6 months to 6 years (N=750) | Total (N=1000) |
|-------------|----------------------------|----------------------------------|-----------------------|
| Age (y) | 0.36 (0.17–0.50) | 3.81 (0.51–6.98) | 2.73 (0.17–6.98) |
| Weight (kg) | 5.64 (3.52–9.83) | 17.31 (5.15–60.43) | 14.47 (3.52–60.43) |

*Data are median (range)

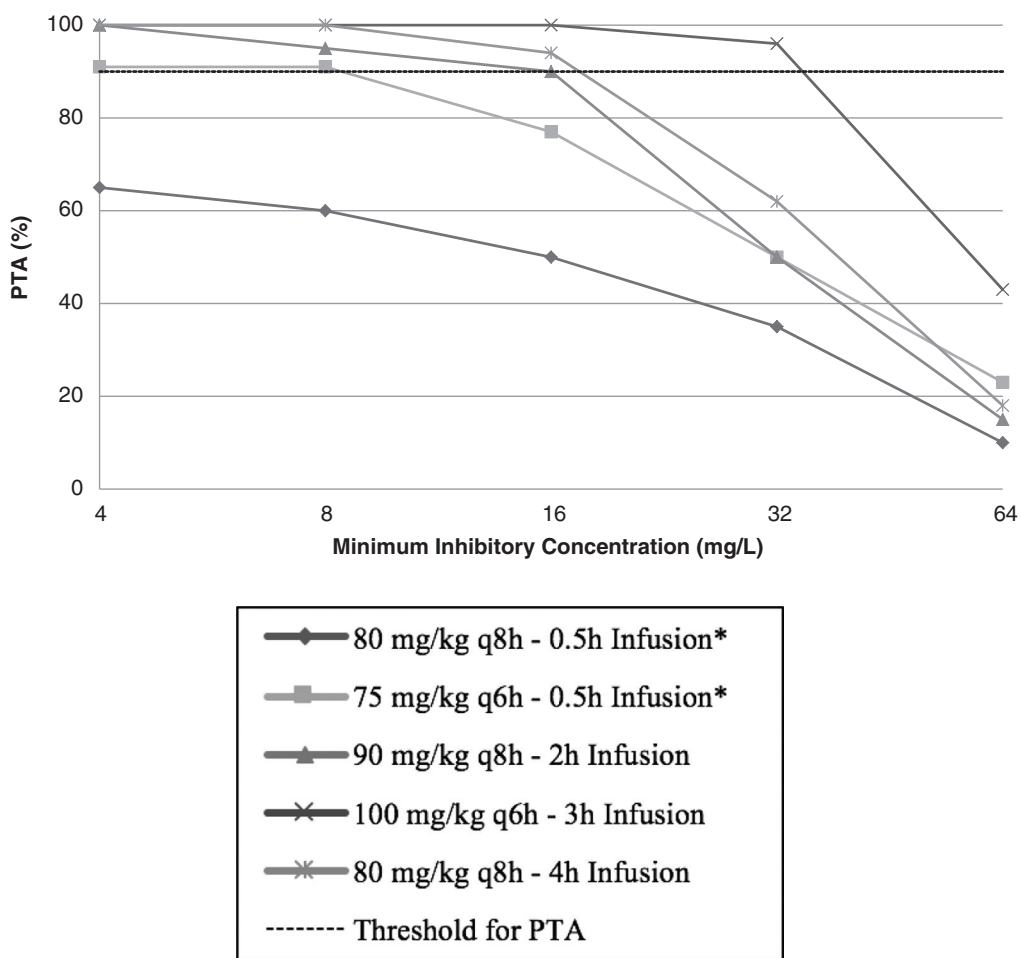


FIG. 1 PTA¹ by MIC² for free piperacillin concentrations $\geq 50\%$ of the dosing interval in infants > 2–6 months.

