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REVIEW

Dose optimization of β-lactam antibiotics in children: from population pharmacokinetics to individualized therapy

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ABSTRACT

Introduction: β-Lactams are the most widely used antibiotics in children. Their optimal dosing is essential to maximize their efficacy, while minimizing the risk for toxicity and the further emergence of antimicrobial resistance. However, most β-lactams were developed and licensed long before regulatory changes mandated pharmacokinetic studies in children. As a result, pediatric dosing practices are poorly harmonized and off-label use remains common today.

Areas covered: β-Lactam pharmacokinetics and dose optimization strategies in pediatrics, including fixed dose regimens, therapeutic drug monitoring, and model-informed precision dosing are reviewed.

Expert opinion/commentary: Standard pediatric doses can result in subtherapeutic exposure and non-target attainment for specific patient subpopulations (neonates, critically ill children, e.g.). Such patients could benefit greatly from more individualized approaches to dose optimization, beyond a relatively simple dose adaptation based on weight, age, or renal function. In this context, Therapeutic Drug Monitoring (TDM) and Model-Informed Precision Dosing (MIPD) emerge as particularly promising avenues. Obstacles to their implementation include the lack of strong evidence of clinical benefit due to the paucity of randomized clinical trials, of standardized assays for monitoring concentrations, or of adequate markers for renal function. The development of precision medicine tools is urgently needed to individualize therapy in vulnerable pediatric subpopulations.

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Beta-lactam; therapeutic drug monitoring; toxicity; model-informed precision dosing; PK/PD; dosing optimization

1. Introduction

β-Lactams remain the most widely prescribed class of antibiotics in children across diverse health-care settings, from outpatient treatment for common childhood infections [1] to the management of life-threatening conditions in the pediatric intensive care unit [2]. Due to their broad antimicrobial spectrum, high efficacy and relatively low toxicity, empirical therapy is most common. All β-lactam antibiotics, which include penicillins, cephalosporins, monobactams, and carbapenems, exert their bactericidal activity through inhibition of cell wall synthesis via binding to penicillin-binding proteins [3]. Recent studies suggest that the release of DNA-damaging superoxides is an additional mechanism contributing to their bactericidal action [4]. This bacterial killing is time-dependent, meaning the pharmacokinetic/pharmacodynamic (PK/PD)-driver of efficacy is considered to be the percentage of the time that protein-free, active drug concentrations remain above the minimal inhibitory concentration (MIC) of the suspected pathogen throughout the dosing interval (% *f*T>MIC) [5,6]. There is no consensus on optimal PK/PD targets for β-lactams in adults or children; the suggested values range from 40% *f*T>MIC in non-critically ill patients to 100% *f*T >4×MIC in patients on the intensive care unit [7]. As β-lactams are small and hydrophilic molecules, their pharmacokinetics (PK) are characterized by a relatively low volume of distribution (Vd), mostly corresponding to the extracellular fluid space, and predominant renal clearance in unchanged form through glomerular filtration. Most β-lactams are characterized by low plasma protein-binding (1–20%) and short half-lives (1–2 h). Nevertheless, some specific β-lactam agents do exert relatively high protein binding rates (e.g. ceftriaxone, flucloxacillin, ticarcillin, temocillin, cloxacillin, oxacillin,

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Article highlights

- Antibiotic dosing in pediatrics is too often based on allometric scaling from the adult dose.
- Pharmacokinetics in children can be unpredictable, particularly in the youngest and the most severely ill.
- Therapeutic drug monitoring (TDM) of β-lactams is not performed in routine but may help to adjust the dose once the steady state has been reached.
- Defining the dose a priori based on model-informed precision dosing (MIPD) is a promising new approach, yet robust evidence for its clinical benefit remains lacking

cefazolin, cefoxitin, cefamandole, ertapenem) [8,9]. Despite their relatively broad therapeutic window and acceptable safety profile, β-lactam allergy and hypersensitivity remain a contra-indication to the use of these agents. Beta-lactam allergy is reported in 5–8% of the children in Europe and North America, and the associated maculopapular rash is estimated to affect less than 2% of the pediatric population [10,11]. Drug-related toxicities include acute kidney injury (i.e. piperacillin/tazobactam [12]), neurotoxicity (i.e. cefepime, imipenem [13]), and pseudolithiasis (i.e. ceftriaxone [14]). These risks are more important if high dosages are used [15].

Successful antimicrobial therapy relies not only on the choice of the correct antibiotic and timely administration but also on the appropriateness of the dosing regimen [16]. An ideal dosing regimen achieves drug exposure profiles capable of maximizing bacterial killing to cure the infection, whilst avoiding the risk for drug-induced toxicity and the emergence of antimicrobial resistance. However, optimizing dosing strategies in children is challenged by the limited availability of PK studies in pediatric populations. Many standard β-lactam regimens are still being based on extrapolation of data from adults, as most of these drugs were licensed long before regulations demanded PK studies in children [17]. However, directly scaling down pediatric doses from an adult based on weight (i.e. mg/kg) can be problematic and inappropriate for a number of reasons. Children undergo age-specific developmental changes in drug PK. These effects are the most pronounced in the youngest due to physiological immaturity of organs, systems, and metabolic pathways. Indeed, neonates and young infants typically show altered (i) oral drug absorption due to different gastric pH and stomach emptying time, (ii) volume of distribution due to lower plasma protein concentration and a higher body water composition, and (iii) elimination due to immature liver and renal function [18,19]. Compared to the term neonates, premature neonates show additional gestational age-dependent differences in drug PK and are at the highest risk for inadequate drug dosing and pharmacotherapy [20]. A key concern for optimal β-lactam dosing in neonates is their impaired renal clearance (due to immature glomerular filtration and tubular section), resulting in prolonged drug half-lives and increased systemic exposure [21]. In addition to these developmental changes, disease-related factors can further enhance PK variability in children. This is particularly true for critically ill children (of any age) on the Pediatric Intensive Care Unit (PICU), where critical illness-related pathophysiological changes, inflammatory status, and ICU-specific therapeutic interventions can significantly alter the PK of antibiotics and other commonly used drugs. A complete overview of these factors has been reviewed elsewhere [22]. A major challenge to adequate therapy using β-lactams with renal elimination in the PICU is the sudden and drastic changes in renal function that commonly occur during critical illness. Critically ill pediatric patients with Augmented Renal Clearance (ARC) rapidly eliminate β-lactams and show decreased plasma drug concentrations, in contrast to those with Acute Kidney Injury (AKI) who clear these agents at a reduced rate and experience increased systemic exposure [23].

