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Population pharmacokinetics of piperacillin in febrile children receiving cancer chemotherapy: the impact of body weight and target on an optimal dosing regimen

Anders Thorsted[1], Anders N. Kristoffersson[1]†, Sabine F. Maarbjerg[2], Henrik Schrøder[2], Mikala Wang[3], Birgitte Brock[4]‡, Elisabet I. Nielsen[1] and Lena E. Friberg[1]*

[1]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; [2]Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark; [3]Department of Clinical Microbiology, Aarhus University Hospital, Aarhus, Denmark; [4]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark

*Corresponding author. Tel: +46 18 471 4685; Fax: +46 18 471 4003; E-mail: lena.friberg@farmbio.uu.se
†Present address: Pharmetheus AB, Uppsala, Sweden.
‡Present address: Steno Diabetes Center Copenhagen, Gentofte, Denmark.

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Background: The β-lactam antibiotic piperacillin (in combination with tazobactam) is commonly chosen for empirical treatment of suspected bacterial infections. However, pharmacokinetic variability among patient populations and across ages leads to uncertainty when selecting a dosing regimen to achieve an appropriate pharmacodynamic target.

Objectives: To guide dosing by establishing a population pharmacokinetic model for unbound piperacillin in febrile children receiving cancer chemotherapy, and to assess pharmacokinetic/pharmacodynamic target attainment (100% *f*T>1×MIC and 50% *f*T>4×MIC) and resultant exposure, across body weights.

Methods: Forty-three children admitted for 89 febrile episodes contributed 482 samples to the pharmacokinetic analysis. The typical doses required for target attainment were compared for various dosing regimens, in particular prolonged infusions, across MICs and body weights.

Results: A two-compartment model with inter-fever-episode variability in CL, and body weight included through allometry, described the data. A high CL of 15.4 L/h (70 kg) combined with high glomerular filtration rate (GFR) values indicated rapid elimination and hyperfiltration. The target of 50% *f*T>4×MIC was achieved for an MIC of 4.0 mg/L in a typical patient with extended infusions of 2–3 (q6h) or 3–4 (q8h) h, at or below the standard adult dose (75 and 100 mg/kg/dose for q6h and q8h, respectively). Higher doses or continuous infusion were needed to achieve 100% *f*T>1×MIC due to the rapid piperacillin elimination.

Conclusions: The licensed dose for children with febrile neutropenia (80 mg/kg q6h as a 30 min infusion) performs poorly for attainment of $fT_{>MIC}$ pharmacokinetic/pharmacodynamic targets. Given the population pharmacokinetic profile, feasible dosing regimens with reasonable exposure are continuous infusion (100% *f*T>1×MIC) or prolonged infusions (50% *f*T>4×MIC).

Introduction

The combination of fever and neutropenia in patients receiving chemotherapy for treatment of cancer is an ominous warning of serious infection and a major cause of morbidity, mortality and increased costs due to hospitalization.[1,2] Neutropenia, defined as an absolute neutrophil count below 0.5×10^9 neutrophils/L, renders the patient highly susceptible to infection. In such situations, multiple guidelines recommend administration of initial (empirical) antibiotic therapy.[3,4] While multiple factors come into play when choosing an antibiotic (individual risk, infection history, renal dysfunction and local epidemiology of bacterial pathogens and antimicrobial resistance) a β-lactam antibiotic covering Gram-negative bacteria is generally recommended.[5]

For antibiotic administration and resulting effectiveness (pharmacodynamics), the pharmacokinetic behaviour, i.e. the

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shape of the concentration–time curve in the population of interest, is important when choosing a dosing regimen. For β-lactams, antibacterial activity is related to the time for which the free drug concentration stays above the MIC ($fT_{>MIC}$).[6] In neutropenic animals, bacteriostasis is reached for dosing regimens with 35%–40% $fT>1\times MIC$, and near maximal effect is achieved at 60%–70%.[6] Stricter targets of 100% $fT>1\times MIC$ or 50% $fT>4\times MIC$ are frequently used,[7] with therapeutic effect assumed to increase and risk of resistance development to reduce.[8] A common regimen is administration by a short bolus-like infusion (SI), but extended infusion (EI) and continuous infusion (CI) offer increased $fT_{>MIC}$[9–11] (provided that concentrations are above the MIC in question). While prolonged infusions may improve clinical outcomes such as mortality,[12] reduced tissue penetration has also been reported,[13] and more evidence of impact on clinical outcomes is required.

It is important to define antibiotic pharmacokinetics in the target population, as drug pharmacokinetics vary among individuals and as disease may introduce pathophysiological changes that affect *V* and/or the rate of elimination.[14] Integration of plasma concentration samples from multiple individuals in a population pharmacokinetic model determines both typical behaviour and variability in drug pharmacokinetics. This aids in identifying and quantifying how pharmacokinetic parameters are related to patient covariates such as age, body weight or kidney function.[15] The impact of covariates on the antibiotic concentration–time course can assist in optimizing the starting dose, which can later be refined by further adjustment according to therapeutic drug monitoring, if feasible.[7]

Piperacillin/tazobactam (ratio 8:1) is a β-lactam/β-lactamase inhibitor combination with broad-spectrum antibacterial activity, often administered as empirical treatment for bacterial infections.[16] In adults, a dose of 4000 mg is normally administered intermittently by SI three or four times daily, with a maximum daily dose of 16000 mg. To reach comparable daily exposures (as measured by the AUC), a dose of 100 mg/kg three times daily was predicted to be required in children over 9 months of age suffering from intra-abdominal infection.[17] However, achieving similar daily AUCs does not translate to the achievement of $fT_{>MIC}$ pharmacodynamic targets, as the shape of the concentration–time profile determines target attainment. Therefore, further investigation of alternative dosing regimens is warranted.

