Target attainment in beta-lactam antibiotic plasma concentrations in pediatric intensive care patients: achieving adequate target exposures?

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30-06-2023

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Abstract

Introduction: Infectious diseases are a common cause of admission to the pediatric intensive care unit (PICU). These critical severe illnesses are associated with a high morbidity and mortality, and an extended PICU stay. Early initialization of adequate treatment with antibiotics is crucial for optimizing survival and limiting PICU stay. Beta-lactam antibiotics are frequently used for the treatment of infectious diseases in the PICU. However, recent research has indicated that the current treatment strategy in the PICU leads to sub- or supra-therapeutic beta-lactam plasma concentrations. For this reason, the aim of this preliminary analysis is to analyze whether current antibiotic dosing regimens of frequently used beta-lactam antibiotics achieve adequate target attainment in PICU patients.

Methods: This prospective, observational, two-center pharmacokinetic and pharmacodynamics study was performed at two PICU departments in the Netherlands. We enrolled PICU patients treated with intravenous therapy of cefotaxime, ceftazidime, ceftriaxone, cefuroxime, flucloxacillin or meropenem. The primary endpoint was to determine the extent of plasma samples within the therapeutic window. Secondly, the percentage of unbound concentration above the minimum inhibitory concentration (MIC) at 100% of the dosing interval ($fT > MIC_{ECOFF}$ and $fT > 4x\ MIC_{ECOFF}$) was determined.

Results: A total of 68 patients contributing 174 antibiotic plasma samples were included in this analysis. We observed a wide variety in plasma concentrations for the various study antibiotics. We identified supra-therapeutic antibiotic concentrations for ceftazidime, ceftriaxone and flucloxacillin. However, in case of cefotaxime, cefuroxime and meropenem the pharmacodynamic target (PDT) of 100% $fT > MIC_{ECOFF}$ was not achieved in all samples. The percentage of plasma samples that achieved this target were respectively 91.89% for cefotaxime, 100% for ceftazidime, 100% for ceftriaxone, 65.22% for cefuroxime, 100% for flucloxacillin, and 73.81% for meropenem. Furthermore, when a PDT of 100% $fT > 4x\ MIC_{ECOFF}$ was used these percentages decreased further with an 1.8 – 2.8-fold percentage decrease in comparison with the target of 100% $fT > MIC_{ECOFF}$.

Conclusion: Current beta-lactam dosing regimens in PICU patients lead to a wide range of plasma concentrations. In this preliminary analysis, sub- and supra-therapeutic antibiotic exposures have been demonstrated. For ceftazidime, ceftriaxone and flucloxacillin relatively high plasma concentrations were observed. For this reason, therapeutic drug monitoring has to be considered for these beta-lactams in the PICU. Furthermore, desired PDT of 100% $fT > MIC_{ECOFF}$ did not get achieved in all plasma samples of cefotaxime, cefuroxime and meropenem. Applying a PDT of 100% $fT > 4x\ MIC_{ECOFF}$ was responsible for lower target attainment percentages. To conclude, there is a need to further investigate the relation between target attainment and clinical outcomes to assess if dosing of beta-lactams should be optimized for PICU patients.

Introduction

Infectious diseases, particularly sepsis, are a leading cause of pediatric admissions to the pediatric intensive care unit (PICU) (1, 2). It is demonstrated that 5.4% of PICU admissions are due to non-bloodstream infections and 12.9% are because of bloodstream infections (3). These critical severe illnesses are associated with a mortality rate up to 25% which may increase to 50% in case of existing comorbidities (1, 2). Additionally, health care-associated infections such as central line-associated bloodstream infections, ventilator-associated pneumonia, and catheter-associated urinary tract infections, arise commonly during PICU hospitalization while not initially present during admission (4). Early initialization of adequate treatment with antibiotics is crucial for optimizing survival and limiting PICU stay (5-7).

Beta-lactam antibiotics are frequently used antibiotics for the treatment of infectious diseases in the PICU. This group of antibiotics consists of penicillins, cephalosporins, monobactams, and carbapenems. The mechanism of action for these antibiotics is to inhibit the synthesis of the peptidoglycan layer of bacterial cell walls and have a time-dependent bactericidal effect. Hence the unbound plasma concentration needs to remain above the minimum inhibitory concentration (MIC) during treatment (8, 9). However, consensus about pharmacodynamic thresholds for beta-lactam antibiotics is lacking, resulting in doubts which values for target attainment should be used in daily clinic (10).

PICU patients are characterized by a complicated physiological state and altered pharmacokinetic parameters. For instance, administration of intravenous fluids may lead to an increased distribution volume. As a consequence of infection, fluid shifts from the intravascular compartment to the interstitial compartment can occur due to endothelial damage and capillary leakage. Other examples such as altered renal and liver function may result in modified drug clearance. Hypoalbuminemia due to severe infections may result in a change in unbound fractions (11). All these changes together may result in sub- or supra-therapeutic antibiotic exposure and as a consequence lead to therapeutic failure, toxicity, or enhance antibiotic resistance. In addition to the above-mentioned pharmacokinetic changes, PICU patients are often infected by less susceptible micro-organisms, making treatment more challenging (12). For this reason, it is a challenge to achieve appropriate antibiotic exposure in PICU patients.