¹PTA: Probability of Target Attainment

²MIC: Minimum Inhibitory Concentration

*Standard recommended regimens

TABLE 4 Recommended Dosing Regimens

| Reference | Age Group | Daily Dose (mg/kg/day) | Time Interval Between Doses (hours) |
|--|--------------|------------------------|-------------------------------------|
| Pediatric and Neonatal Dosage Handbook (28) Red Book (33) | 2-< 9 months | 240 | 8 |
| | ≥ 9 months | 300 | 8 |
| Sanford (32) | > 28 days | 300 | 6 |

Data from: Taketomo et al.³¹, Gilbert et al.³⁵, and American Academy of Pediatrics.³⁶

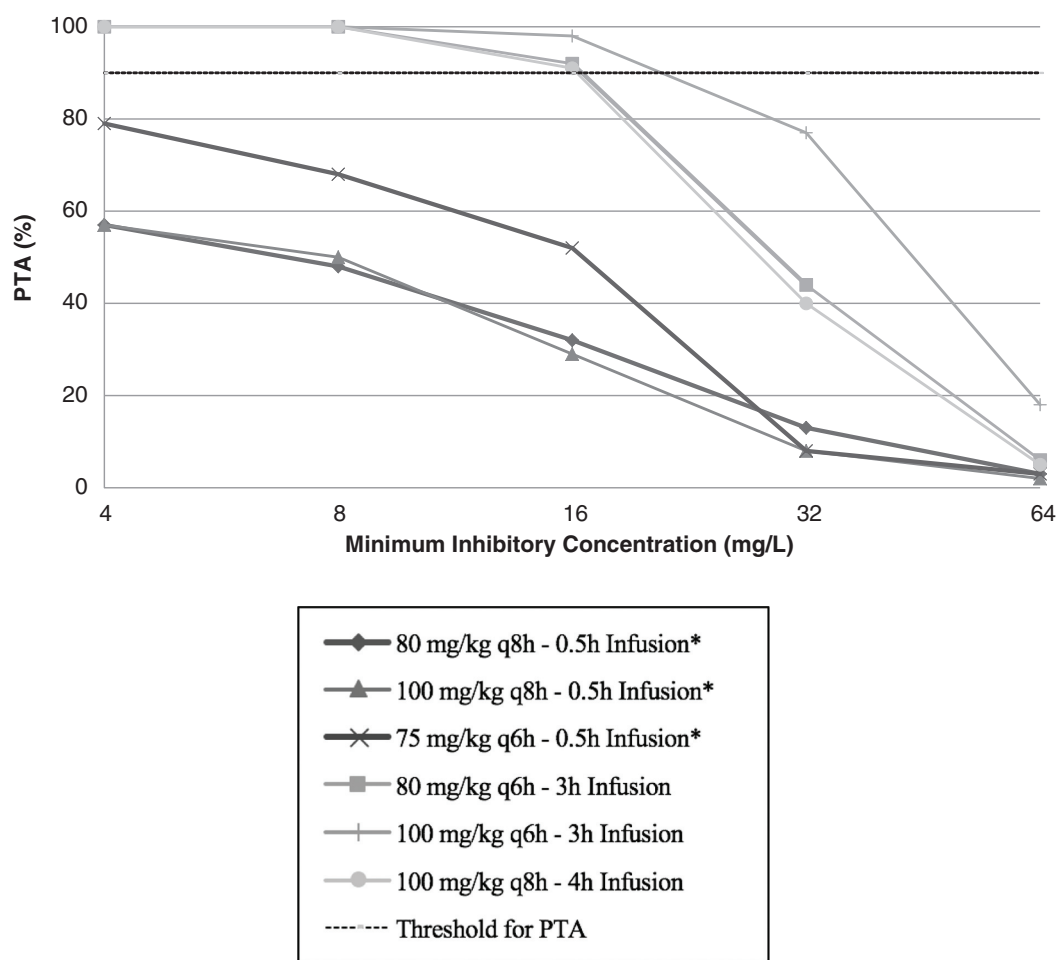


FIG. 2 PTA¹ by MIC² for free piperacillin concentrations ≥ 50% of the dosing interval in children > 6 months–6 years.