Thus, one antibiotic dose does not fit all pediatric patients. In subpopulations where the inter- and interpatient variability is relatively limited, e.g. older children with mild infections, conventional dosing regimens adapted to age or weight can achieve therapeutic drug exposure for the majority of patients. However, in pediatric populations where PK is known to be unpredictable due to age-related or pathophysiological changes, e.g. newborns with sepsis, this approach may result in subtherapeutic exposure. This can potentially lead to treatment failure, the formation of drug-tolerant persister bacteria, or the acquisition of mutations associated with genotypic resistance. Conversely, supratherapeutic drug exposure can lead to drug-induced toxicity and side effects. Indeed, a recent prospective study among critically ill patients of various age groups showed that children were significantly less likely than adults to achieve PK/PD targets with standard antibiotic doses [24]. Another PK study on amoxicillin-clavulanic acid, piperacillin-tazobactam, or meropenem revealed that at least 65% of pediatric ICU patients receiving standard dosing regimens showed subtherapeutic drug exposure [23]. Clearly, this specific subpopulation would benefit greatly from a more individualized approach to dosing. This can be achieved through therapeutic drug monitoring (TDM), an approach that is a common practice for antibiotics such as aminoglycosides or vancomycin [25], but has only recently been gaining popularity for β-lactams in both adults and children [26–28]. However, conventional TDM is commonly performed once steady-state concentrations have been reached (which theoretically takes 4 to 5 times the half-life of the drug) before dose adaptation based on the results. As early initiation of the right drug at the right dose is critical to reduce morbidity and mortality in patients with severe infections (the 'golden hour' of antimicrobial therapy) [29], this means that such TDM-guided dose adaptations may come too late to result in major clinical benefits. 'Model-informed precision dosing' (MIPD) combines early (i.e. pre-steady state) TDM results with population PK models and individual patient information (age, weight, and renal function) to help predict the steady state drug concentrations and inform dose adaption if required to ensure timely initiation of adequate antibiotic treatment [30,31]. To date, scientific evidence that β-lactam TDM- and MIPD-informed precision dosing can lead to improved clinical outcomes is lacking. Nevertheless, a recent study in critically ill children receiving piperacillin-tazobactam showed a clear association between plasma drug concentrations measured during the first 24 hours of treatment and the risk for the onset of drug-associated acute kidney injury, indicating the potential of pediatric MIPD to reduce β-lactam toxicity [32].

In this review, we provide an overview of the population PK of β-lactam antibiotics and of the various dose optimization

strategies in children. The literature search for this review was performed during the period of March–September 2023 in the PubMed.gov database and included keywords related to the terms 'β-lactam' ('Beta-lactam,' names of the specific β-lactam agents listed in Table 1), 'pharmacokinetics' ('PK,' 'population pharmacokinetics,' 'pop-PK,' 'pharmacokinetics/pharmacodynamics,' 'PK/PD,' 'model,' 'exposure'), 'pediatric' ('child,' 'infant,' 'toddler,' 'neonate'), 'dose' ('regimen,' 'nomogram,' 'standard dose,' 'allometric,' 'dose optimization'), 'Therapeutic Drug Monitoring' and 'Model-Informed Precision Dosing' ('MIPD,' 'precision dosing,' 'individualized dosing'). We also share our expert opinion on the challenges and opportunities to implement β-lactam precision dosing for vulnerable pediatric subpopulations in the coming years.

2. Population pharmacokinetics of β-lactams in children

Population pharmacokinetic (pop-PK) modeling can be used to characterize drug PK, to understand the impact of specific covariates on PK and to determine the appropriate doses to achieve therapeutic drug exposure in pediatric patients. Until relatively recently, antibiotic PK data in children was mostly limited to drugs that are routinely monitored in clinical care, such as vancomycin and aminoglycosides. Yet over the past decade, many new studies focusing on β-lactams PK have become available. In Table 1, we provide a summary of current studies that have developed a pop-PK model for β-lactams in pediatric patients spanning all age groups, from neonates to adolescents. We excluded studies conducted exclusively in adults and those employing combined pop-PK models for non-β-lactam antibiotics or other drugs. Despite the identification of over 70 studies on β-lactam pop-PK in pediatrics [15], the data is notably limited compared to the relative wealth of information available for adults [109]. Through our literature review, we observed trends in pediatric PK data for β-lactams, including the (i) most commonly investigated drugs, (ii) study designs and analysis methodologies, and (iii) significant covariates.

First, regarding the studied β-lactam, most pop-PK models have been published for meropenem, next to piperacillin-tazobactam, cefepime, ceftazidime, and ceftriaxone. For the other β-lactam antibiotics, a limited number of models is available, often developed in smaller studies. No pop-PK models are available for a number of older (flucloxacillin, cefuroxime) and new β-lactams currently under development (ceftaroline, cefiderocol).

Second, regarding study design and data analysis, most studies were prospectively designed. Such a prospective design is desirable in pop-PK studies to collect sufficiently rich (e.g. area under the curve, AUC) PK data. Retrospectively studied routine TDM data mostly consist only of trough concentrations, which generally do not allow for detailed modeling and robust dosing simulations. Data from different PK studies is sometimes pooled to reach a larger sample size. Most studies were monocentric and only a minority took place in a multicenter setting, hence limiting their external generalizability. The study population spanned across all pediatric age groups, including neonates, infants, and adolescents. Several models have been developed in specific populations at risk for under- or overexposure, e.g. critically ill children, asphyxiated neonates, cystic fibrosis, and patients receiving extracorporeal support. PK/PD target attainment was commonly included alongside pop-PK analysis but was determined in very heterogenous ways for different studies (and is therefore not included in Table 1). Nevertheless, nearly all studies revealed poor target attainment, highlighting the need for improved dosing strategies across various pediatric populations.