The pharmacokinetics of piperacillin has been determined in adults[18,19] and children suffering from febrile neutropenia[20] as well as in children admitted to the ICU.[21,22] The aim of this study was to provide dosing recommendations for febrile children receiving cancer chemotherapy and assess the impact of pharmacodynamic targets on the dose required for target attainment across dosing regimens. A sparse sampling design, where the time above a threshold could be adequately determined by subsequent modelling, was proposed using optimal design methodology and a population pharmacokinetic model was developed based on the data gathered.

Patients and methods

Study design

The study was a prospective and descriptive study at the Department of Pediatric Oncology, Aarhus University Hospital, Aarhus, Denmark, between 1 April 2016 and 31 January 2018 (EudraCT: 2016-00466-33). The Danish Medicines Agency, The National Committee on Health Research Ethics (ESDH: 1-10-72-342-15) and the Danish Data Protection Agency approved the study. Informed consent was required, with parents or guardians providing consent for children younger than 15 years of age.

Patient population

The study included children aged 6 months to 18 years suffering from cancer and chemotherapy-induced fever, who started empirical treatment with piperacillin/tazobactam and had a central venous catheter available. Fever was defined as presence of a single temperature measurement above 38.0°C. Children could participate on more than one occasion in the case of multiple febrile episodes. Children that were breastfed exclusively or who had a central venous catheter from which blood sampling was not feasible were excluded.

The following covariates were registered at each febrile episode: body weight, height, age, sex, serum creatinine, type of cancer and whether neutropenia ($<0.5\times10^9$ neutrophils/L), severe neutropenia ($<0.1\times10^9$ neutrophils/L) or bacteraemia (yes/no) were present. Individual glomerular filtration rate (GFR) was derived from serum creatinine measurements using the Schwartz formula for children.[23]

Study drug and design for blood sample collection

Piperacillin/tazobactam (Tazocin®, ratio 8:1) was administered intravenously as a 5 min SI approximately every 8 h. A daily piperacillin dose of 300 mg/kg was administered across three doses and capped at 16000 mg corresponding to the adult dose.

Sampling times were optimized in the PopED 2.13 optimal design tool[24] given a prior piperacillin pharmacokinetic model for febrile paediatric patients.[20] The optimization focused on providing information on the population pharmacokinetics and the individual $fT_{>MIC}$, which are presented in greater detail in Appendix S1 (available as Supplementary data at *JAC* Online) and was similar to a previously described approach.[25] Based on the prior two-compartment model, $fT_{>MIC}$ was mainly determined by the terminal elimination phase (β-parameter) and a design criterion was formulated that enabled sampling time optimization for maximized precision in both primary population pharmacokinetic parameters and the β-parameter.

Each patient had three blood samples drawn during two dosing intervals (six blood samples per subject). Patients belonging to group A had blood samples drawn at 10–30 min, 4–5 h and 7–8 h after drug administration, while patients in group B had blood samples drawn at 1.5–2 h, 4–5 h and 7–8 h after administration, with additional samples taken on a consecutive day if possible. After samples from the first 12 patients (23 fever episodes) were available, an interim evaluation led to an updated design based on the patient population to date (see Supplementary data). As a result, the optimal sampling times for the two last samples were changed to 3.5–4.5 h and 6.5–7.5 h after drug administration for both groups. Exact sampling times and piperacillin/tazobactam dosing history was registered and implemented in the dataset.

UPLC

The free concentrations of piperacillin in sera were assessed using UPLC preceded by ultra-filtration (UHPLC, Agilent 1290, Agilent Technologies, USA), described in detail previously.[25,26] Intra-run (total) imprecisions (coefficient of variation) were 10.2% (15.3%) at 4.5 mg/L and 4.7% (8.2%) at 15.6 mg/L. The lower limit of quantification (LLOQ) was 0.5 mg/L.

Pharmacokinetic modelling

A population pharmacokinetic model was developed using NONMEM 7.4.3 (ICON Development Solutions, Gaithersburg, MD, USA)[27] aided by Perl-Speaks-NONMEM and Piraña.[28] Model parameters were estimated using the Laplacian method with interaction and M3[29] for accurate consideration of observations below the assay LLOQ. Statistical selection between two nested models was made with a likelihood-ratio test of their objective

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function values (OFVs), assuming that the OFVs follow a χ^2 distribution (a ΔOFV = −3.84 significant at P=0.05 for one additional parameter). Additionally, residual goodness-of-fit plots and visual predictive checks (VPCs)[30] aided model selection and evaluation.

Model development assessed one- or two-compartment models and included inter-individual variability (IIV) in parameters (with log-normally distributed individual parameters). Inter-occasion variability (IOV) was assessed with an occasion defined as a febrile episode. Furthermore, as the study population consisted of children, body weight was expected to be a key covariate to include early in model development in addition to assessment of kidney maturation.[31] This was in line with allometry, where the size of a physiological process follows a power relationship to body weight, with fixed exponents of 0.75 and 1.0 for CLs and *V*s, respectively.[32] Screening of remaining covariates (age, GFR, sex, bacteraemia and neutropenia) was done on pharmacokinetic parameters by means of stepwise covariate modelling (SCM)[33] after an acceptable base model had been established, with forward search (P<0.05) and backwards deletion (P<0.01). Continuous covariates were tested through linear, piecewise linear (hockey-stick) or power relationships centred on the median covariate value for continuous covariates and as a shift in the typical value for the least common category for categorical covariates.[33]

MICs and pharmacokinetic/pharmacodynamic targets

The two pharmacokinetic/pharmacodynamic targets of 50% *f*T>4×MIC (free piperacillin concentration maintained above four times the MIC for at least half of the dosing interval) and 100% *f*T>1×MIC (free piperacillin concentration maintained above the MIC for the entire dosing interval) were evaluated.