¹PTA: Probability of Target Attainment

²MIC: Minimum Inhibitory Concentration

*Standard recommended regimens

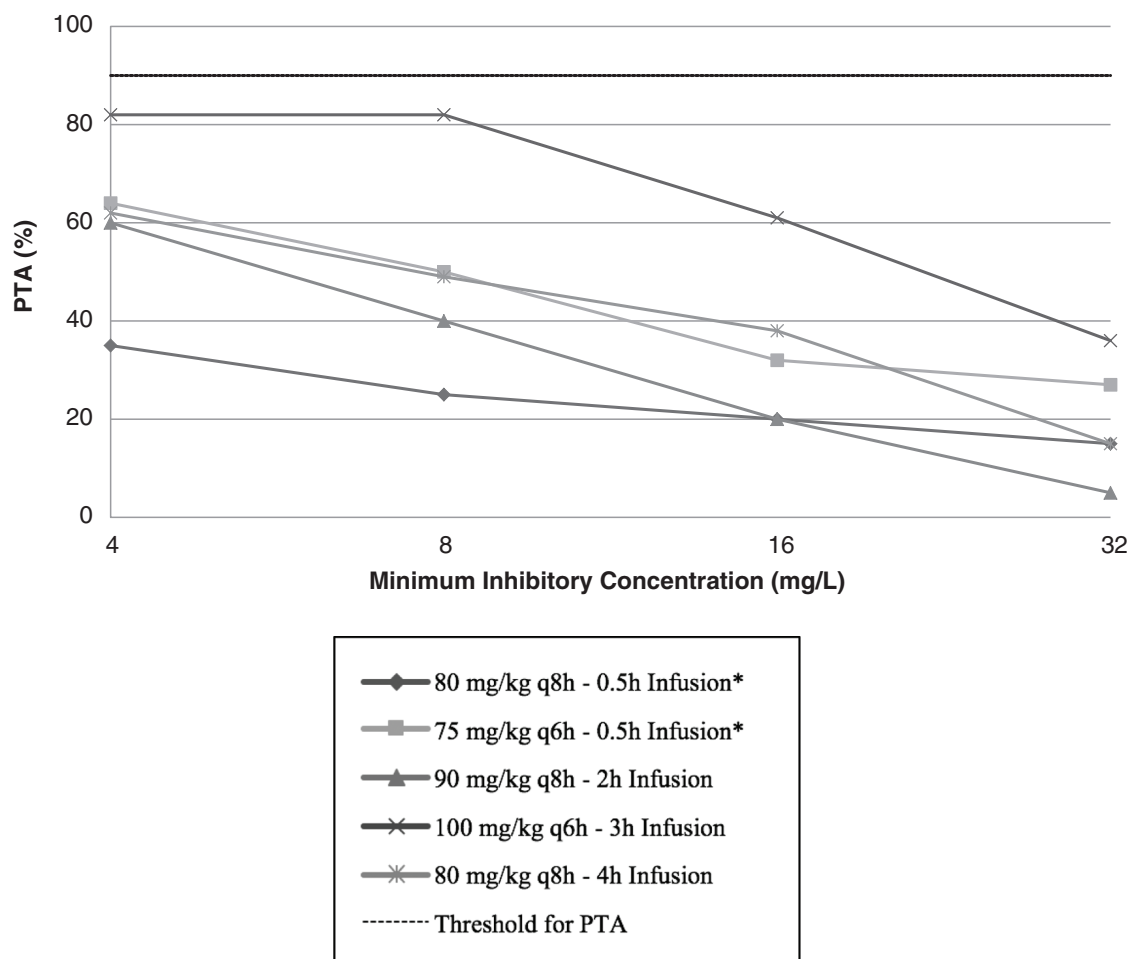


FIG. 3 PTA¹ by MIC² for free piperacillin concentrations = 100% of the dosing interval in infants > 2–6 months.

¹PTA: Probability of Target Attainment

²MIC: Minimum Inhibitory Concentration

*Standard recommended regimens

Figures 1–4 illustrate PTAs of currently recommended dosing regimens (Table 4) and the minimum daily dosing and infusion time achieving optimal PTAs at MICs of 16 mg/L for every tested dosing interval (every 4, 6, and 8 hours) using $fT > MIC \geq 50\%$ and $fT > MIC = 100\%$ of the dosing interval, respectively. Overall, PTA decreased as MIC and age increased, and none of the tested dosing regimen did achieve the $fT > MIC = 100\%$ target.