Third and final, we identified the most important covariates in the published pop-PK models that indicate the major determinants for β-lactam exposure in children: renal function, maturational factors, body temperature, and extracorporeal support. All pediatric β-lactam pop-PK models include a fixed effect of body weight on Vd and CL (i.e. allometric scaling). Body weight was the only covariate to consistently affect Vd in children. Several covariates were consistently found to reduce interindividual variability (IIV) in CL. The renal function estimated based on the Revised Schwartz Formula is the most consistent covariate on CL for all β-lactam antibiotics and is retained in the pop-PK models of more than 20 independent studies [44–46,54,62–64,66–70,76,78,81,83,87,94,99,110]. Nevertheless, despite the predominant renal clearance of β-lactams, renal function appears to be less commonly retained in pediatric β-lactam pop-PK models than in adult ones. This is particularly the case in neonates, possibly due to the fact that the included body size descriptors capture the maturation of renal function to a larger extent than the traditional renal function markers which show limited sensitivity to changes in renal function in this patient population. Specific maturational factors, such as post-menstrual age, post-natal age, and gestational age, which are often retained in neonates and young children as significant covariates in CL may thus be more suitable to explain interpatient PK variability in this population than renal function. Other significant PK covariates that are mentioned in multiple studies are body temperature [36,42,69,111] and extracorporeal support system [52,66,80,81,85,99]. Whole-body hypothermia is known to increase β-lactam exposure by reducing renal elimination. The influence of lower body temperatures on exposure is especially prominent during the first post-natal days, as observed in asphyxiated neonates. Extracorporeal support (such as Extracorporeal Membrane Oxygenation (ECMO) or Renal Replacement Therapy (RTT) is also a known risk factor for altered drug exposure due to potential drug sequestration into the circuit and hemodilution due to circuit priming. Drug sequestration, leading to a higher clearance due to adsorption to the ECMO circuit, is mostly relevant for lipophilic drugs; hemodilution, leading to a higher volume of distribution, may be more relevant for hydrophilic drugs such as β-lactams [22].

3. β-lactam dose optimization strategies in children

Pop-PK models described in the previous section can be used to inform optimized dosing strategies in pediatric patients. Such strategies can take the form of fixed dose regimens or a simple dose stratification, based on one or a few covariates identified during pop-PK analysis. In case of extensive PK

Table 1. Summary of the available* β-lactam population pharmacokinetic studies performed in pediatric patients.

β-lactam antibiotic	Reference	Study design	Population and age range	Pop-PK method and model	Covariate effects
Amoxicillin	D'Agate et al. 2020 [33]	Retrospective using data from another trial	Neonates with sepsis ($n = 44$); 1-56 d	2-compartment model with allometric scaling	PNA on CL Sepsis on Vc Sepsis on Vp
	Wu et al. 2021 [34]	Prospective, monocentric, open-label study	Infants ($n = 47$); 0.09-2 yrs	NONMEM; 2-compartment model with first-order elimination and allometric scaling	None
	Tang et al. 2019 [35]	Prospective, multicentric study	Neonatal ICU patients ($n = 187$); 1-37 d	NONMEM; 2-compartment model with first-order elimination and allometric scaling	GA, and PNA on CL
	Bijleveld et al. 2018 [36]	Prospective multicentric study	Neonatal ICU patients ($n = 80$); 2-5 d	NONMEM; 2-compartment model and allometric scaling	PNA, Temperature, UO, and GA on CL
	Pullen et al. 2006 [37]	Prospective, monocentric study	Neonates ($n = 150$); 0-9 d	ANOVA; 1-compartment model with allometric scaling	None
	Charles et al. 1997 [38]	Prospective monocentric study	Low birthweight infants ($n = 40$); 1-3 d	NONMEM; 1-compartment model	CW and gentamicin use on CL
Amoxicillin-clavulanate	De Cock et al. 2015 [39]	Prospective, monocentric, open-label study	Pediatric ICU patients ($n = 50$); 0.08-15 yrs	NONMEM; Amoxicillin 3-compartment model with allometric scaling Clavulanic acid 2-compartment model with allometric scaling	Amoxicillin PMA, TM_{50}, Cystatin C and vasopressor use on CL Clavulanic acid PMA, TM_{50}, Cystatin C use on CL
Benzyl-penicillin	Kado et al. 2022 [40]	Prospective monocentric study	Pediatric patients ($n = 20$); 5-21 yrs	NONMEM; 2-compartment with allometric scaling	BMI cutoff of 26 kg/m^2 on T1/2
	Padari et al. 2018 [41]	Prospective monocentric study	Neonates ($n = 17$); NA	NONMEM; 2-compartment with allometric scaling	PMA on CL
	Bijleveld et al. 2018 [42]	Prospective multicentric observational study	Neonates with hypothermia ($n = 41$); 2-5 d	NONMEM; 2-compartment with allometric scaling	PNA, body temperature, GA and multiorgan failure on CL
Cefazolin	Schmitz et al. 2021 [43]	Pooled analysis of three prospective studies (healthy adults $n = 1$, children $n = 2$)	Healthy adults ($n = 24$) and pediatric patients receiving surgical prophylaxis ($n = 38$); 10-53 yrs	NONMEM; 2-compartment with linear elimination and allometric scaling	None
	Salvador et al. 2020 [44]	Prospective monocentric study	Critically ill children with MSSA infection ($n = 39$); 0.1-17 yrs	MONOLIX; 1-compartment with first-order elimination and allometric scaling	$eGFR_{Schwartz}$ on CL
	De Cock et al. 2017 [45]	Prospective monocentric study	Children undergoing cardiac surgery with CPB ($n = 56$); 6d-15 yrs	NONMEM; 2-compartment with first-order elimination plus an additional compartment for the effect of CPB, saturable protein binding and allometric scaling	$eGFR_{Schwartz}$ on CL Serum albumin on protein binding
	Schmitz et al. 2015 [46]	Prospective open-label multicentric study	Pediatric patients receiving surgical prophylaxis ($n = 12$); 10-12 yrs	NONMEM; 2-compartment with linear elimination and allometric scaling	$CrCl_{Schwartz}$ on CL
	De Cock et al. 2014 [47]	Posthoc analysis of a prospective monocentric study	Neonates ($n = 36$); 1-30 d	NONMEM; 1-compartment with saturable protein binding	Current body weight on Vd Birth body weight and PNA on CL Serum albumin on protein binding

(*Continued*)

Table 1. (Continued).