Recent research has indicated that the current treatment strategy in the PICU leads to sub-therapeutic beta-lactam concentrations. A study by Cies et al. demonstrated that target attainment only occurred in 5% of critically ill pediatric patients (13). Another recent study by van der Heggen et al. has identified that 25.5% of patients achieved target attainment when applying a target of 100% $fT > MIC_{ECOFF}$ and only 7.6% in case of a target of 100% $fT > 4x\ MIC_{ECOFF}$ (14). A study by Hartman et al. has demonstrated that target attainment with cefotaxime was high for susceptible pathogens ($fT > MIC_{ECOFF}$ 95.6% and $fT > 4x\ MIC_{ECOFF}$ 91.2%) in contrast to less susceptible pathogens ($fT > MIC_{ECOFF}$ 55.1% and $fT > 4x\ MIC_{ECOFF}$ 14.7%) (15). Because of the above-mentioned observation, the likelihood to achieve target attainment in the PICU might be reduced.

As mentioned before, only a few other studies have identified target attainment of beta-lactams in PICU patients. In most of these studies the number of antibiotics that are included in the analysis are limited (14, 15). Or exclusion criteria are rigid, by which the analysis focusses on specific patient groups. For example, in the study by Cies et al. only PICU patients with sepsis who were on

extracorporeal therapy with extracorporeal membrane oxygenation (ECMO) or continuous veno-venous hemofiltration (CVVH) were included (13). Therefore, a large group of PICU patients that receive beta-lactam therapy are left out, by which no statements about target attainment can be made for the remaining part of PICU patients. For this reason, this study creates an more complete overview of target attainment in PICU patients for several beta-lactam antibiotics without strict exclusion criteria.

In order to further elucidate the current situation at the PICU, we aim to determine to what extent the unbound plasma concentrations of select beta-lactam antibiotics as observed in PICU patients are within the therapeutic window. Secondly, we will demonstrate to what degree target attainment is achieved during treatment.

Methods

Study design

This prospective, observational, two-center pharmacokinetic and pharmacodynamics (PK/PD) study was performed at the PICU department of the Sophia Children's Hospital Erasmus University Medical Center (EMC), Rotterdam and Wilhelmina Children's Hospital University Medical Center Utrecht (UMCU), Utrecht.

Study population and size

Patients admitted to the PICU treated with intravenous therapy of cefotaxime, ceftazidime, ceftriaxone, cefuroxime, flucloxacillin, or meropenem were included.

In order to be eligible for enrollment patients were:

- Aged <18 years
- Expected to receive intravenous antibiotic therapy of the target antibiotic >2 days
- Recruited within 36 hours after start of antibiotic therapy
- Written informed consent has been obtained from the patients or their legally authorized representatives

Potential subjects who met any of the following criteria were excluded:

- Written informed consent was not obtained
- Prematurity (<37 weeks)
- History of anaphylaxis for the study antibiotics
- Study antibiotics were stopped before sampling commenced
- Prophylactic treatment
- ECMO
- Hemodialysis (HD) or CVVH

A formal sample size calculation was not required because of the non-comparable study design. For this reason the sample size calculation was based on $fT > MIC_{ECOFF}$ pharmacodynamic target (PDT) prevalence of 60% (95% CI 52 – 68%), as has been found in a comparable performed study in adults in the intensive care unit (ICU) (9). For a sample size of 145 patients, it was estimated based on the results of the EXPAT study in adults, that 97 patients achieved PDT. Therefore, a number of 145 patients was anticipated to be sufficient (16). The study is still including patients, this thesis may be interpreted as a preliminary analysis.

Study procedures

In this study a daily screening was performed using the hospitals Electronic Patient File (EPF) HiX. PICU patients that received a study antibiotic were screened for eligibility by the inclusion- and exclusion criteria. Eligible patients or their legally authorized representatives were informed about the study to obtain informed consent. After informed consent, patients were registered and given a subject identification code (SIC).

Sample collection and analysis

To determine plasma concentrations of the study antibiotics a blood sampling strategy was used as shown in Figure 1. If an arterial catheter was in place for standard clinical care, a trough (t= 0) and

peak (t= 10 – 30 min) 250 – 500µl sample were drawn. Additionally, during routine morning lab sampling an extra sample was drawn for five consecutive days. For patients without an arterial catheter, blood was drawn by venipuncture or finger prick by standard of care procedures. Therefore, blood sampling times were completely dependent on routine lab sampling to prevent extra punctures. As a consequence, the blood sampling regimen was different for patients without arterial access. For all patients sampling stopped after the 7th sample, or if antibiotic treatment was ceased earlier. The exact sampling times were recorded during the study procedures.

