Population pharmacokinetics of piperacillin in febrile children receiving cancer chemotherapy
the impact of body weight and target on an optimal dosing regimen
Thorsted, Anders; Kristoffersson, Anders N.; Maarbjerg, Sabine F.; Schrøder, Henrik; Wang, Mikala; Brock, Birgitte; Nielsen, Elisabet I.; Friberg, Lena E.

Published in:
The Journal of antimicrobial chemotherapy

DOI:
10.1093/jac/dkz270

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

Document license:
CC BY-NG

Citation for published version (APA):
Thorsted, A., Kristoffersson, A. N., Maarbjerg, S. F., Schrøder, H., Wang, M., Brock, B., ... Friberg, L. E. (2019). Population pharmacokinetics of piperacillin in febrile children receiving cancer chemotherapy: the impact of body weight and target on an optimal dosing regimen. The Journal of antimicrobial chemotherapy, 74(10), 2984-2993. https://doi.org/10.1093/jac/dkz270
Population pharmacokinetics of piperacillin in febrile children receiving cancer chemotherapy: the impact of body weight and target on an optimal dosing regimen

Anders Thorsted¹, Anders N. Kristoffersson¹†, Sabine F. Maarbjerg², Henrik Schrøder², Mikala Wang³, Birgitte Brock⁴‡, Elisabet I. Nielsen¹ and Lena E. Friberg¹*

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

Received 10 February 2019; returned 23 March 2019; revised 22 May 2019; accepted 28 May 2019

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% \( f_{T.1} \% \text{MIC} \) and 50% \( f_{T.4} \% \text{MIC} \)) 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% \( f_{T.4} \% \text{MIC} \) 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% \( f_{T.1} \% \text{MIC} \) 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 \( f_{T.1} \% \text{MIC} \) pharmacokinetic/pharmacodynamic targets. Given the population pharmacokinetic profile, feasible dosing regimens with reasonable exposure are continuous infusion (100% \( f_{T.1} \% \text{MIC} \)) or prolonged infusions (50% \( f_{T.4} \% \text{MIC} \)).

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 x 10⁹ 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
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 ($t_{\text{MIC}}$). In neutropenic animals, bacteriostasis is reached for dosing regimens with 35%–40% $t_{\text{MIC}}$ and near maximal effect is achieved at 60%–70%.$^6$ Stricter targets of 100% $t_{\text{MIC}}$ or 50% $t_{\text{MIC}}$ are frequently used, with therapeutic effect assumed to increase and risk of resistance development to reduce. A common regimen is administration by a short bolus-like infusion (SI), but extended infusion (EI) and continuous infusion (CI) offer increased risk of resistance development to reduce. A common regimen is administration by a short bolus-like infusion (SI), but extended infusion (EI) and continuous infusion (CI) offer increased.$^6$ 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, weight, body height, and sex. $^{15}$ Reduced tissue penetration has also been reported, 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.$^{16}$ 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, weight, body height, and sex. $^{15}$ Reduced tissue penetration has also been reported, 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.$^{16}$ 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, weight, body height, and sex. $^{15}$ Reduced tissue penetration has also been reported, 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.$^{16}$ 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, weight, body height, and sex. $^{15}$ Reduced tissue penetration has also been reported, 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.$^{16}$ 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, weight, body height, and sex. $^{15}$ Reduced tissue penetration has also been reported, 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.$^{16}$ 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, weight, body height, and sex. $^{15}$ Reduced tissue penetration has also been reported, 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.$^{16}$ 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, weight, body height, and sex. $^{15}$ Reduced tissue penetration has also been reported, 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.$^{16}$ 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, weight, body height, and sex. $^{15}$ Reduced tissue penetration has also been reported, and more evidence of impact on clinical outcomes is required.