Estimates of MIC_{50} and MIC_{90} for piperacillin/tazobactam were derived from an internal MIC study that assessed 165 pathogenic isolates from paediatric patients with malignant disease (from 2004 to 2013). In addition, the piperacillin/tazobactam MIC breakpoint of 16.0 mg/L for *Pseudomonas* spp. from EUCAST was used to represent a high MIC.[34]

To illustrate the typical free concentration–time course of piperacillin in the study population and the impact of identified covariates, predictions of 300 mg/kg/day administration by SI or EI (as a 3 h infusion), both q8h, and CI were performed. Furthermore, the relationship between MIC and the typical dose required to attain the two pharmacokinetic/pharmacodynamic targets was established for a number of dosing regimens at steady-state conditions, consisting of CI, SI (5 min infusion q8h) and EI with varying infusion lengths (1–4 h, both q6h and q8h). Additionally, the licensed dosing regimen for piperacillin in children with febrile neutropenia was assessed (30 min infusion of 80 mg/kg given q6h). To facilitate discussion of the impact of the choice of pharmacokinetic/pharmacodynamic target, regimens were compared with respect to the dose required for target attainment at steady-state conditions and the resulting exposure (AUC_{ss}) and peak concentration ($C_{max,\,ss}$). The impact of unexplained variability in the population was illustrated with a 90% prediction interval (i.e. 5th–95th percentile of simulated profiles) based on 1000 simulated patients.

Results

Patient characteristics

Forty-three patients were included with characteristics shown in Table 1. The patients contributed 482 piperacillin samples (19 below the LLOQ) across 89 fever episodes (1–4 per patient). The data are shown in Figure 1, with no clear systematic change in the time course between febrile episodes within a patient.

Pharmacokinetic modelling

Final parameter estimates with uncertainty are included in Table 2. In Figure 2, VPCs demonstrate an acceptable model fit of the total dataset (Figure 2a), proportion of samples below the LLOQ (Figure 2b) and across age intervals (Figure 2c). Samples followed two-compartment disposition (ΔOFV = −18.7 over one-compartment) with first-order elimination from the central compartment ($t_{1/2,\alpha}$ of 0.708 h and $t_{1/2,\beta}$ of 10.1 h at 70 kg). Differences between patients were described with an IIV term on CL, but with addition of IOV in CL (between fever episodes) the model fit improved (ΔOFV = −260.4) and the IIV term became insignificant, indicating that children differed from one fever episode to another to the same degree as between each other. IOV in CL for sampling occasions within a fever episode was not statistically significant.

Inclusion of individual body weight in line with standard allometry (fixed exponents of 0.75 and 1.0) improved the fit (ΔOFV = −49.4) although the unexplained variability in CL did not decrease. Forward assessments by SCM (P<0.05) identified three linear relationships and following the backwards deletion step (P<0.01) age on CL and central *V* remained, with estimates of the covariate effects leading to higher (weight-adjusted) parameter values at lower ages. Further assessment showed that inclusion of age on CL independent of inclusion of age on *V* was insignificant (ΔOFV = −0.001). Additionally, randomization testing showed that the actual ΔOFV required for significance at P<0.01 for inclusion of age on *V* (ΔOFV = −11.1) was higher than the theoretical value of −6.63 and higher than that observed following inclusion (ΔOFV = −7.77).[35] Therefore, only body weight was included in the final model. Evaluation of GFR as a covariate for CL did not improve the model fit despite being mechanistically reasonable for a renally cleared drug (different parameterizations were tested, with the largest drop being ΔOFV = −2.54). Assessment of kidney maturation[31] through the following relationship:

$$CL = \theta_{CL} \times \left(\frac{WT}{70}\right)^{0.75} \times \left(\frac{PMA^{3.4}}{PMA^{3.4} + 47.7^{3.4}}\right)$$

where θ_{CL} is the population estimate of CL, WT refers to body weight and PMA refers to postmenstrual age,[31] did not lead to significant improvement in fit (ΔOFV=0.286).

Typical free concentration–time courses are illustrated in Figure 3 for dosage regimens of 300 mg/kg/day (capped at 16 000 mg) according to: (i) SI (three 5 min infusions); (ii) EI (three 3 h infusions); and (iii) CI. The internal MIC study resulted in MIC_{50} and MIC_{90} estimates of 2.0 and 4.0 mg/L, respectively, illustrated in the graph along with the EUCAST breakpoint MIC of 16.0 mg/L for *Pseudomonas* spp. It is evident that children with lower body weight typically achieve lower exposure.

Target attainment

The relationship between MIC and the dose (mg/kg) required to achieve the two pharmacokinetic/pharmacodynamic targets at steady-state is shown in Figure 4 for 10 regimens and three body weights of 15, 40 and 65 kg. For 50% *f*T>4×MIC, CI and EI of 2 and 3 h (q6h) or 3 and 4 h (q8h) achieve the target for MIC_{90} (4.0 mg/L) with doses at or below the standard adult dose. Individuals with lower body weight require higher doses (in mg/kg) for target attainment, although the difference diminishes with longer infusions. Conversely, the doses required to achieve 100% *f*T>1×MIC

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are 1.4–7.7 times larger than standard doses and, except for CI, none of the regimens achieves the target for MIC_{90} (4.0 mg/L) for all studied body weights. Generally, to achieve 100% $fT>1\times MIC$, higher doses are required for corresponding MICs compared with 50% $fT>4\times MIC$, illustrating that the short $t_{1/2}$ of piperacillin is limiting for attainment of 100% $fT>1\times MIC$.