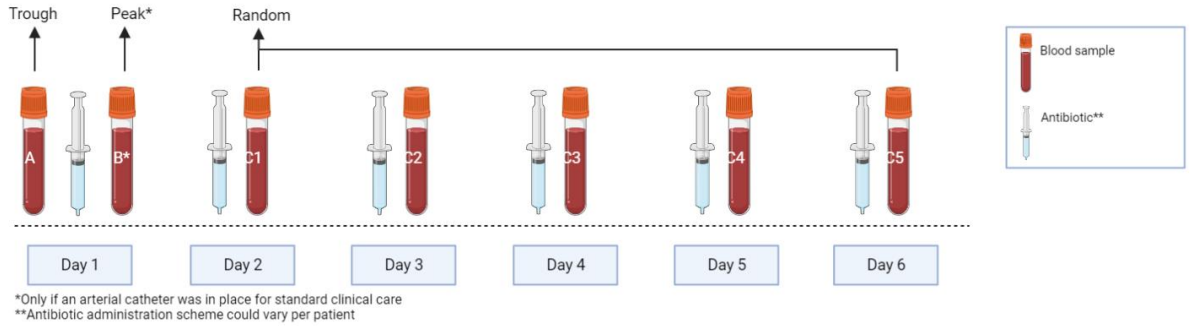

Figure 1: Blood sampling strategy

Blood samples were stored in the fridge at 2-8 °C. Subsequently, all samples were centrifuged at 3000 rpm for six minutes within 24 hours after collection. The plasma was transferred in cryo-vials for frozen storage at -80 °C until analysis. Plasma concentrations were determined by multi-analyte UPLC-MS/MS (17). The method was comprehensibly validated according to the Food and Drug Administration (FDA) guidance on bioanalytical method validation (18).

Primary endpoints

The objective of this study was to analyze whether current antibiotic dosing regimens of frequently used beta-lactam antibiotics achieve target attainment in PICU patients. For this analysis we used the plasma concentrations that were obtained after a minimum of an hour after administration of the study antibiotic to avoid inclusion of peak concentrations. In order to illustrate the target attainment, we aimed to determine the amount of plasma samples within the therapeutic window. The therapeutic window consisted of three different areas: a blue area (ƒC < MIC_{ECOFF}) that indicated a suboptimal exposure, a green area (ƒC = 1-10x MIC_{ECOFF}) that indicated the target exposure, and a red area (ƒC > 10x MIC_{ECOFF}) that indicated a threshold for supra-therapeutic exposure.

Furthermore, the percentage of plasma samples which did achieve the target of 100% (ƒT > MIC_{ECOFF} and ƒT > 4x MIC_{ECOFF}) was determined for all samples (16). For each of the antibiotics, the epidemiological cut-of (ECOFF) of the presumed pathogens was used i.e., the highest MIC for organisms devoid of phenotypically detectable acquired resistance mechanisms, as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (19). The following EUCAST epidemiological cut-of (MIC_{ECOFF}) values were used: cefotaxime 4 mg/L (*Staphylococcus aureus*), ceftazidime 4 mg/L (*Pseudomonas aeruginosa*), ceftriaxone 0.125 mg/L (*Enterobacterales*), cefuroxime 8 mg/L (*Escherichia coli*), flucloxacillin 1 mg/L (*Staphylococcus aureus*), and meropenem 2 mg/L (*Pseudomonas aeruginosa*). To assess the suitability of dosing regimens considering ƒT > MIC_{ECOFF} and ƒT > 4× MIC_{ECOFF}, a MIC distribution of 0.03125–128 mg/L was tested for target attainment of each of the study antibiotics.

Results

Patient characteristics

Overall, a total of 68 patients contributing 174 antibiotic plasma samples were included in this preliminary analysis. Baseline patient demographic data, antibiotic data, and clinical outcomes, are summarized in Table 1. The median postnatal age was 78 days and 60% of the participating PICU patients was male. The median PICU length of stay (LOS) was 13 days, and mortality rate was 6.2%. Clinical data of participating patients are summarized in Table 2, this data was extracted from patient files in HiX. The medians of important inflammatory markers were as follows: white blood cell count (WBCC) was 14 x10^9/L, and C-reactive protein (CRP) was 56 mg/L. The median albumin was 19 g/L, aspartate aminotransferase (ASAT) 67 U/L, alanine transaminase (ALAT) 37 U/L, urea 4 mmol/L, and estimated glomerular filtration rate (eGFR) was 84 – 87 mL/min/1.73 m^2 among participating PICU patients.