β-lactam antibiotic	Reference	Study design	Population and age range	Pop-PK method and model	Covariate effects
Cefepime	de Cacqueray et al. 2022 [48]	Two-center prospective study	Critically ill children ($n = 59$); 1.1 m-17.6 yrs		BW eGFR
	Al-Shaer et al. 2020 [49]	Pooled analysis of one pediatric and one adult study	Pediatric ($n = 36$) and adult patients ($n = 230$); 2.1 mos. −16.4 yrs (pediatric study)	Pmetrics; 2-compartment with allometric scaling	$eGFR_{Cockcroft\text{-}Gault}$ and age group (child/adult) on the total elimination rate constant
	Liu et al. 2020 [50]	Pooled analysis of four studies (3 in adults; 1 in children)	Hemato-oncological adults with febrile neutropenia ($n = 21$), critically ill adults ($n = 13$) and pediatric patients ($n = 36$); 22-82 yrs (adults); 2 mos −16 yrs (children)	Pmetrics; 2-compartment with allometric scaling	$eGFR_{Cockcroft\text{-}Gault}$ on the total elimination rate constant
	Zhao et al. 2020 [51]	Prospective open-label monocentric study	Neonates ($n = 85$); 1-25 d	NONMEM; 1-compartment with first-order elimination and allometric scaling	PMA and SCr on CL
	Zuppa et al. 2019 [52]	Prospective multicentric observational study	Infants supported by ECMO ($n = 17$); 1.3-22.2 mos	NONMEM;2-compartment with linear elimination and allometric scaling	CRRT on CL Blood transfusion on Vc
	Shoji et al. 2016 [53]	Pooled analysis of two studies	Pediatric patients ($n = 91$); 0.03-197.3 mos	NONMEM; 2-compartment with allometric scaling	PMA and SCr on CL GA on Vd
	Lima-Rogel et al. 2008 [54]	Prospective monocentric study	Neonates with severe hospital-acquired infection ($n = 41$); 6-58 d	NONMEM; 1-compartment with first-order elimination	BSA on V and CL $eGFR_{Schwartz}$ on CL
	Capparelli et al. 2005 [55]	Pooled analysis of two monocentric studies	Neonates ($n = 55$); 1-62 d	NONMEM; 1-compartment with first-order elimination	PNA on Vd SCr on CL
Cefotaxime	Hartman et al. 2022 [56]	Prospective monocentric study	Critically ill children ($n = 52$); 0.03-17.7 yrs	NONMEM; 2-compartment with allometric scaling	None
	Maksoud et al. 2018 [57]	Prospective monocentric study	Children with sickle cell disease ($n = 78$); 1.1-18.7 yrs	NONMEM; 1-compartment with first-order elimination and allometric scaling	Presence of acute chest syndrome on CL
	Béranger et al. 2018 [58]	Prospective monocentric study	Critically ill children ($n = 49$); 0.2-229 m	MONOLIX; 1-compartment with first-order elimination and allometric scaling	PNA on CL
	Leroux et al. 2016 [59]	Prospective open-label multicentric study	Neonates and young infants ($n = 100$); 0-69 d	NONMEM; 2-compartment with first-order elimination and allometric scaling	GA and PNA on CL
Ceftazidime	Van der Veer MAA et al. 2023 [60]	Prospective observational multicentric study	Asphyxiated neonates ($n = 35$); 2-5.3 d	NONMEM; 1-compartment with first-order elimination	PNA and body temperature on CL
	Li et al. 2021 [61]	Prospective open-label monocentric study	Neonates and young infants ($n = 146$); 1-81 d	NONMEM; 1-compartment with first-order elimination and allometric scaling	GA, PNA on CL
	Bui et al. 2020 [62]	Prospective open-label multicentric study	Critically ill children ($n = 188$); 28 d-12 yrs	NONMEM; 2-compartment with first-order elimination and allometric scaling	$eGFR_{Schwartz}$ and cystic fibrosis on CL
	Cojutti et al. 2019 [63]	Retrospective monocentric cohort study	Pediatric HSCT patients with febrile neutropenia ($n = 46$): 0.5-16 yrs	Pmetrics; 2 -compartment	$eGFR_{Schwartz}$ and BSA on CL Height on Vd
	Shi et al. 2018 [64]	Prospective open-label monocentric study	Infants ($n = 51$); 0.1-2y	NONMEM; 1-compartment with first-order elimination and allometric scaling	$eGFR_{Schwartz}$ on CL
	Wang et al. 2018 [65]	Prospective monocentric study	Neonates ($n = 43$); 0-60 d	NONMEM; 1-compartment	PMA on CL Body weight on Vd

(*Continued*)

Table 1. (Continued).

β-lactam antibiotic	Reference	Study design	Population and age range	Pop-PK method and model	Covariate effects
Ceftazidime-avibactam	Franzese R et al. 2021 [66]	Pooled analysis of Phase 1-2 trials ($n = 3$)	Pediatric patients (ceftazidime, $n = 154$; avibactam, $n = 153$); 3 mos −17 yrs	NONMEM; 2-compartment with first order elimination and allometric scaling	$eGFR_{Schwartz}$ on CL (>2 yrs) or PMA on CL (≤2 yrs) cIAI, HAP/VAP, ASN, CHN on CL (ceftazidime) cUTI, cIAI, HAP/VAP, ventilator, ASN, CHN, JPN on Vc (ceftazidime) ESRD, dialysis, cIAI, APACHE II on CL (avibactam) cIAI, cUTI, HAP/VAP, ventilator on Vc (avibactam)
Ceftolozane-tazobactam	Arrieta AC et al. 2020 [67]	Retrospective subgroup analysis of a Phase 1 trial	Hospitalized pediatric patients ($n = 18$, cystic fibrosis $n = 9$); 2-17 yrs	NONMEM; 2-compartment with first order elimination and allometric scaling	$eGFR_{Schwartz}$ on CL. Presence of infection on CL (tazobactam). Similar weight-normalized plasma PK parameters between CF and non-CF patients (ceftolozane).
	Larson KB et al. 2019 [68]	Retrospective subgroup analysis of a Phase 1 trial	Hospitalized pediatric patients (ceftolozane, $n = 31$; tazobactam, $n = 30$); 7 d-17 yrs	NONMEM; 2-compartment with first order elimination and allometric scaling	$eGFR_{Schwartz}$ on CL.
Ceftriaxone	Tang Girdwood et al. 2022 [69]	Prospective observational monocentric study	Critically ill children ($n = 184$); 1 mos-30 yrs (6.5% aged > 18y)	NONMEM; 2-compartment with allometric scaling	PMA, eGFR (Schwartz for children, CKD-EPI for > 18y), daily blood pH and daily highest temperature on CL
	Hartman et al. 2021 [70]	Prospective two-center study	Critically ill children ($n = 45$); 0.1-16.7 yrs	NONMEM; 2-compartment with and allometric scaling and a protein binding model with saturable protein binding	$eGFR_{Schwartz}$ on CL
	Wang et al. 2020 [71]	Prospective open-label monocentric study	Infants with community-acquired pneumonia ($n = 66$); 0.1-2 yrs	NONMEM; 1-compartment with first-order elimination and allometric scaling	Age on CL
	Khan et al. 2020 [72]	Prospective open-label monocentric study	Children with community-acquired pneumonia ($n = 99$); 2-11.7 yrs	NONMEM; 1-compartment with first-order elimination and allometric scaling	none
	Standing et al. 2018 [73]	Three-center open-label Phase II study	Infants and young children with severe acute malnutrition ($n = 81$); 2-45 mos	NONMEM; 3-compartment with allometric scaling and a Michaelis-Menten model for concentration and albumin-dependent protein binding	Edema on Vd Age-corrected serum creatinine Serum albumin on protein binding
	Blumer et al. 2005 [74]	Prospective monocentric study	Children planned for elective tonsillectomy ($n = 153$); 2-12 yrs	Nonparametric expectation maximization program; 2-compartment with concentration independent protein binding	NA
Imipenem	Dao et al. 2022 [75]	Retrospective single center study	Neonates in ICU ($n = 85$); 2.1-153 d	NONMEM; 1-compartment with allometric scaling	PNA, GA, SCr on CL
	Dong et al. 2019 [76]	Prospective single center open-label study	Children with hematological malignancies ($n = 56$); 2.03-11.83 yrs	NONMEM 2-compartment with first-order elimination and allometric scaling	Age and $eGFR_{Schwartz}$ on CL
	Yoshizawa et al. 2013 [77]	Retrospective study using raw data from other papers	Neonates ($n = 60$); 0-34 d	NONMEM 1-compartment with first-order elimination	None
			Children ($n = 39$); 3-16.2 yrs	NONMEM; 2-compartment with bi-exponential elimination	None