The licensed 30 min infusion and the 3 h EI q8h regimens are further explored in Figure 5, with comparison of the typical dose required for target attainment at an MIC of 4.0 mg/L and the resulting AUC_{ss} and $C_{max,\,ss}$. For the licensed dosing regimen, target achievement requires doses from 0.67–1.96 and 1.98–5.78 times the standard 80 mg/kg (50% $fT>4\times MIC$ and 100% $fT>1\times MIC$, respectively). These doses result in $C_{max,\,ss}$ below or up to 3-fold that observed following SI dosing (~500 mg/L in Figure 3). For EI, the dose required for 50% $fT>4\times MIC$ is below the standard 100 mg/kg/dose, resulting in reasonable peak concentrations and comparably low AUC_{ss}, whereas the doses required for achievement of 100% $fT>1\times MIC$ are similarly high as for the licensed regimen, but with lower $C_{max,ss}$.

Table 1. Overview of patient characteristics

Characteristic	Median (IQR) [range] or *n*/*N* (%)
Subjects (*n*=43)	
age (years)	12 (7–14) [1–18]
male subjects	27/43 (63)
Fever episodes (*n*=89)	
body weight (kg)	39.4 (24.5–51.8) [9.5–107]
GFR (mL/min/1.73 m^2)	172.4 (139.8–210.8) [87.0–425.8]
fever days (days)	1 (1–3) [0–7]
peak temperature (°C)	38.8 (38.4–39.5) [36.9–41.7]
episodes with neutropenia	77/89 (87)
episodes with bacteraemia	10/89 (11)

Discussion

The work presented here establishes a population pharmacokinetic model for the free concentration–time course of piperacillin in febrile children receiving cancer chemotherapy. A sizable study population contributed data (Figure 1) and pharmacokinetics differed between fever episodes, rather than between patients. At 4 h (dosing interval midpoint) approximately half of the samples were below MIC_{90} (4.0 mg/L) with only a few observed concentrations $\geq 4\times MIC_{90}$, indicating a need for higher doses with the employed SI regimen.

Included individuals were biased towards higher ages, with a single 1 year-old and three 2 year-olds, limiting dosing recommendations to children between 2 and 18 years old. Patients had normal weight for age, but the values of estimated GFR were high (IQR of 140–211) indicating hyperfiltration, seen previously in critically ill children.[20,22,36] Previously, one- and two-compartment models for piperacillin in critically ill children have been reported,[21,22,36,37] but with rapid and more pronounced peripheral distribution. As the sampling design was based on one of these studies,[36] an interim design update was performed to limit information loss due to LLOQ samples. In addition to differences in patient populations, the apparent deviation in model parameters could be due to a reduced number of LLOQ samples in this study due to study design. The peripheral distribution is mainly evident at the end of a dosing interval (Figure 3), where the typical free concentrations are already below the reference MICs.

The impact of body weight on the pharmacokinetic profile is clear from Figure 3, with shortened $t_{1/2}$s at lower body weights due to the impact of allometric scaling illustrated and discussed previously,[38] suggesting that target attainment will directly depend on individual characteristics and their impact on the shape of the free concentration–time profile. A relationship between individual GFR and CL makes mechanistic sense based on knowledge of the β-lactam elimination pathway[39] and has been identified in adults,[18] but

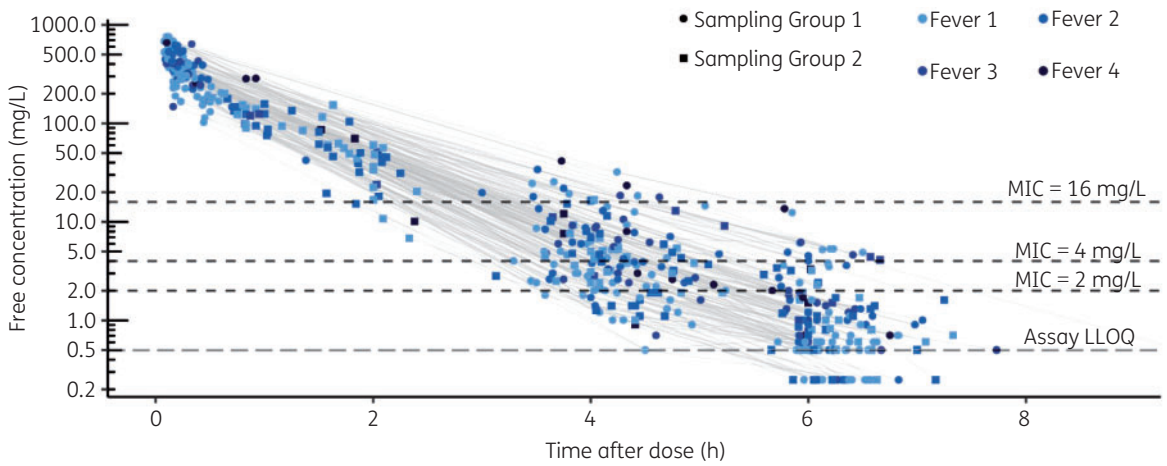

Figure 1. Overview of the piperacillin free concentration samples (points) collected across up to four febrile episodes from the included subjects (see legend). The lines connect observations from a sampling interval in an individual and the shape of the points shows if the patients belonged to sampling group 1 or 2 (described in Patients and methods). The dashed horizontal lines indicate the piperacillin/tazobactam MIC breakpoint for *Pseudomonas* spp. according to EUCAST (16 mg/L), the MIC_{90} (4 mg/L) and MIC_{50} (2 mg/L) from an internal MIC study, and the assay LLOQ (0.5 mg/L) with observations below set to half this value in the figure. This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

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Table 2. Final parameter estimates and variances from the population analysis including uncertainty and shrinkage[a]