In infants >2 to 6 months, standard 0.5h infusions reached optimal PTAs up to MICs of 8 mg/L (90mg/

kg/dose every 6 hours and every 8 hours; 75 mg/kg/dose every 6 hours, and 130 mg/kg/dose every 8 hours). More specifically, the recommended dosing regimen of 75 mg/kg/dose every 6 hours infused over 0.5 hours (300 mg/kg/day)³⁵ had PTAs of 91%, 91% and 77% against bacteria with MICs of 4, 8, and 16 mg/L, respectively. The alternate recommended dose of 80 mg/kg/dose every 8 hours infused over 0.5 hours (240 mg/kg/day)^{31,36} had PTAs of 65%, 60% and 50% against bacteria with MICs of 4, 8 and 16 mg/L, respectively. For the same daily dose of

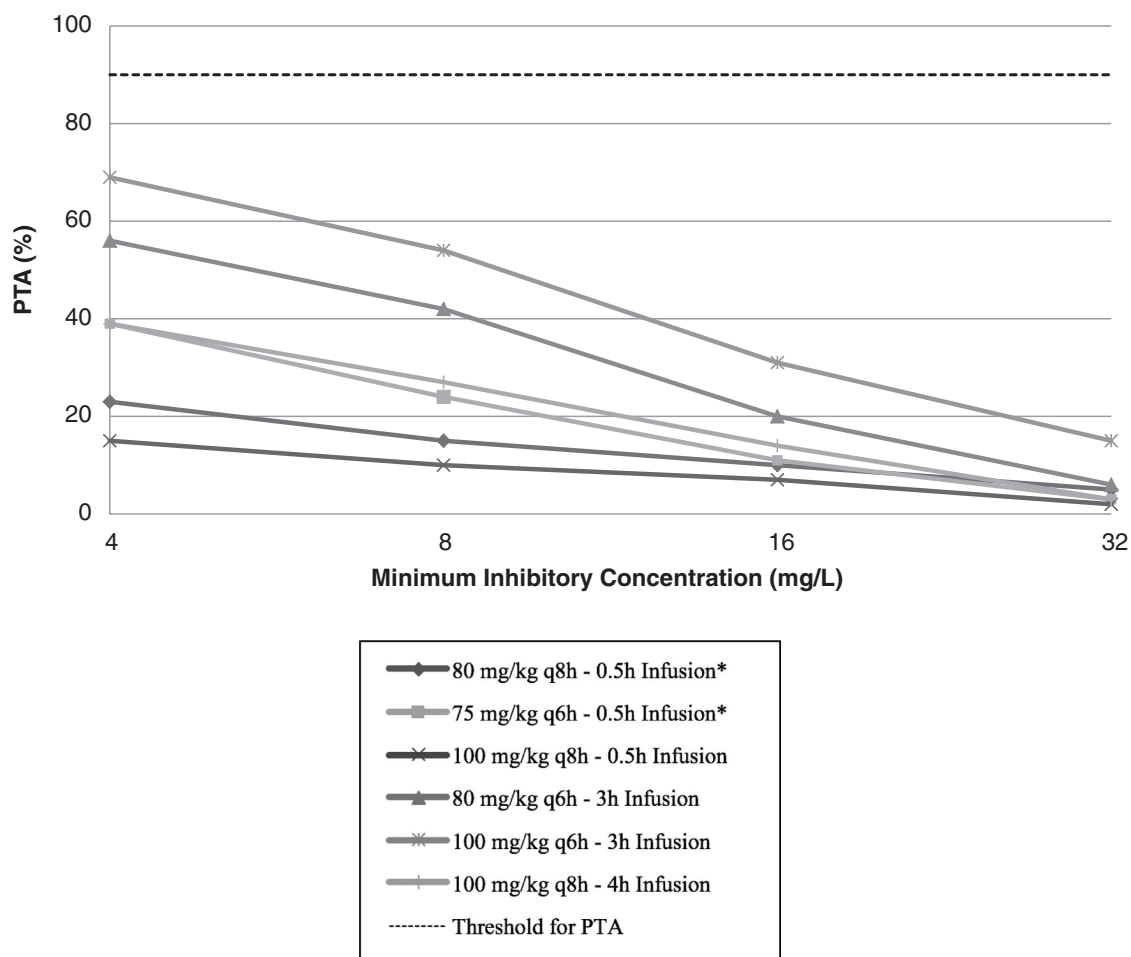


FIG. 4 PTA¹ by MIC² for free piperacillin concentrations = 100% of the dosing interval in children > 6 months–6 years.

¹PTA: Probability of Target Attainment

²MIC: Minimum Inhibitory Concentration

*Standard recommended regimens

240 mg/kg/day, an infusion time of 4 hours (80 mg/kg/dose every 8 hours infused over 4 hours; daily infusion time of 12 hours) was required to reach a PTA \geq 90% at a MIC of 16 mg/L. The minimum daily infusion time to reach PTAs \geq 90% at a MIC of 16 mg/L was 6 hours (90 mg/kg/dose every 8 hours over 2 hours infusion; 270 mg/kg/day; 90% PTA). At a MIC of 32 mg/L, the only dosing regimen reaching PTAs \geq 90% was 100 mg/kg/dose every 6 hours as a 3 hours infusion (400 mg/kg/day; 96% PTA).

In children > 6 months to 6 years, none of the tested regimens infused over 0.5 hours reached \geq 90% PTA at MICs of 4 mg/L. In this age group, the recommended dose of 75 mg/kg/dose every 6 hours infused over 0.5 hours (300 mg/kg/day)³⁵ achieved surrogate PD target of 79%, 68% and 52% at MICs of 4, 8 and 16 mg/L, respectively. The alternate recommended dosing regimen in infants < 9m of 80 mg/kg/dose every 8 hours^{31,36} reached PTAs of 57%, 48%, and 32% over the same range of MICs, respectively. A dose of 100 mg/kg/dose every 8 hours infused over 0.5 hours (300