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 ($<0.5 \times 10^9$ neutrophils/L), severe neutropenia ($<0.1 \times 10^9$ 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®) 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 given a priori piperacillin pharmacokinetic model for febrile paediatric patients.$^{20}$ The optimization focused on providing information on the population pharmacokinetics and the individual $t_{\text{MIC}}$, 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, $t_{\text{MIC}}$ was mainly determined by the terminal elimination phase ($\beta$-parameter) and a design criterion was formulated that enabled sampling time optimization for maximized precision in both primary population pharmacokinetic parameters and the $\beta$-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), as described in detail previously.$^{26}$ 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) aided by Perl- Speaks-NONMEM and Prana.$^{28}$ Model parameters were estimated using the Laplacian method with interaction and M3 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
function values (OFVs), assuming that the OFVs follow a $\chi^2$ distribution (a $\Delta$OFV = −3.84 significant at $P=0.05$ for one additional parameter). Additionally, residual goodness-of-fit plots and visual predictive checks (VPCs) 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$\text{s}$, respectively.29 Screening of remaining covariates (age, GFR, sex, bacteriemia and neutropenia) was done on pharmacokinetic parameters by means of stepwise covariate modelling (SCM) 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 of the 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% $fT \geq 4 \times \text{MIC}$ (free piperacillin concentration maintained above four times the MIC for at least half of the dosing interval) and 100% $fT \geq 1 \times \text{MIC}$ (free piperacillin concentration maintained above four times the MIC for the entire dosing interval) were evaluated. Estimates of MIC$\text{so}$ and MIC$\text{so}$ 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 q6h, 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$\text{ss}$) and peak concentration (C$\text{max}$, 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 ($t_{1/2b}$ of 0.708 h and $t_{1/2b}$ 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 fewer 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 maturation31 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 $\theta_{CL}$ is the population estimate of CL, WT refers to body weight and PMA refers to postmenstrual age,34 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$\text{so}$ and MIC$\text{so}$ 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% $fT > 4 \times \text{MIC}$, CI and EI of 2 and 3 h (q6h) or 3 and 4 h (q8h) achieve the target for MIC$\text{so}$ (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% $fT > 1 \times \text{MIC}$
are 1.4–7.7 times larger than standard doses and, except for CI, none of the regimens achieves the target for MIC₉₀ (4.0 mg/L) for all studied body weights. Generally, to achieve 100% T₁/₂ > 1 × MIC, higher doses are required for corresponding MICs compared with ably low AUCₜₜ and Cₘₚₓₚₓ. 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% T₁/₂ > 4 × MIC and 100% T₁/₂ > 1 × MIC, respectively). These doses result in Cₘₚₓₚₓ below or up to 3-fold that observed following SI dosing (∼500 mg/L in Figure 3). For EI, the dose required for 50% T₁/₂ > 4 × MIC is below the standard 100 mg/kg/dose, resulting in reasonable peak concentrations and comparably low AUCₜₜ, whereas the doses required for achievement of 100% T₁/₂ > 1 × MIC are similarly high as for the licensed regimen, but with lower Cₘₚₓₚₓ.

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 m²)         | 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 MIC₇₀ (4.0 mg/L) with only a few observed concentrations > 4 × MIC₉₀, 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 dosage 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. Previously, one- and two-compartment models for piperacillin in critically ill children have been reported, but with rapid and more pronounced peripheral distribution. As the sampling design was based on one of these studies, 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 T₁/₂ at lower body weights due to the impact of allometric scaling illustrated and discussed previously, 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 and has been identified in adults, but...
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 sepsis25 (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/dose17 (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
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 $\frac{f_{T}}{1}$ up to an MIC of 32.0 mg/L, which is unsurprising considering the infusion is ongoing for 50% of the dosing interval. In our study, we assessed a stricter target of $\frac{f_{T}}{4}$, suitable in critically ill patients, in addition to the commonly applied target for piperacillin of $\frac{f_{T}}{1}$ up to 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 C₁ h/L) lower than in adults (322 mg C₁ h/L).

To achieve the target of 100% $\frac{f_{T}}{1}$, 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. The target of 50% $\frac{f_{T}}{4}$ is achieved at doses of 40–80 mg/kg for an MIC of 4.0 mg/L. This figure appears in colour in the online version of JAC and in black and white in the printed version of JAC.

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 MIC₉₀ (4 mg/L) and MIC₅₀ (2 mg/L) from internal data, and the assay LLOQ (0.5 mg/L).
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 $C_{\text{max}}$) for selected dosing regimens.

Compared with previous models for piperacillin in critically ill children,\textsuperscript{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 $f_{T>\text{MIC}}$ 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,\textsuperscript{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 were not quantified.