Parameter (units)	Parameter description	Estimate	(RSE%) [SHR%]
CL (L/h)	Elimination CL	15.4[b]	(3.7)
V_c (L)	Central *V*	16.0[b]	(4.8)
Q (L/h)	Inter-compartmental CL	0.237[b]	(9.6)
V_p (L)	Peripheral *V*	3.40[b]	(34)
CV% CL	Inter-fever-episode variability in CL	16.6%	(11) [5.2]
CV% ERR	Proportional residual error	33.2%	(4.7) [12]

[a]CV%, coefficient of variation as a percentage; RSE, relative standard error; SHR, shrinkage.
[b]Typical estimates for a patient with a body weight (WT) of 70 kg, according to the allometric relationships: $CL_{typical,individual}=CL_{typical,70\,kg}\times(WT_{individual,\,kg}/70\,kg)^{0.75}$ and $V_{typical,individual}=V_{typical,70\,kg}\times(WT_{individual,kg}/70\,kg)^{1.0}$.

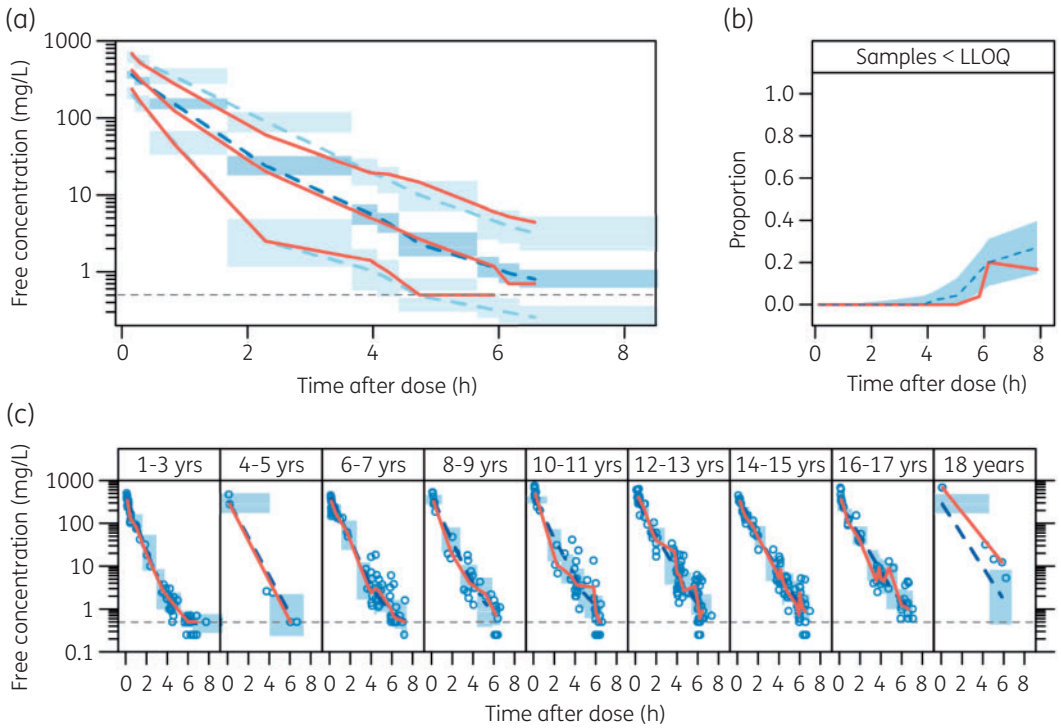

Figure 2. VPC based on the final model, for (a) the data above the LLOQ; (b) the proportion of samples below the LLOQ; and (c) the dataset split into age intervals. In (a), the blue dashed lines and shaded areas represent the median, 5th and 95th percentiles of model simulations and their corresponding 95% confidence intervals, while the red solid lines represent the median, 5th and 95th percentiles of the observed data. In (b), the blue dashed line and shaded area represent the simulated proportion of samples below the LLOQ (0.5 mg/L) and corresponding 95% confidence intervals, while the red solid line represents the observed proportion. In (c), the blue dashed lines and shaded areas represent the median of model simulations and corresponding 95% confidence intervals, while the blue circles represent observations and the red solid lines the median of the observations. The horizontal dashed lines in (a) and (c) indicate the assay LLOQ of 0.5 mg/L. This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

none of the parameterizations tested reached statistical significance. This could be due to the relatively narrow distribution of GFR in the study and because the population are likely hyperfiltrators. This may explain high CL (15.4 L/h) in comparison with studies in adult sepsis[25] (8.58 L/h) or septic shock[26] (3.6 L/h). The CL estimated in the current population (15.4 L/h) is, however, similar to previous studies in critically ill children,[20–22,36,37] with estimates ranging from 12.6 to 20.9 L/h (mean 15.3 L/h), also observed for central *V* (range 9.0–30.1 L, mean 19.0 L) compared with our estimate of 16 L.

Based on the developed model, we aimed to identify the typical dose needed for target attainment across dosing regimens compared with the utilized dose of 100 mg/kg/dose[17] (Figure 4). The dose required for pharmacokinetic/pharmacodynamic target attainment is highly dependent on the target in question and related to the shape of the concentration–time profile resulting from a