(*Continued*)

Table 1. (Continued).

β-lactam antibiotic	Reference	Study design	Population and age range	Pop-PK method and model	Covariate effects
Meropenem	Zyryanov et al. 2023 [78]	Retrospective/observational single center study	Preterm neonates ($n = 66$); NA	PMetrics package; 1- compartment with first-order elimination	$eGFR_{Schwartz}$, BW, PCA on T1/2 BW, PCA, on Vd
	Wu et al. 2022 [79]	Prospective multicentric study	Neonates ($n = 78$); 1-113 d	NONMEM; 1-compartment model with first-order elimination and allometric scaling	Age on CL
	Thy et al. 2022 [80]	Prospective, observational study	Pediatric ICU patients on CRRT ($n = 27$); Median [IQR] 4 [0-11] yrs	MONOLIX; 1-compartment model with first-order elimination and allometric scaling	Qeff on CL
	Wang et al. 2021 [81]	Prospective, monocentric, observational study	Pediatric patients with sepsis ($n = 25$); 0.71-3.88 yrs	NONMEM; 2-compartment model with first-order elimination and allometric scaling	$eGFR_{Schwartz}$ on non-CRRT CL
	Zylbersztajn, et al. 2021 [82]	Prospective, multicentric study	Children with ECMO ($n = 9$); 2 m-11y	PMetrics; 2-compartment model with first-order elimination	BW on Vc
	Yonwises et al. 2021 [83]	Prospective, open label, monocentric study	Critically ill infants ($n = 35$); 1.13-22.5 mos	NONMEM; 1-compartment model with first-order elimination and allometric scaling	$eGFR_{Schwartz}$ on CL
	Lima-Rogel et al. 2021 [84]	Prospective, monocentric study	Neonates admitted to NICU ($n = 30$); 5-28 d	NONMEM; 1-compartment model with first-order elimination	$eGFR_{Schwartz}$ on CL BSA and fluticasone on Vd
	Saito et al. 2020 [85]	Retrospective monocentric study	Critically ill children ($n = 34$); 0.03-14.6 yrs	Phoenix NLME; 2-compartment model with first-order elimination	$eGFR_{Schwartz}$, SIRS on CL CRRT on Vc
	Wang et al. 2020 [86]	Prospective multicentric open-label study	Critically ill children or infants with sepsis, meningitis, severe pneumonia ($n = 57$); 0.101-14.4 yrs	NONMEM; 2-compartment model with first-order elimination and allometric scaling	$eGFR_{Schwartz}$ on CL
	Rapp et al. 2020 [87]	Prospective monocentric study	PICU patients ($n = = 40$); 16.8-187.2 mos	MONOLIX; 2-compartment model with first order elimination and allometric scaling	$eGFR_{Schwartz}$ on CL
	Cies et al. 2017 [88]	Retrospective monocentric study	PICU patients ($n = 9$); 1-9 yrs	PMetrics; 2-compartment model with first order elimination	None
	Pettit et al. 2016 [89]	Prospective, multicentric, open label study	Pediatric cystic fibrosis patients ($n = 30$); 8-17 yrs	PMetrics; 2-compartment model with first-order elimination and allometric scaling	None
	Padari et al. 2012 [90]	Prospective open-label, multicentric study	Neonates given meropenem as short infusion ($n = 9$) or long infusion ($n = 10$); NA	NONMEM; 1-compartment model with allometric scaling	PMA on CL
	Smith et al. 2011 [91]	Prospective, multicentric study	Infants ($n = 200$); 1-92 d	NONMEM; 1-compartment model with first-order elimination	Albumin on Vd SCr and PMA on CL
	Ohata et al. 2011 [92]	Open-label phase 3 study	Pediatric patients ($n = 50$); 0-13 yrs	NONMEM; 2-compartment model with zero-order infusion and allometric scaling	None
	Ikawa et al. 2010 [93]	Retrospective with data pooled from different studies	Pediatric patients ($n = 40$); 0.2–14.8 yrs	NONMEM; 2-compartment model with allometric scaling	None
	van den Anker et al. 2009 [94]	Prospective multicentric study	Newborn patients ($n = 38$); 2-28 d	NPAG; 2-compartment model with zero-order infusion and first-order elimination	BW and $eGFR_{Schwartz}$ on CL $eGFR_{Schwartz}$ on Vc
	Bradley et al. 2008 [95]	Prospective single dose trial	NICU patients ($n = 37$); 1-61 d	NONMEM; 1-compartment model with first-order elimination	SCr and PCA on CL
	Du et al. 2006 [96]	Retrospective study collecting data from previous trials	Pediatric patients ($n = 99$); 0.08-17.33 yrs	NONMEM; 2-compartment model with allometric scaling	$eGFR_{Cockcroft-Gault}$ on CL
	Parker et al. 1995 [97]	Prospective multicentric trial	Pediatric patients ($n = 65$); 2 months-12 yrs	NONMEM; 2-compartment model with allometric scaling	CrCL and age on CL

(*Continued*)

Table 1. (Continued).