Table 1: baseline demographic characteristics, antibiotic data, and clinical outcomes

Characteristics		**All (n = 68)**
Demographic data		
Postnatal age (days)		78 [22, 1150]
Gestational age (weeks)		38.0 [36.4, 39.6]
Postmenstrual age (weeks)		43 [40, 50]
Sex (male/female)		
	Female	27 (40%)
	Male	41 (60%)
Length (cm)		60 [51, 131]
Weight (kg)		4 [3, 16]
BMI		14.4 [12.9, 16.8]
Comorbidities		
	Cardiovascular	12 (19%)
	Gastrointestinal	5 (7.8%)
	Respiratory	4 (6.3%)
	Skeletal	2 (3.1%)
	Other	3 (6.3%)
	None	38 (59%)
Surgery		
	Yes	5 (7.5%)
	No	63 (92.5%)
Use of vasopressors		
	Yes	27 (40%)
	No	41 (60%)
Use of concomitant antibiotics*		
	Yes	44 (65%)
	No	24 (35%)
Antibiotic data		
	Cefotaxime	10 (15%)
	Ceftazidime	1 (1.5%)
	Ceftriaxone	21 (31%)
	Cefuroxime	20 (29%)
	Flucloxacillin	2 (2.9%)
	Meropenem	14 (21%)
Clinical outcomes		
PICU LOS (days)		13 [6, 35]
28-day mortality		
	Alive	61 (94%)
	Decreased	4 (6.2%)

Values are presented as numbers (%), or median n [25%–75% interquartile range]. *BMI* body mass index, *PICU LOS* pediatric intensive care unit length of stay, calculated from the start of study antibiotic until PICU discharge

*One or more additional antibiotics

Table 2: clinical data of all patients included

Characteristics	All (n = 68)
Clinical data	
WBCC (x10^9/L)	14 [9, 18]
PCT (µg/L)	1 [0, 8]
CRP (mg/L)	56 [16, 126]
Albumin (g/L)	19 [15, 26]
Urea (mmol/L)	4 [3, 8]
ASAT (U/L)	67 [39, 373]
ALAT (U/L)	37 [24, 144]
Creatinine (µmol/L)	35 [22, 59]
eGFR (mL/min/1.73 m^2)	
Postnatal age < 1 year	87 [61, 115]
Postnatal age > 1 year	84 [29, 110]

Values are presented as median n [25%–75% interquartile range]. *WBCC* white blood cell count, *PCT* procalcitonin, *CRP* C-reactive protein, *ASAT* aspartate aminotransferase, *ALAT* alanine transaminase, *eGFR* estimated glomerular filtration rate, calculated with Schwartz formula for children >1 year and calculated with: normal creatinine value/measured creatinine value *100 for children <1 year

Beta-lactam plasma concentrations

Boxplots of observed unbound plasma concentrations illustrating the therapeutic window for several beta-lactams are shown in Figure 2. The blue area indicated a suboptimal exposure (ƒC < MIC_{ECOFF}), the green area indicated the target exposure (ƒC = 1-10x MIC_{ECOFF}), and the red area indicated a threshold for supra-therapeutic exposure (ƒC > 10x MIC_{ECOFF}). The plasma concentration ranges of the study antibiotics are demonstrated in Table 3. A large variability was observed in the plasma concentrations of the various beta-lactam antibiotics. Besides wide ranges of plasma concentrations, we identified high antibiotic concentrations that indicate a threshold for supra-therapeutic exposure for ceftazidime, ceftriaxone, and flucloxacillin. Meropenem, cefuroxime and cefotaxime showed good agreement with the proposed therapeutic window.