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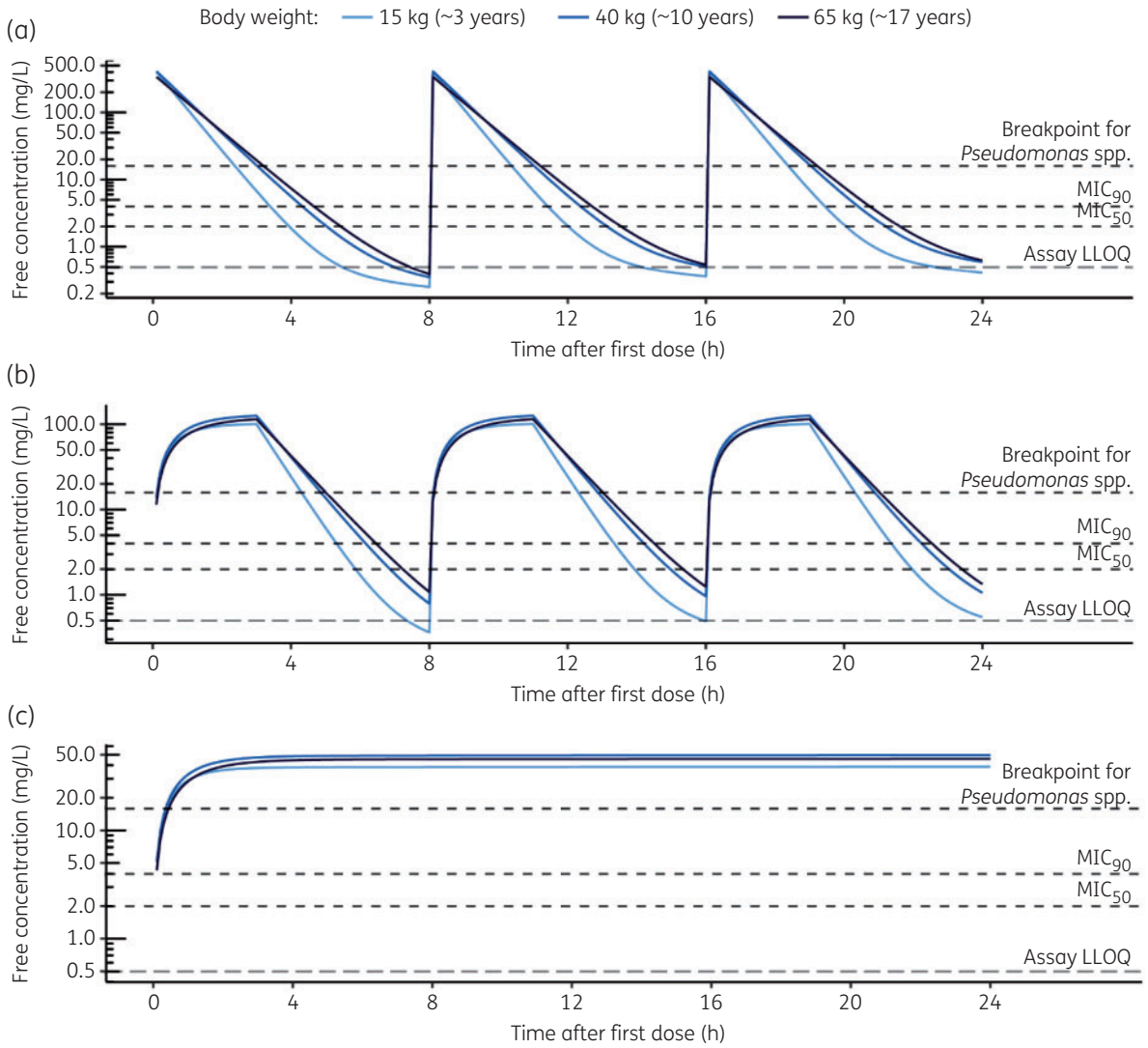

Figure 3. Typical predictions of the piperacillin free concentration time course for individuals with body weights of 15, 40 and 65 kg (see legend), following a total dose of 300 mg/kg/day. Different regimens are: (a) SI given at 8 h intervals (q8h); (b) EI over 3 h given at 8 h intervals (q8h); and (c) CI. The dashed horizontal lines indicate the piperacillin/tazobactam MIC breakpoint for *Pseudomonas* spp. according to EUCAST (16 mg/L), the MIC_{90} (4 mg/L) and MIC_{50} (2 mg/L) from internal data, and the assay LLOQ (0.5 mg/L). This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

given regimen. Previous studies of piperacillin in critically ill children found that 100 mg/kg/dose given as a 3 h infusion q6h would achieve a target of 50% *f*T>1×MIC up to an MIC of 32.0 mg/L,[20,36] which is unsurprising considering the infusion is ongoing for 50% of the dosing interval. In our study, we assessed a stricter target of 50% *f*T>4×MIC, suitable in critically ill patients,[7] in addition to the commonly applied target for piperacillin of 100% *f*T>1×MIC,[18,20–22,25] as successful target attainment based on prolonged infusions may only reach concentrations just above the pathogen MIC (a variable often determined with high uncertainty). From Figure 4, it appears that a CI dosing regimen would be required to achieve 100% *f*T>1×MIC for most MICs at reasonable doses, especially at low body weights, while higher doses may be needed to achieve 50% *f*T>4×MIC at higher MICs (16.0 mg/L).

To achieve the target of 100% *f*T>1×MIC, the applied dose needs to be increased many-fold irrespective of the licensed regimen or EI, as illustrated in Figure 5, leading to high peak concentration and exposure, with potential toxicity issues.[40] The target of 50% *f*T>4×MIC is achieved at doses of 40–80 mg/kg for an MIC of 4.0 mg/L by administering piperacillin as a 3 h EI q8h, i.e. lower than the standard 100 mg/kg/dose and resulting in steady-state exposures (182–248 mg·h/L) lower than in adults (322 mg·h/L).[17] Considering the uncertainty in MIC determination, application of a dosing regimen with a lower dose, because it achieves the target for an MIC of 4.0 mg/L, may be hazardous. However, it appears that prolonged infusions running for 3 h of a dosing interval or longer are suitable with respect to the required dose and resulting exposure metrics in the typical patient (for an MIC of 4.0 mg/L).