β-lactam antibiotic	Reference	Study design	Population and age range	Pop-PK method and model	Covariate effects
Piperacillin-tazobactam	Thy et al. 2022 [98]	Retrospective monocentric study	Pediatric patients undergoing CRRT ($n = 32$); 0.6-11 yrs	MONOLIX; 1-compartment model with first order elimination and allometric scaling	residual diuresis on CL
	Butragueño-Laiseca. et al. 2022 [99]	Prospective monocentric trial	Pediatric patients undergoing CRRT ($n = 32$); 3 months-15 yrs	NONMEM; 2-compartment model with allometric scaling	$eGFR_{Schwartz}$ and Height on renal CL Surface area of filter on CRRT CL
	Thibault et al. 2019 [100]	Prospective, open-label, monocentric study	Pediatric patient receiving extended PTZ infusions ($n = 89$); 2 mos –6 yrs	NONMEM; 2-compartment model with first-order elimination and allometric scaling	Piperacillin furosemide on CL Tazobactam furosemide on CL
	Thorsted et al. 2019 [101]	Prospective monocentric study	Pediatric patients with cancer or chemotherapy induced fever ($n = 43$); 1-18 yrs	NONMEM; 2-compartment model with first-order elimination and allometric scaling	
	Béranger et al. 2019 [102]	Prospective study	Pediatric patient with normal or augmented renal clearance ($n = 50$); 0.1-18 yrs	MONOLIX; 1-compartment model with first-order elimination and allometric scaling	eGFR on CL PELOD-2 score on Vi
	De Cock et al. 2017 [103]	Prospective monocentric study	Pediatric ICU patients ($n = 47$); 0.17-15 yrs	NONMEM; 2-compartment models with first-order elimination and allometric scaling	Piperacillin PMA and TM_{50} on CL Tazobactam PMA and TM_{50} on CL
	Nichols et al. 2016 [104]	Prospective monocentric study	Pediatric ICU patients receiving extended PTZ infusions ($n = 12$); 1-9 yrs	NONMEM; one-compartment models with zero-order infusion and first-order elimination and allometric scaling	Tazobactam sex on CL
	Cies et al. 2014 [105]	Prospective monocentric study	Pediatric oncology patients ($n = 21$); 3-10 yrs	PMetrics; 2-compartment model with first-order elimination and allometric scaling	None
	Cies et al. 2015 [106]	Prospective monocentric study	Pediatric ICU patients ($n = 13$); 9 mos-6 yrs	BigNPAG; 2-compartment model with first-order elimination and allometric scaling	None
	Li et al. 2013 [107]	Prospective monocentric study	Critically ill neonates ($n = 71$); mean (±SD); 0-61 d	NONMEM; 2-compartment models with first-order elimination and allometric scaling	Piperacillin PNA on CL Tazobactam PNA on CL
	Cohen-Wolkowiez et al. 2012 [108]	Prospective, multicentric, open label trial	Neonatal ICU patients ($n = 56$); 1-77 d	NONMEM; 1-compartment model with allometric scaling	SCr on CL

ASN: non-Chinese, non-Japanese Asian; BMI: Body-mass index; BSA: body surface area; BW: body weight; CHN: Chinese; cIAI : complicated intra-abdominal infection; CKD-EPI: chronic kidney disease- Epidemiology Collaboration; CF: cystic fibrosis; CL: Clearance; CrCL: Creatinine clearance; CRRT: continuous renal replacement therapy; CPB: cardiopulmonary bypass; cUTI: complicated urinary tract infection; CW: current weight; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; GA: gestational age; HAP/VAP: hospital-/ventilator-associated pneumonia; ICU: intensive care unit; JPN: Japanese; PCA: post-conception age; PMA: postmenstrual age; PNA: postnatal age; Q: intercompartmental clearance; Qeff: continuous renal replacement therapy effluent flow rate; SCr: serum creatinine; SIRS: systemic inflammatory response syndrome; TM_{50}: Maturation half-life; UO: urinary output; Vd: volume of distribution; Vc: volume of central compartment; Vp: Volume of peripheral compartment. *literature data collection: September 2023.

variability, covariate-based dosing may prove inadequate to achieve therapeutic drug exposure and attain pharmacological targets. In this case, a step-up toward more individualized and complex approaches, such as TDM-guided dosing and MIPD, may be warranted. An illustrative example of a complex clinical scenario where individualized β-lactam dosing proves beneficial is highlighted in a recent case report by Dumangin et al. Here, a preterm infant with impaired renal function suffering from a multi-drug resistant Enterobacterial bloodstream infection was safely and effectively treated with temocillin following a TDM-based dose adjustment [112].

3.1. Fixed dosing regimens

Historically, there were limited antibiotic PK/PD studies in children, and most β-lactam drug dosing regimens were empirically derived from adults on a milligram per kilogram basis. Most commonly, β-lactam compounds were licensed before the European Pediatric Regulation came into force, ensuring pediatric drug development for all new compounds. As a result, off-label and unlicensed antibiotic use ranged from 20% to 90% in children, depending on the pediatric subpopulation [113,114]. For those antibiotics with a dosing regimen in the drug label, the drug dosing regimens are decades old. If new PK/PD information becomes available, this is not regularly updated in the product label and is mostly dependent on the willingness of the Marketing Authorization Holder. In 2013, the Pediatric Committee published an inventory list of pediatric needs in different therapeutic areas for both off-patent and new medicinal products. In the list of antimicrobial classes, several penicillins, cephalosporins and carbapenems were listed [115]. As a result of off-label and unlicensed dosing, a large heterogeneity in β-lactam dosing regimens are used in clinical practice, as indicated in global antibiotic surveys [116–118]. Increasingly, national and international formularies are the main resource for pediatric drug dosing guidelines used in routine practice [119]. Most commonly, it is not clear from these formularies which references are used as a basis for guideline development. It also remains unclear whether the heterogeneity in these dosing guidelines is affecting antibiotic efficacy and safety in children.