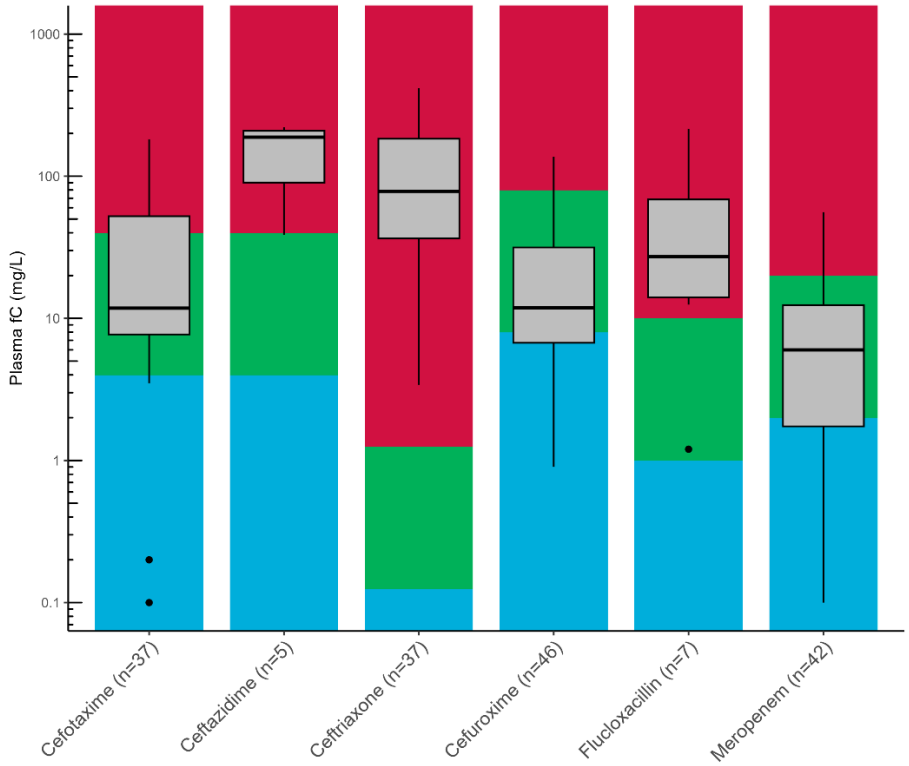

Figure 2: Boxplots (median, 25th and 75th percentiles) of unbound (ƒC) plasma concentrations observed in PICU patients treated with several beta-lactam antibiotics. The green areas indicate the target exposure (ƒC = 1-10 x MIC_{ECOFF}), the blue areas indicate suboptimal exposure (ƒC < 1x MIC_{ECOFF}), and the red areas indicate threshold for dose reduction (ƒC > 10x MIC_{ECOFF}). The numbers of samples (*n*) are presented per antibiotic

Table 3: minimum and maximum plasma concentrations of study antibiotics

Antibiotics	Samples (n)	Minimum (mg/L)	Maximum (mg/L)
Cefotaxime	37	0.1	181.6
Ceftazidime	5	38.7	221.8
Ceftriaxone	37	3.4	416.2
Cefuroxime	46	0.9	137.4
Flucloxacillin	7	1.2	215.4
Meropenem	42	0.1	55.8

Target attainment for several beta-lactam antibiotics to reach the PDTs of 100% ƒT > MIC_{ECOFF} and 100% ƒT > 4x MIC_{ECOFF} for a range of MICs (0.03125 to 128 mg/L) are shown in Figure 3. For ceftazidime and flucloxacillin a limited number of samples were included in this preliminary analysis. In case of cefotaxime, 91.89% of samples achieved a PDT of 100% ƒT > MIC_{ECOFF} when the current MIC value of 4 was applied. For cefuroxime, only 65.22% of samples achieved a PDT of 100% > ƒT MIC_{ECOFF} when the current MIC value of 8 was used. In case of meropenem 73.81% of samples achieved this target. For ceftriaxone, all samples achieved the above-mentioned target. Moreover, when a PDT of 100% ƒT > 4x MIC_{ECOFF} was used the percentages of samples of all study antibiotics that achieved target attainment decreased further. In this case, target attainment was not 100% for all study samples with an exception for ceftazidime. For cefotaxime, a 2-fold percentage decrease was observed when a PDT of 100% ƒT > 4x MIC_{ECOFF} was applied. For cefuroxime, adjustment of PDT to 100% ƒT > 4x MIC_{ECOFF} caused for a 2.8-fold reduction. Moreover, when looking at meropenem a 1.8-fold percentage decrease was illustrated when a 100% ƒT > 4x MIC_{ECOFF} PDT was used. An overview of the exact target attainment percentages for current MIC-values are demonstrated in Table 4. In the appendix S Table 1 and S Table 2 illustrate the exact percentages of samples that achieved PDT for the distribution of MIC values (0.03125–128 mg/L).

Table 4: Target attainment percentages for study antibiotics

Antibiotic	Samples (n)	Target attainment (%) if 100% ƒT > MIC_{ECOFF}	Target attainment (%) if 100% ƒT > 4x MIC_{ECOFF}
Cefotaxime	37	91.89%	45.95%
Ceftazidime	5	100%	100%
Ceftriaxone	37	100%	97.30%
Cefuroxime	46	65.22%	23.91%
Flucloxacillin	7	100%	85.71%
Meropenem	42	73.81%	40.48%