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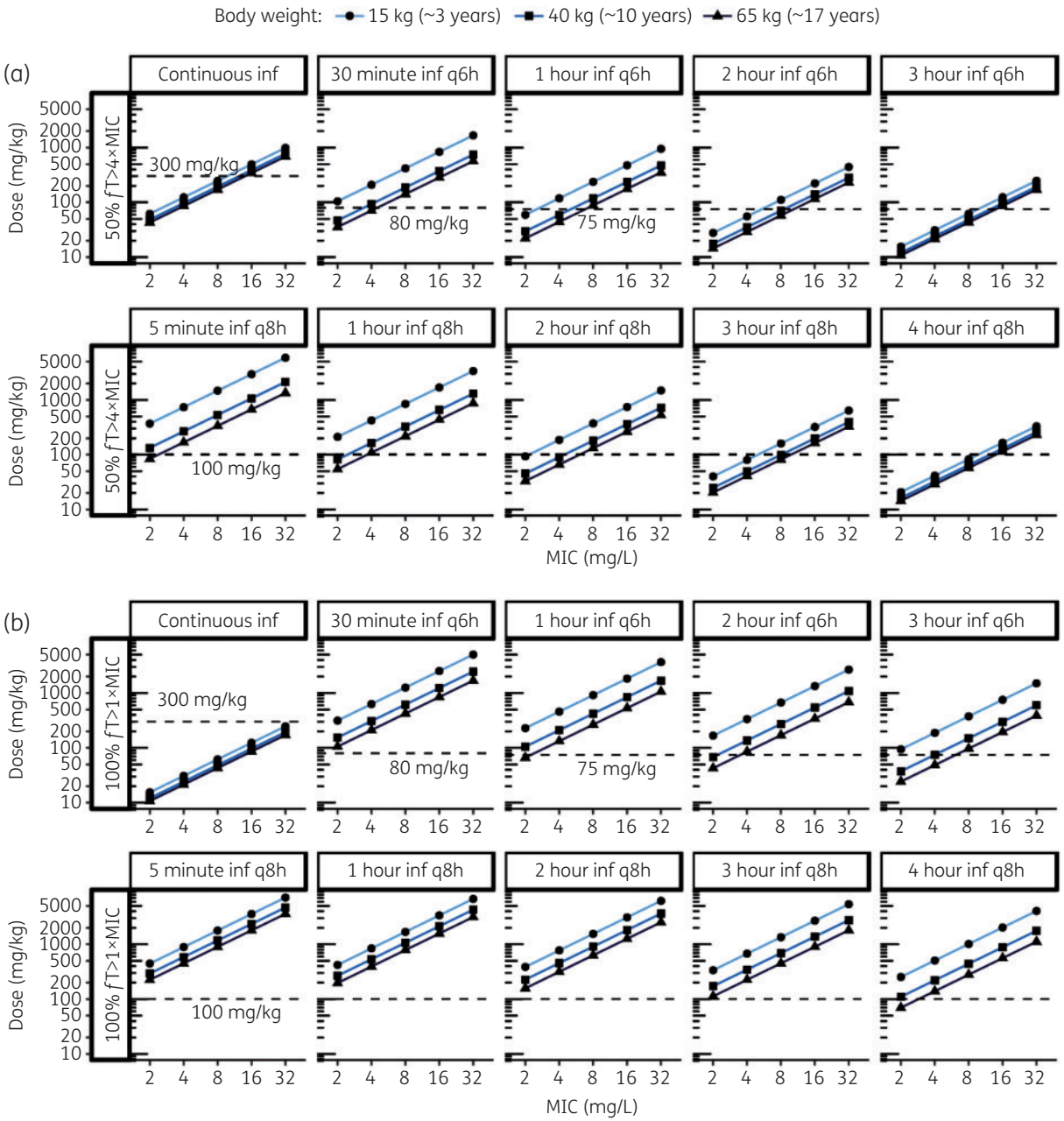

Figure 4. Relationship between the dose required (in mg/kg) to achieve a pharmacodynamic target of (a) 50% *f*T>4×MIC and (b) 100% *f*T>1×MIC at steady-state conditions, for a range of MICs. The relationship is shown for CI, SI given three times per day (q8h) and EI of various lengths given three or four times per day (q6h or q8h), for a typical patient with body weight of 15, 40 and 65 kg as indicated by the legend. The dashed horizontal lines indicate the typical dose for q6h (75 mg/kg/dose) or q8h (100 mg/kg/dose) dosing, or the licensed dose for children with febrile neutropenia (Summary of Product Characteristics, 80 mg/kg/dose given q6h as a 30 min infusion). inf, infusion. This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

In summary, there might be a wide difference in the dose required for achievement of various pharmacokinetic/pharmacodynamic targets. When the optimal target is uncertain, it is recommended to explore several targets and report associated measures of exposure (e.g. AUC and C_{max}) for selected dosing regimens.

Compared with previous models for piperacillin in critically ill children,[20–22,37] the current study population had samples from multiple dosing intervals and across hospital admissions according to a design that was optimized to quantify the $fT_{>MIC}$ more precisely. This quality of data may be higher than when collected from routine therapeutic drug monitoring, although the number of individuals in some age bands (especially young children) should have been higher. In comparison with a previous study in a similar population,[20] our analysis determined the free piperacillin concentration in samples and did not discard samples below the LLOQ. A potential limitation of the study is that tazobactam concentrations