Figure 4. Relationship between the dose required (in mg/kg) to achieve a pharmacodynamic target of (a) 50% $f_{T>4\times\text{MIC}}$ and (b) 100% $f_{T>1\times\text{MIC}}$ 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.
were not measured. Pharmacokinetic properties similar to those of piperacillin have been shown for tazobactam in critically ill children, 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 IC50 for tazobactam, the suggested dosing regimens are unlikely 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...
dose in relation to MIC and exposure metrics was demonstrated. Administration by EI achieved a target of 50% FT→4×MIC for a reasonable range of doses, whereas the 100% FT→1×MIC target required higher doses for both SI and EI regimens, owing to the short t1/2 of piperacillin, which can be overcome by administration via CI. However, for the target of 50% FT→4×MIC and high MIC values, CI performed similarly to prolonged infusions.

Acknowledgements
Parts of the optimal design (Supplementary data) were presented at the European Congress of Clinical Microbiology and Infectious Disease, 2017 (Abstract P1188).

Funding
This work was partially funded by JPIAMR (2015-06826; Swedish Research Council).

Transparency declarations
None to declare.

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

References
1 Basu SK, Fernandez ID, Fisher SG et al. Length of stay and mortality associated with febrile neutropenia among children with cancer. C Clin Oncol 2005; 23: 7958–66.
2 Lyman GH, Michels SL, Reynolds MW et al. Risk of mortality in patients with cancer who experience febrile neutropenia. Cancer 2010; 116: 5555–63.
3 Lehnebrucker T, Phillips R, Alexander S et al. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. J Clin Oncol 2012; 30: 4427–38.
4 FreiRi Feld AG, Bow EJ, Sepkowitz KA et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52: e56–93.
5 Meckler G, Lindemulder S. Fever and neutropenia in pediatric patients with cancer. Emerg Med Clin North Am 2009; 27: 525–44.
6 Drusano GL. Antimicrobial pharmacodynamics: critical interactions of ‘bug and drug’. Nat Rev Microbiol 2004; 2: 289–300.
7 Huttner A, Harbath S, Hope WW et al. Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother 2015; 70: 3178–83.
8 Roberts JA, Kruger P, Paterson DL et al. Antibiotic resistance-what’s dosing got to do with it? Crit Care Med 2008; 36: 2433–40.
9 Roberts JA, Kirkpatrick CM, Roberts MS et al. First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. Int J Antimicrob Agents 2010; 35: 156–63.
10 Roberts JA, Kirkpatrick CM, Roberts MS et al. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother 2009; 64: 142–50.
11 Roberts JA, Roberts MS, Robertson TA et al. Piperacillin penetration into tissue of critically ill patients with sepsis–bocus versus continuous administration? Crit Care Med 2009; 37: 926–33.
12 Vardakos KZ, Voulgaris GL, Maiaros A et al. Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis 2018; 18: 108–20.
13 Oesterreicher Z, Minichmayr I, Sauermann R et al. Pharmacokinetics of doripenem in plasma and epithelial lining fluid (ELF): comparison of two dosage regimens. Eur J Clin Pharmacol 2017; 73: 1609–13.
14 Lortholary O, Lefort A, Tod M et al. Pharmacodynamics and pharmacokinetics of antibacterial drugs in the management of febrile neutropenia. Lancet Infect Dis 2008; 8: 612–20.
15 Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development. CPT Pharmacometrics Syst Pharmacol 2012; 1: e6.
16 Gin A, Dilay L, Karlowsky JA et al. Piperacillin-tazobactam: a β-lactam/β-lactamase inhibitor combination. Expert Rev Anti Infect Ther 2007; 5: 365–83.
17 Tornoe CW, Twyzerskij JJ, Imaisi MA et al. Optimising piperacillin/tazobactam dosing in pediatrics. Int J Antimicrob Agents 2007; 30: 320–4.
18 Sime FB, Hahn U, Warner MS et al. Using population pharmacokinetic modeling and Monte Carlo simulations to determine whether standard doses of piperacillin in piperacillin-tazobactam regimens are adequate for the management of febrile neutropenia. Antimicrob Agents Chemother 2017; 61: e00311–17.
19 Sime FB, Roberts MS, Warner MS et al. Altered pharmacokinetics of piperacillin in febrile neutropenic patients with hematological malignancy. Antimicrob Agents Chemother 2014; 58: 3533–7.
20 Cies JJ, Jain J, Kuti JL. Population pharmacokinetics of the piperacillin component of piperacillin/tazobactam in pediatric oncology patients with fever and neutropenia. Pediatr Blood Cancer 2015; 62: 477–82.
21 Nichols K, Chung EK, Knoderer CA et al. Population pharmacokinetics and pharmacodynamics of extended-infusion piperacillin and tazobactam in critically ill children. Antimicrob Agents Chemother 2016; 60: 522–31.
22 De Cock P, van Dijkman SC, de Jaeger A et al. Dose optimization of piperacillin/tazobactam in critically ill children. J Antimicrob Chemother 2017; 72: 2002–11.
23 Schwartz GJ, Muñoz A, Schneider MF et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009; 20: 629–37.
24 Nyberg J, Bazzoli C, Ogungbenro K et al. Methods and software tools for design evaluation in population pharmacokinetics-pharmacodynamics studies. Br J Clin Pharmacol 2015; 79: 6–17.
25 Andersen MG, Thorsted A, Storgaard M et al. Population pharmacokinetics of piperacillin in sepsis patients: should alternative dosing strategies be considered? Antimicrob Agents Chemother 2018; 62: e02306-17.
26 Obrrink-Hansen K, Juul RV, Storgaard M et al. Population pharmacokinetics of piperacillin in the early phase of septic shock: does standard dosing result in therapeutic plasma concentrations? Antimicrob Agents Chemother 2015; 59: 7018–26.
27 Beal SL, Sheiner LB, Boeckmann AJ et al. NONMEM 7.4.3 Users Guides. (1989-2018). Hanover, MD, USA: ICON Development Solutions, 2018.
28 Keizer RJ, Karlsson MO, Hooker A. Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol 2013; 2: e50.
29 Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 2001; 28: 481–504.
30 Bergstrand M, Hooker AC, Wallin JE et al. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J 2011; 13: 143–51.
Piperacillin population pharmacokinetics in febrile children