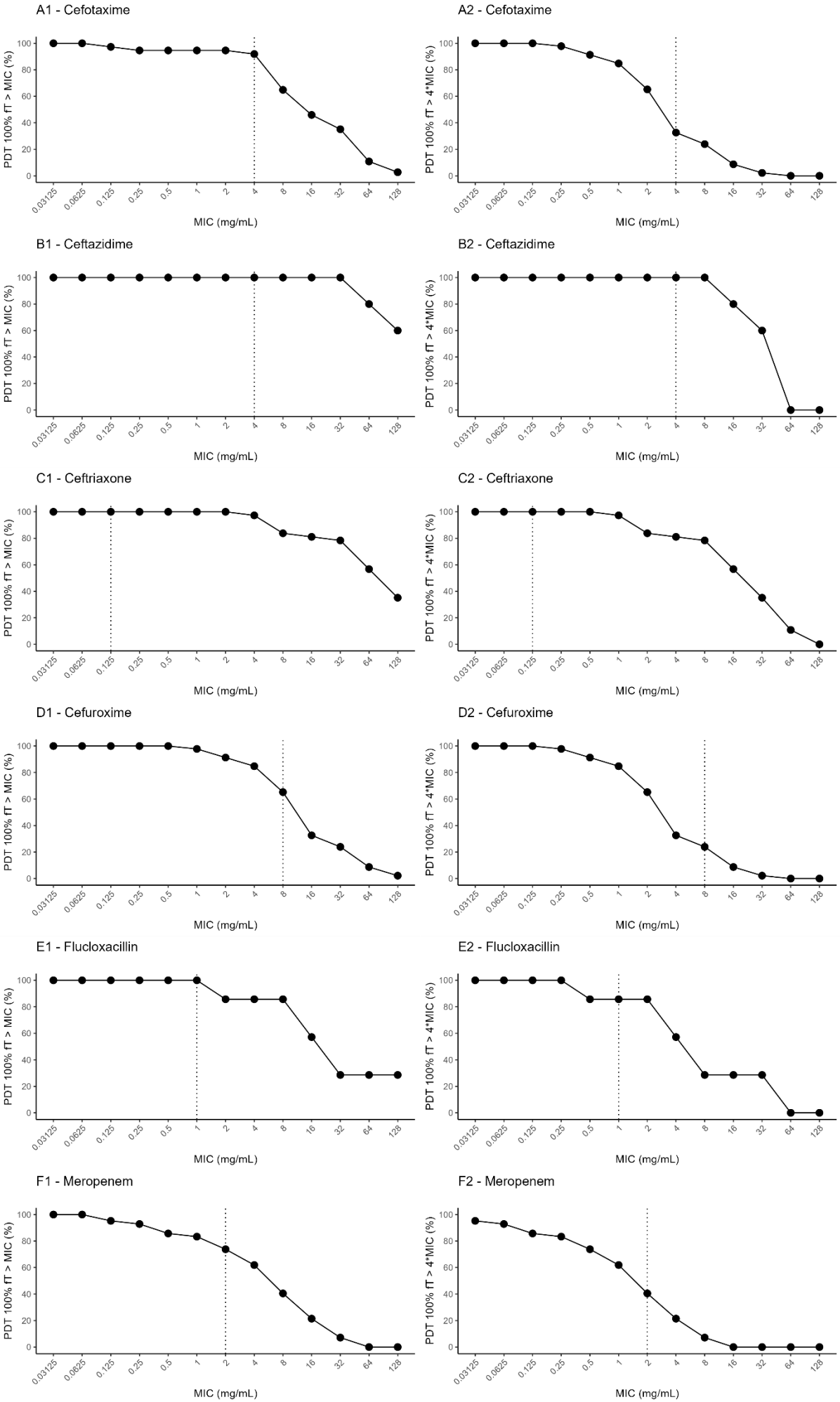

Figure 3: Target attainment in PICU patients for several beta-lactam antibiotics to reach a target of 100% ƒT > MIC_{ECOFF} (A1–F1) and 100% ƒT > 4 x MIC_{ECOFF} (A2-F2) for a range of MICs (0.03125 to 128 mg/L). The dotted horizontal line indicates the intercept with the EUCAST epidemiological cut-off (ECOFF) breakpoints: cefotaxime 4 mg/L (*Staphylococcus aureus*), ceftazidime 4 mg/L (*Pseudomonas aeruginosa*), ceftriaxone 0.125 mg/L (*Enterobacterales*), cefuroxime 8 mg/L (*Escherichia coli*), flucloxacillin 1 mg/L (*Staphylococcus aureus*), and meropenem 2 mg/L (*Pseudomonas aeruginosa*).

Discussion

In this preliminary analysis we describe to what extent the unbound plasma concentrations of several beta-lactam antibiotics as observed in PICU patients are within the therapeutic window. Secondly, we demonstrate to what degree target attainment is achieved for a range of MICs in this population. The plasma concentrations of different beta-lactams were variable in this study, and particularly high concentrations of ceftazidime, ceftriaxone, and flucloxacillin have been observed (Figure 2). Moreover, not all samples of cefotaxime, cefuroxime, and meropenem achieved target attainment when a target of 100% ƒT > MIC_{ECOFF} was applied. When a target of 100% ƒT > 4x MIC_{ECOFF} was as applied, the attainment percentages fell further (Figure 3). However, considering the small number of ceftazidime and flucloxacillin samples in this preliminary analysis, results for these antibiotics need to be interpreted with caution.

The laboratory values demonstrated in Table 2 could not be related to target attainment, since all patients' plasma concentrations were not assessed individually but pooled. Furthermore, laboratory values were complicated to interpret because of the difference in reference range per age group. Regardless of the mentioned variability in reference ranges in pediatrics, there were several observations in this population taking median postnatal age into account.