mg/kg/day), as recommended for infants and children > 9m,^{31,36} reached PTAs of 57%, 50% and 29% at MICs of 4, 8 and 16 mg/L, respectively. The same daily dose (300 mg/kg/day) had to be infused over 4 hours (100 mg/kg/dose every 8 hours) to reach PTAs $\geq 90\%$ at MICs up to 16 mg/L. The minimum daily infusion time to reach PTAs $\geq 90\%$ at a MIC of 16 mg/L was 12 hours (80 mg/kg/dose every 6 hours over 3 hour infusion; 320 mg/kg/day; 92% PTA). None of the simulated dosing regimen reached PTAs at MICs > 16 mg/L in this age group.

DISCUSSION

To our knowledge, this is the first study to evaluate various dosing regimens in a broad population of simulated infants and children representative of what is seen in pediatric hospitals. Results showed that simulated extended infusions were associated with higher PTAs in infants and children from 2 months to 6 years. The benefit of extended infusions in terms of higher target attainment rates was more significant after 6 months of age. Given a standard maximum dose of 400 mg/kg/day, none of the routinely used 0.5h infusion regimens reached $fT > MIC \geq 50\%$ of the dosing interval at MICs > 8mg/L for infants 2–6 months and at MICs ≥ 4 mg/L for older children.

Gram-negative bacteria are frequently implicated in severe infections. A retrospective study of 321 children in septic shock recently showed that gram-negative bacteria represent 32% of the isolated organisms.⁴ *Escherichia coli* was among the 3 most frequent bacteria isolated, and *Pseudomonas aeruginosa* was the 5th most frequent. TZP remains an excellent choice for empiric therapy of acute infections, given its broad spectrum, and a susceptibility rate of 98% for *E. Coli* and 93% for *Pseudomonas*.³⁷ However, TZP efficacy decreases as bacteria MIC increases. Empiric therapy should therefore take into account local susceptibility patterns as well as suspected causative organisms. In a study collecting susceptibility data in 15 Canadian hospitals (1 pediatric hospital and 10 hospitals treating infants and children), the 90th percentile of MICs (MIC₉₀) was 4 mg/L for *E. Coli*, 16 mg/L for extended-spectrum β -lactamase (ESBL)-producing *E. Coli*, and reaching 64 mg/L for *Pseudomonas*.³⁷