Overall, a tendency toward intensified dosing for off-patent β-lactam antibiotics is observed over the years for a couple of reasons. Preliminary evidence indicates that subtherapeutic β-lactam exposure in children is also linked to therapeutic failure and the development of antimicrobial resistance [7,23,120]. Historical dosing regimens do not account either for the decreasing susceptibility of important pathogens or for the increasing importance of nosocomial infections often caused by difficult-to-treat bacteria typical of the hospital environment. In 2020, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) changed the definitions of susceptibility categories from one level of susceptible (S) and two levels of non-susceptible (Intermediate (I) and Resistant (R)) to two levels of susceptible (S = Susceptible, using a standard dosing regimen and I = Susceptible, Increased exposure) and one resistant [121]. This leads to the necessity of development of two dosing regimens for many β-lactam compounds: 'standard' dosing regimens and 'high' dosing regimens for infections with selected pathogens, which are only treatable when higher antibiotic concentrations are attained. A dosing table with dosing regimens for increased exposure in adults is currently available on the EUCAST website [122]. This table still requires translation into dosing and administration in children and a EUCAST task force is currently working on this item [123]. As is the case in adults on the ICU, augmented renal clearance in critically ill children has been linked to subtherapeutic drug exposure and a possible need for higher dosing [15,23]. Finally, β-lactam compounds are considered a broad therapeutic range drugs, despite toxicity thresholds not being well defined in children [13,26,124,125].

Since the European Pediatric Regulation came into force in 2007, more attention has been given to the development of pediatric dosing regimens for new β-lactams. As part of the regulatory submission, the European Medicines Agency specifically requires PK studies designed to achieve similar antibiotic exposure in children as in adults but accept efficacy to be extrapolated from adult studies [126]. Nevertheless, dosing requirements in special pediatric patient populations (e.g. preterm and term neonates, patients with augmented renal clearance or renal insufficiency) remain rarely provided (Table 2). Current strategies for the development of pediatric dosing regimens mainly focus on PK/PD target attainment. A mostly used approach to derive PK/PD optimized β-lactam dosing regimens is to perform stochastic Monte Carlo simulations. With this approach, individual concentration–time profiles are generated for 1000 to 10,000 simulated patients, using a previously developed PK model. Optimized dosing regimens for the whole population or subpopulations (e.g. increased or reduced renal clearance) are then selected using a probability of target attainment evaluation (PTA) with criteria for target PTA of minimum 90% against a predefined fT > MIC. Published therapeutic PK/PD targets for β-lactams in children range widely from ≥40% *f*T>MIC to 100% *f*T > 4×MIC [7,22]. Extended and continuous infusions and intermittent infusions, possibly using nomograms for different subpopulations (e.g. augmented renal clearance) have been suggested to maximize *f*T>MIC with the aim to improve efficacy [15]. An important practical issue related to prolonged or continuous infusion to optimize dosing strategies is that the patient should have a separate infusion line available for drug administration to avoid potential drug incompatibilities [132]. Pediatric patients often have limited intravenous access and receive most drugs by intravenous administration. Especially in children with minor illness and (immunocompromised) children with cancer, one single lumen central catheter is most commonly used for all intravenous drug administrations and blood sampling in order to prevent bacterial infection [133]. Peripheral venous access is not often available for the same reason. This dosing strategy also does not account for the large inter- and intra-patient variability in exposure over time that can occur in different pediatric subpopulations and, in most pediatric hospitals, fixed intermittent β-lactam infusions remain still the standard-of-care. More advanced dose optimization strategies seem necessary for further tailored treatment in children.

Table 2. Summary of pediatric drug dosing information in the summary of product characteristics (SPC) for newer β-lactam antibiotics.

Compound	Labeled pediatric indications	Labeled age categories	Dosing regimen for neonates available	Dosing regimen for renal insufficiency (CrCl ≤50 mL/min/1.73 m^2)	Dosing regimen for augmented renal clearance
Ceftazidime/avibactam [127]	• Complicated intra-abdominal infection • Complicated urinary tract infection • Hospital-acquired pneumonia, including ventilator-associated pneumonia	3 months-18 years	No	Yes. Dose adaptation scheme available for all ages from 3 months.	No
Ceftaroline [128]	• Complicated skin and soft tissue infections • Community-acquired pneumonia	Term neonates-18 years	Yes. 6 mg/kg every 8 hours (60 minute infusion time)	Yes. Dose adaptation scheme available for all ages from 2 years.	No
Ceftolozane/tazobactam [129]	• Complicated intra-abdominal infection • Complicated urinary tract infection • Acute pyelonephritis	Neonates >32 weeks and 7 days postnatal age to 18 years	Yes. 20/10 mg/kg every 8 hours (60 minute infusion time).	No	No
Meropenem-vaborbactam [130]	Data not available. The SPC states that 'Vaborem should not be used in children or adolescents under 18 years of age. This is because it is not known if the medicine is safe to use in these age groups.' A Pediatric Investigation Plan is available [131].				

3.2. Traditional therapeutic drug monitoring (TDM)-guided dosing

The main goal of TDM is to guide clinical dosing decisions to achieve optimal drug exposure in patients. In the past, antibiotic TDM primarily aimed at preventing toxicity of drugs with narrow therapeutic windows (e.g. aminoglycosides, vancomycin), particularly in critically ill patients. Today, its scope is broadened, encompassing the maximization of therapeutic efficacy across diverse antimicrobial agents and patient populations. Conventional antibiotic dosing regimens in pediatric patients are determined by factors such as body weight, age, or nomograms and adjusted for renal function when necessary. This approach can be suboptimal and insufficient to reach predefined PK/PD target values. For certain antibiotics, TDM is routinely employed to enhance the attainment of pharmacological targets, thereby minimizing therapeutic failure and potential toxicity. The method finds particular relevance for drugs with narrow therapeutic indexes or complicated PK profiles. Its appliance for β-lactam antibiotics, which are often used empirically and considered relatively safe, is limited to date [134]. Based on the Surviving Sepsis Campaign, an effort has been put in to extend the infusion times and apply TDM for β-lactam antibiotics. This strategy is particularly crucial for managing critically ill patients, as it aims to mitigate the impact of pathophysiological alterations induced by the severity of the illness. Furthermore, it addresses the significant variability in drug exposure observed in this patient group, thereby facilitating a more balanced and effective approach to antibiotic therapy [135].

Although the toxicity profile of β-lactam antibiotics is generally considered mild, there is emerging evidence to support the utility of monitoring for potential toxicities associated with the upper ranges of drug exposure. Specifically, piperacillin-tazobactam has been documented to exert nephrotoxic effects, as corroborated by a recent study where 16 out of 107 evaluated patients were classified as potentially experiencing piperacillin-associated acute kidney injury [32]. This risk appears significantly increased in combination with vancomycin [136]. In addition, carbapenems, particularly imipenem and panipenem, are considered the most nephrotoxic beta-lactams. Consequently, they are used in combination with an Organic Anion Transporter (OAT)-inhibitor (such as the renal dehydropeptidase inhibitor cilastatin or betamipron) to limit their internalization in renal tubular cells [137,138]. Moreover, a recent case report highlighted the role of increased ceftriaxone concentrations in serum and cerebrospinal fluid in an (adult) patient with ceftriaxone-associated encephalopathy [139]. Ceftriaxone, like cefazolin, is also known to cause biliary pseudolithiasis, particularly in children. Concerning the neurotoxic risk of β-lactam antibiotics, their pro-convulsant effects, especially with cefazolin and cefepime, should be noted [140]. Overall, these findings highlight the susceptibility of particular risk groups to adverse drug reactions, advocating for the implementation of TDM as a proactive measure to mitigate toxicity risks in these vulnerable cohorts.