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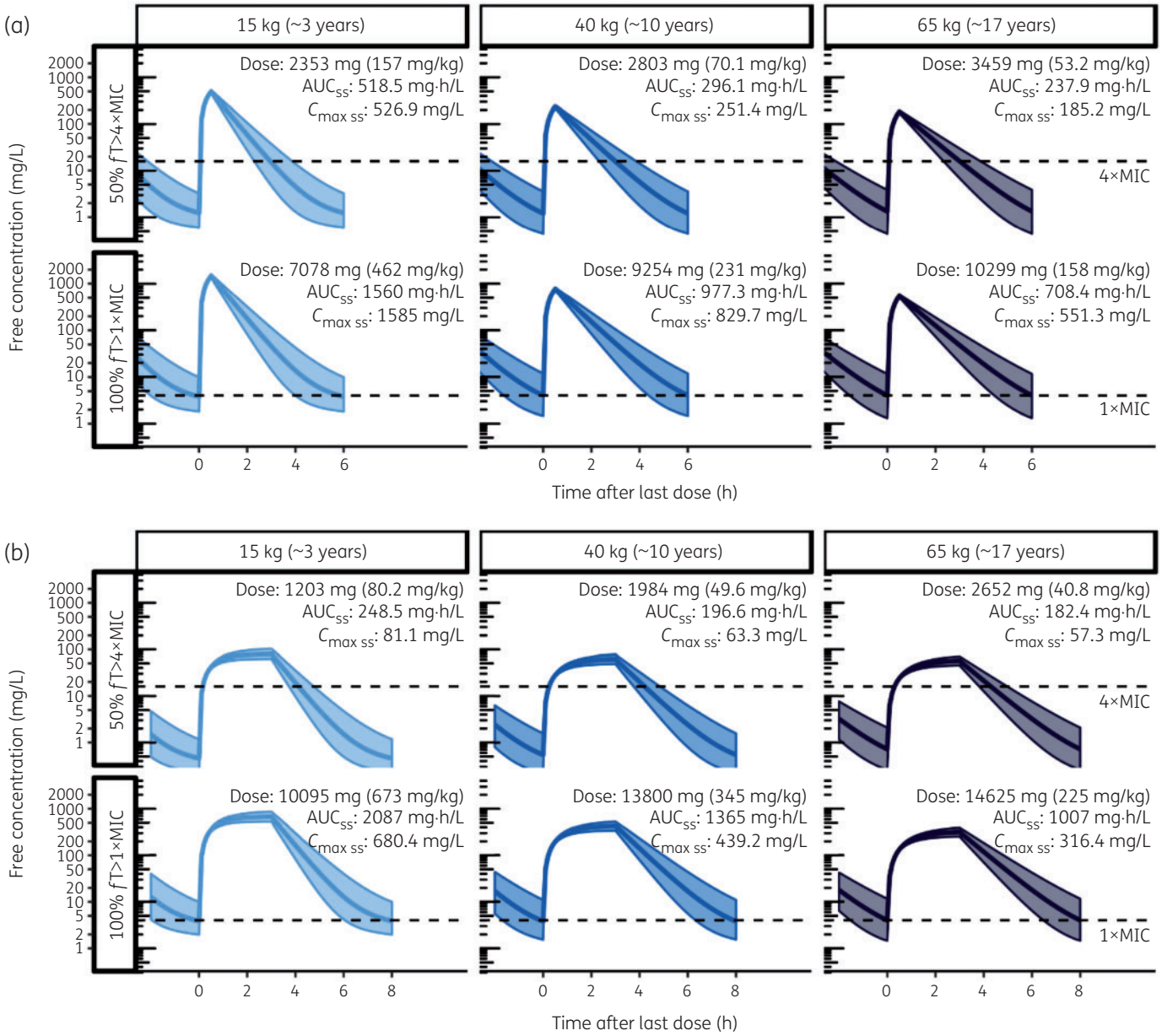

Figure 5. Overview of free concentration–time profile, AUC_{ss} and $C_{max,\ ss}$ for the dose required, at steady-state conditions for a typical patient with body weight of 15, 40 and 65 kg, to reach pharmacodynamic targets of 50% *f*T>4×MIC and 100% *f*T>1×MIC. The relationships are illustrated for two dosing regimens: (a) the Summary of Product Characteristics-recommended regimen for children with febrile neutropenia (30 min infusion given q6h); and (b) EI 3 h q8h (3 h infusion given three times per day). The panels show the median time course (thick line) and the 90% prediction interval based on the population pharmacokinetic model (shaded area). The dashed horizontal lines indicate the target concentration (for a pathogen with MIC of 4.0 mg/L, the MIC_{90}). This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

were not measured. Pharmacokinetic properties similar to those of piperacillin have been shown for tazobactam in critically ill children,[21,22] and as the reported estimates of piperacillin CL are similar (piperacillin CL of 13.4 and 15.4 L/h and tazobactam CL of 10.1 and 13.3 L/h at 70 kg), similar behaviour of tazobactam is expected in the current study population. Based on this and generally low *in vitro* IC_{50} for tazobactam,[41] the suggested dosing regimens are unlike to result in inadequate tazobactam coverage.

In conclusion, a population pharmacokinetic model was developed to describe free piperacillin in febrile children treated for cancer with chemotherapy. The model revealed the importance of body weight on the shape of the individual concentration–time profile and inadequate treatment of patients at lower body weights with respect to pharmacokinetic/pharmacodynamic target attainment. Through simulations from the model, the impact of pharmacokinetic/pharmacodynamic targets on the required

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dose in relation to MIC and exposure metrics was demonstrated. Administration by EI achieved a target of 50% *f*T>4×MIC for a reasonable range of doses, whereas the 100% *f*T>1×MIC target required higher doses for both SI and EI regimens, owing to the short $t_{1/2}$ of piperacillin, which can be overcome by administration via CI. However, for the target of 50% *f*T>4×MIC and high MIC values, CI performed similarly to prolonged infusions.

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Transparency declarations

None to declare.

Supplementary data

Appendix S1 is available as Supplementary data at *JAC* Online.

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