According to clinical breakpoints for piperacillin, enterobacteriaceae and *P. aeruginosa* are susceptible when MIC ≤ 16 mg/L.³⁴ In our opinion, appropriate dosing regimens should therefore achieve effective TZP exposure for MICs up to 16 mg/mL, using the smallest possible doses and infusion time.

In infants > 2 to 6 months of age, 2 dosing regimens were closely considered as the most appropriate; while the 90 mg/kg/dose every 8h infused over 2 hours, represented a 13% increase in the daily dose compared with the 80 mg/kg/dose every 8 hours over 4 hours (270 vs. 240 mg/kg/day), the daily infusion time was 50% lower (6 vs. 12 hours). Given the significantly shorter daily infusion time, the 90 mg/kg/dose every 8 hours infused over 2 hours was preferred in this age group. In the older age group, 100 mg/kg/dose every 8 hours infused over 4 hours (300 mg/kg/day) fulfilled our criteria for the most appropriate dosing regimen. Recommended dosing regimens used in routine care (75 to 100 mg/kg/dose every 6 or 8 hours) were not optimal at MICs > 8 mg/L for infants > 2 to 6 months of age, and ≥ 4 mg/L for children older than 6 months of age. More frequent dosing (every 4 hours) with standard 0.5 hours infusions did not reach optimal PTAs at MICs of 16 mg/L. For bacteria with MICs > 16 mg/L, 100 mg/kg/dose every 6 hours as a 3 hours infusion (400 mg/kg/day) reached the surrogate PD target in infants > 2–6 months at MICs of 32 mg/L. In children older than 6 months, none of the simulated dosing regimens reached optimal PTAs at MICs > 16 mg/L. Therapeutic possibilities may then include higher daily doses, continuous infusion, or the use of an alternative antibiotic.²²

Although our suggested dosing regimens require prolonged infusion times, no change in the standard dilution (200 mg/mL) of the TZP IV solution is theoretically needed. Consequently, our suggested regimens do not necessarily imply an increase in daily total fluid intake (TFI). However, feasibility needs to be evaluated, especially in young infants for whom further dilution may be required to ensure a minimum volume. Hypothetically, further dilution of the TZP IV solution may be obtained to ensure a conservative minimal infusion rate of 10 mL/h. This could represent up to 60 mL/day (90 mg/kg/dose every 8 hours; 2 hour infusion) in infants > 2 to 6 months, and 120 mL/day

(100 mg/kg/day every 8 hours; 4 hour infusion) in children > 6 months. These volumes represent 17% and 23% of recommended TFI in infants of 2 and 6 months of age,³⁸ respectively, using the lowest weights included in our study. The need for such dilution will have to be evaluated prospectively, where other factors should be taken into account including the remainder IV fluid intake, and drug compatibilities. Moreover, the minimum accepted rate to keep a patent vein varies between institutions.

Our findings on higher PTAs with extended infusions are in agreement with published literature in children and adults.^{13,14,16,24,25,27,28,39} The only pediatric clinical trial using intermittent extended TZP infusions was performed in 12 critically ill children (1–9 years of age) (28). Their PK simulations based on a population PK model derived using 4 hour infusions suggest higher PTAs compared to our results. According to this previous study, standard 0.5 hour infusion time and extended infusion times were equivalent for MICs \leq 8mg/L (28). They used a clearance (CL) of 0.22 ± 0.07 L/h/kg, which is in the lower range of those used in the present study, and a larger volume of distribution (V) of 0.43 ± 0.16 L/kg. This divergence may be explained by a difference in the population characteristics, as they enrolled exclusively critically ill children hospitalized in intensive care unit. Some level of undetected renal dysfunction due to underlying conditions in the critically ill population may also explain a longer $fT > MIC$.