31 Rhodin MM, Anderson BJ, Peters AM et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr Nephrol* 2009; 24: 67–76.

32 Mahmood I. Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. *Clin Pharmacokinet* 2014; 53: 327–46.

33 Jonsson EN, Karlsson MO. Automated covariate model building within NONMEM. *Pharm Res* 1998; 15: 1463–8.

34 European Committee on Antimicrobial Susceptibility Testing (EUCAST). Clinical Breakpoints. http://www.eucast.org/clinical_breakpoints/.

35 Wahlby U, Jonsson EN, Karlsson MO. Assessment of actual significance levels for covariate effects in NONMEM. *J Pharmacokinet Pharmacodyn* 2001; 28: 231–52.

36 Cies JJ, Shankar V, Schlichting C et al. Population pharmacokinetics of piperacillin/tazobactam in critically ill young children. *Pediatr Infect Dis J* 2014; 33: 168–73.

37 Beranger A, Benaboud S, Urien S et al. Piperacillin population pharmacokinetics and dosing regimen optimization in critically ill children with normal and augmented renal clearance. *Clin Pharmacokinet* 2018; 58: 223–33.

38 Standing JF. Understanding and applying pharmacometric modelling and simulation in clinical practice and research. *Br J Clin Pharmacol* 2017; 83: 247–54.

39 Derendorf H, Dalla Costa T. Pharmacokinetics of piperacillin, tazobactam and its metabolite in renal impairment. *Int J Clin Pharmacol Ther* 1996; 34: 482–8.

40 Quinton MC, Bodeau S, Kontar L et al. Neurotoxic concentration of piperacillin during continuous infusion in critically ill patients. *Antimicrob Agents Chemother* 2017; 61: e00654-17.

41 Paukner S, Hesse L, Prezelj A et al. In vitro activity of LK-157, a novel tricyclic carbapenem as broad-spectrum β-lactamase inhibitor. *Antimicrob Agents Chemother* 2009; 53: 505–11.