For example, the albumin reference range for newborns up to 15 days old is 25 – 46 g/L (20). When this range is compared with the albumin values in our study population, taking the median postnatal age into account, it can be concluded that the median albumin value was relatively low. This could indicate a hypoalbuminemia among part of the participating PICU patients in this study. Unbound plasma concentrations of drugs with a certain high protein bound fraction, such as ceftriaxone and flucloxacillin, can alter due to hypoalbuminemia. It is demonstrated that hypoalbuminemia increases the distribution volume and clearance of beta-lactams (21). An increased distribution volume may lead to a shift from the central compartment to the peripheral compartment in which the plasma concentrations can decrease. Moreover, an increase in drug clearance may as well result in a lower plasma concentration due to faster renal excretion. This statement is in contrast with our findings, as plasma concentrations of ceftriaxone and flucloxacillin were above the threshold for supra-therapeutic exposure. For a more precise understanding of hypoalbuminemia's effects on antibiotic exposure, it is necessary to determine protein bound plasma concentrations.

There were also disparities with other laboratory values. It has been shown that the creatinine and therefore eGFR reference values also differ in the first year of life (22). Analyzing the creatinine and eGFR medians indicate a normal kidney function among participating participants. Many patients admitted to the PICU display augmented renal clearance (ARC) (23). This is characterized by an increased physiological renal function due to enhanced renal perfusion and glomerular hyperfiltration. Possibly as a result of systemic inflammation, by which hemodynamic alterations such as vasodilatation, an increased cardiac output, and an enhanced renal blood flow might occur. Furthermore, administration of intravenous fluids and vasopressors may lead to a further increase in glomerular filtration. This may result in an enhanced drug elimination in case of renally excreted drugs by which sub-therapeutic antibiotic exposure could develop (23). Above-mentioned phenomenon was not in line with our results as relatively high beta-lactam concentrations were observed.

A study by Abdulla et al. in the adult ICU population has also identified a great variability in plasma concentrations (9). However, this study observed a large target non-attainment in the study population in which observed plasma concentrations were generally low. Remarkably, a part of plasma concentrations of ceftriaxone and ceftazidime samples were above the threshold for dose reduction which corresponds with our results in the pediatric population. Yet the observed plasma concentrations in the PICU population were in comparison with the adult population relatively high. For this reason, the results from the EXPAT study in adults cannot be extrapolated to pediatrics.

As demonstrated in Figure 2, high antibiotic concentrations of ceftazidime, ceftriaxone and flucloxacillin were observed. For this reason, it is possible that toxic effects were present in these patients. Common side effects of these study antibiotics are gastrointestinal effects, such as diarrhea, nausea and vomiting (24-28). Other uncommon but more severe toxic effects mentioned in previous adult studies are neurotoxicity and hematological side effects (29). Therefore, it is conceivable that these kind of toxic effects may occur in pediatric patients, especially with the noticed supra-therapeutic antibiotic exposures in this analysis. Because of the identified high concentrations, therapeutic drug monitoring (TDM) for these beta-lactams in pediatrics should be considered to minimize toxicity and antibiotic resistance.

However, despite of wide usage of MIC-based dosing, there is debate about the precision of MIC measurements. Firstly, MIC values are determined with in vitro tests. However, in vitro tests are not entirely representative for predicting the overall bacterial response in vivo (30). This is due to the fact that the concentrations in vivo are dynamic in contrast to in vitro and because of a biological variation within micro-organisms (30, 31). Secondly, the accuracy of MIC values is questionable due to a variation in laboratory assays caused by diversity in equipment and training in different laboratories (30).

Furthermore, as previously mentioned, consensus about the optimal PDT of beta-lactams is lacking (10). A recent review illustrated that a very wide range (40% *f*T> MIC_{ECOFF} to 100% *f*T> 6× MIC_{ECOFF}), of targets has been used in recent studies, demonstrating the lack of a general agreement (32). Wu et al. showed a target attainment of 95.6% for a PDT of 70% *f*T> MIC_{ECOFF} (33). Additionally, a recent study by Franzese et al. demonstrated a target attainment of >90% when a PDT of 50% *f*T> MIC_{ECOFF} was applied (34). These findings illustrate the ongoing debate about which targets are being applied since no clear target is established (13-15).

This analysis has some limitations that should be noted. Firstly, this is a preliminary analysis in which not the entire sample size could be assessed. Due to this reason for some study antibiotics (i.e, ceftazidime and flucloxacillin, there were comparatively less samples available compared to the other study antibiotics. Secondly, the target attainment analysis was performed with all samples with the exception of peak concentrations (samples obtained within one hour after antibiotic administration). This means that not only trough concentrations were used for the target attainment analysis causing the results to be skewed. Trough concentrations are more prone to reach levels below the MIC threshold. However, for this analysis samples within a range >1 hour after administration were assessed.

Thirdly, HD and CVVH are treatments that are quite frequently applied in the PICU and may enhance beta-lactam clearance due to their hydrophilic characteristics (35). Moreover, ECMO affects the PK of beta-lactam antibiotics in which clearance becomes less predictable (36-38) Additionally, including

premature neonates comes with several challenges due to their limit amount of blood volume in which the frequency of blood sampling have to be restricted to a minimum (39). This study excluded premature neonates and participates who were treated with HD, CVVH, or ECMO because of the expectation of not achieving sufficient sample size for these specific subpopulations. However, the exclusion of these subpopulations is a limitation because this results in missing a part of critically ill children with ECMO and HD, or CVVH. Moreover, the PK alterations in premature neonates are also lacking in this analysis.