A second simulation study with 5000 critically ill children 9 months–6 years used a larger V (0.511 ± 0.366 L/kg) and a similar CL (0.299 L/h/kg) to the one used in our study.²⁵ According to their data, only 400 mg/kg/day in continuous infusion or 100 mg/kg/dose infused over 3 hours, every 6 hours (400 mg/kg/day) achieved acceptable PTAs at a MIC of 16 mg/L. These regimens lead to a higher total dose of TZP compared to the one we recommend and thus potentially more adverse effects and toxicity. A continuous infusion implies a near exclusive occupation of a venous access for the duration of the antibiotic treatment, which can be an issue in infants with limited venous access. Our suggested regimens would possibly have achieved satisfying PTAs according to their PK model, but they were not among their simulated regimens.

As opposed to previous studies, we divided our population in different age groups. As previously established, piperacillin PK differs in young children, reaching adult PK behaviour by 2 years of age.³⁰ A slower elimination rate before this age results in higher concentrations throughout the dosing interval. The exact age at which an extended infusion may be beneficial is not well documented in the literature. However, dose-exposure simulations suggest that extended infusion does not provide additional benefit in infants < 2 months, who were consequently excluded from the present study.²⁶ Both Nichols et al. and Cies et al. extrapolated their data from a small sample size (12 and 13 patients respectively), with very few patients < 2 years of age.^{25,28} Our data showed that TZP extended infusions are beneficial to infants as young as 2 months old when targeting bacteria with high MICs (MICs > 8mg/L).

Some limitations should be considered in the interpretation of our results. It should first be mentioned that plasmatic concentrations were the only PD target used and results may not be applicable to other penetration sites. Although TZP PK has been well described in pediatrics, there is no available population PK model in infants and children 2 months to 1 year of age. We therefore had to rely on the only published PK parameters specific to our age groups, which were determined using 0.5 hour infusions.³⁰ Moreover, various underlying conditions were not taken into account. These limitations may have resulted in imprecise concentration predictions. For example, a state of inflammation such as seen in septic shock may increase TZP volume of distribution and renal clearance, and thus decrease initial plasmatic concentrations.^{25,40,41} On the contrary, renal failure may decrease TZP clearances and thus increase plasmatic concentrations. Despite these limitations, this study was a preliminary step to inform dosing in an ongoing prospective clinical trial (NCT #32987). The objective of this PK trial is to develop a population PK model for TZP and therefore determine optimal dosing regimens in 3 subpopulations of infants and children 2 months–6 years with normal kidney function; (1) general pediatrics/surgery, (2) hemato-oncology, (3) critical care. The safety and feasibility of extended-infusion regimens will also be described. TZP extended

infusions have been associated with lower mortality rates and higher clinical cure rates,^{18,19,22} although inconsistently.^{17,21,23} This study was not designed to evaluate clinical outcomes. A prospective study comparing clinical outcomes between extended versus standard infusions is needed in children.

In conclusion, given a maximum daily dose of 400 mg/kg/day, simulated standard infusions of 0.5 hours were insufficient to provide acceptable PTAs for infants > 2 to 6 months at MICs \geq 8mg/L and for children > 6 months to 6 years at MICs \geq 4mg/L. TZP extended infusions allowed to optimize systemic exposure. We suggest dosing regimens of 90 mg/kg/dose every 8 hours as a 2 hour infusion for infants > 2 months to 6 months of age and of 100 mg/kg/dose infused over 4 hours, every 8 hours for children > 6 months to 6 years of age. In cases of resistant bacteria, we suggest a dosing regimen of 100 mg/kg/dose every 6 hours as a 3 hour infusion in infants > 2–6m for MICs up to 32 mg/L. These regimens need to be validated in a prospective clinical trial, and may need to be adjusted according to different factors such as inflammation and altered renal function.

REVIOUS PRESENTATIONS

Abstract presented at the American Conference on Pharmacometrics (ACoP6) held in Arlington, Virginia (USA), October 3rd-9th 2015. Oral presentation at the Gabriel L. Plaa Research Day in Pharmacology, University of Montreal, Montreal (CA), May 20th 2016.

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