Another limitation of this study was reliance on study logistics. Medical staff was accountable for appropriate storage of the plasma samples after collection. Correct storage of beta-lactam containing samples is essential due to instability of these drugs. A recent study by Bahmany et al. identified the stability of beta-lactams. According to this stability study, ceftriaxone, cefuroxime, and meropenem are stabile for 24 hours at room temperature. However, cefotaxime, ceftazidime, and flucloxacillin are stable for at least 24 hours in the fridge (40). Swift and correct storage conditions are required in order to assure sample stability.

Lastly, in this analysis, unbound antibiotic concentrations were measured and not the protein bound concentrations, a correction for protein binding was also not applied. The ratio of bound and unbound high protein binding drugs can be subject to changes, causing a shift to available free concentrations in case of hypoalbuminemia (41).

For future research, the effects of sub- or supra-therapeutic concentrations on clinical outcomes, for instance PICU LOS and mortality need to be further examined. After, the effects of TDM in combination with model-informed precision dosing (MIPD) on target attainment and clinical outcomes in pediatric patients should be investigated. The effects of above-mentioned interventions have been investigated in adult ICU patients in the DOLPHIN trial. This trial illustrated that this method had no significant difference on ICU LOS in comparison with the current antibiotic treatments without MIPD (42). However, this could be investigated in pediatrics to determine whether TDM with MIPD improves clinical outcomes.

Conclusion

To conclude, this preliminary analysis has demonstrated that current dosing regimens of beta-lactam antibiotics in the PICU lead to a wide range of plasma concentrations, often exceeding 10x MIC_{ECOFF}, especially for ceftazidime, ceftriaxone and flucloxacillin. Therefore, TDM has to be considered for these beta-lactams in this population to optimize treatment and prevent toxicity and antibiotic resistance. Additionally, stated pharmacodynamic targets were not achieved in all patients for cefotaxime, cefuroxime, and meropenem. For this reason, there is a need to further investigate target attainment in this population. Especially the relation between sub- and supra-therapeutic exposures on clinical outcomes needs to be further analyzed to determine the current risks concerning beta-lactam antibiotic dosing efficacy in the PICU.

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Appendix

S Table 1: Target attainment percentages with a MIC distribution of 0.03125–128 mg/L when a PDT of 100% ƒT > MIC$_{ECOFF}$ was applied

Antibiotic	0.03125 mg/L	0.0625 mg/L	0.125 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L	4 mg/L	8 mg/L	16 mg/L	32 mg/L	64 mg/L	128 mg/L
Cefotaxime	100%	100%	97.30 %	94.59%	94.59%	94.59%	94.59%	91.89%	64.86%	45.95%	35.14%	10.81%	2.70%
Ceftazidime	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	80%	60%
Ceftriaxone	100%	100%	100%	100%	100%	100%	100%	97.40%	83.78%	81.08%	78.38%	56.76%	35.14%
Cefuroxime	100%	100%	100%	100%	100%	97.83%	91.30%	84.78%	65.22%	32.61%	23.91%	8.70%	2.17%
Flucloxacillin	100%	100%	100%	100%	100%	100%	85.71%	85.71%	85.71%	57.14%	28.57%	28.57%	28.57%
Meropenem	100%	100%	95.24%	92.86%	85.71%	83.33%	73.81%	61.90%	40.48%	21.43%	7.14%	0%	0%

S Table 2: Target attainment percentages with a MIC distribution of 0.03125–128 mg/L when a PDT of 100% ƒT > 4x MIC$_{ECOFF}$ was applied

Antibiotic	0.03125 mg/L	0.0625 mg/L	0.125 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L	4 mg/L	8 mg/L	16 mg/L	32 mg/L	64 mg/L	128 mg/L
Cefotaxime	97.30%	94.59%	94.59%	94.59%	94.59%	91.89%	64.86%	64.86%	35.14%	10.81%	2.70%	0%	0%
Ceftazidime	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	60%	0%	0%
Ceftriaxone	100%	100%	100%	100%	100%	97.30%	83.78%	81.08%	78.38%	56.76%	35.14%	10.81%	0%
Cefuroxime	100%	100%	100%	97.83%	91.30%	84.78%	65.22%	32.61%	23.91%	8.70%	2.17%	0%	0%
Flucloxacillin	100%	100%	100%	100%	85.71%	85.71%	85.71%	57.14%	28.57%	28.57%	28.57%	0%	0%
Meropenem	95.24%	92.86%	85.71%	83.33%	73.81%	61.90%	40.48%	21.43%	7.14%	0%	0%	0%	0%