The lack of widespread implementation of β-lactam TDM in the adult population as standard-of-care stems from multiple interconnected factors [141]. The main obstacle is of a scientific nature: the evidence that TDM-based dosing results in improved clinical outcomes over standard dosing strategies is very limited, in particular in the field of pediatrics. Related to this, it remains unclear which specific pediatric subpopulations would benefit most from such individualized approaches to dose optimization. Practical barriers, including the lack of commercial assays and technical challenges like the need for specialized equipment, limit accessibility. Educationally, the lack of awareness and training among health-care providers creates resistance, while economic

constraints, such as cost and uncertainty about cost-effectiveness, further deter its implementation. For pediatrics, more population-specific barriers need to be addressed. Implementation of TDM for the smallest youngsters may be challenging due to the impact of blood draws on volume depletion and the invasive burden, especially crucial in critically ill patients based on their physical condition. Additionally, local laboratories should have the most optimal assays which require limited blood volume for quantification.

3.3. Model-informed precision dosing (MIPD)

Optimal pharmacotherapy for critically ill patients should ideally be initiated as soon as possible, taking advantage of the 'golden' window within the first few hours after hospitalization to ensure adequate exposure. Model-Informed Precision Dosing (MIPD) is an advanced approach that blends population pharmacokinetic (popPK) modeling with TDM, applying Bayesian principles to assess drug PK. This allows for the potentially needed modification of drug dosages both prior to and during treatment, ensuring tailored therapy for each patient. In contrast to traditional TMD-guided dosing, MIPD provides the opportunity to *a priori* determine an individualized dosing regimen based on patient characteristics, such as age, weight, and renal function, even without blood sampling. Moreover, it provides *a posteriori* guidance in dose optimization based on individualized PK profiles. In the *a posteriori* phase, sparse sampling may be used to inform the patient's model, an especially practical approach in the pediatric population due to constraints in blood volume [142]. Table 3 provides an overview of all the approaches with their respective pros and cons.

To the authors' knowledge, no research investigating the application of MIPD for β-lactam antibiotics in the pediatric population has been published. Conversely, for vancomycin, multiple MIPD studies are available, mainly due to its frequent application as a first-line treatment for Methicillin-resistant *Staphylococcus aureus* (MRSA) treatment and its linear exposure and nephrotoxicity relationship [144,147,148]. These studies reveal that MIPD can result in better antibiotic exposure, enhance efficacy, and minimize toxicity. However, in the adult population, MIPD of β-lactams in critically ill patients has yielded limited insights. For instance, patients with a SOFA-score <8 exhibited an increased ICU length of stay yet demonstrated lower 28-day mortality [149]. Building upon these findings, using pediatric-specific assessment tools such as the Pediatric Logistic Organ Dysfunction (PELOD) score [150], could help identify pediatric subgroups that might benefit from MIPD-guided dosing. Nonetheless, targeted research efforts are required to validate the applicability and efficacy of such approaches within the pediatric context.

Moreover, MIPD presents a potential method for tailoring antibiotic treatment in pediatric patients and may provide clinical benefits eventually leading to better clinical outcomes. However, additional studies, particularly concerning β-lactams, are essential to validate its clinical relevance and cost-effectiveness, addressing the challenges hindering its widespread adoption.

Table 3. The pros and cons of the different approaches toward dose optimization of β-lactam antibiotics in the pediatric population.

Approach	Pros	Cons
Body weight/ nomograms	Readily application/accessible and simple	Limited subpopulation dosing regimens available, may not account for patient's characteristics, less precise
	Suitable for Low- and Middle-Income Countries	Sharp age range cutoffs
		Pre-defined PK targets which may not be universally applicable to all ICU patients
Therapeutic drug monitoring (TDM)	Trough sampling sufficient to determine PTA (%T > MIC)	Steady-state intervention, no acute phase correction of dosing ('golden hour')
		Prone to inter-clinician/country/institution variability in dosing recommendations
		Blood concentrations do not reflect concentrations site of infection
Model informed precision dosing (MIPD)	First time right (*a priori*) dosing	How to select the right model? [143]
	Integration of patient characteristics in model for individualized approach	PopPK Model availability
	Ideal for sparse, time flexible blood sampling	Expertise (education and training) required to work with MIPD software tools – available staff ((clinical) pharmacists)
	Real-time integration of patient data from Electronic Health Record (EHR)	Risk of extrapolation/generalizing of popPK models
	Use of MIC_{ecoff} of the presumed pathogen (local drug resistance epidemiology)	Models without incorporation of inflammatory biomarkers
	Flattening priors to allow for more extreme PK parameter estimation [144]	Model validation available
	Update model with collected data ('(continuous) Learning model') [145]	No evidence of improved clinical outcomes/cost effectiveness for MIPD
	Weighting of data (constant altering patient physiology) [15,146]	Limited access to (timely) β-lactam TDM services
	Knowledge-sharing between institutions which have implemented MIPD of β-lactam antibiotics	
	Identify subpopulations which may benefit from MIPD	
	Model averaging to prevent subpopulation/heterogeneity bias	

4. Conclusion

β-Lactam antibiotics are widely prescribed in pediatric care due to their broad antimicrobial spectrum, high efficacy and relatively low toxicity. Many popular β-lactams were patented in 1950–1980s, long before regulatory authorities such as the EMA demanded PK studies in children to allow market access (2007). Consequently, pediatric doses were extrapolated from the adult PK data and off-label use remains common. Today, the increased availability of pediatric PK data, mainly through academic efforts, has led to updated dosing guidelines for β-lactams in (inter) national pediatric formularies and SmPCs. 'Standard' dosing practices in these documents adjust the dose based on the child's weight or age. Less commonly, dosing is also adapted based on renal function, a key co-variate in the majority of β-lactam pop-PK models because most of these drugs are almost exclusively eliminated by the kidneys. Such standard doses suffice to successfully treat most children in community, ambulatory, and non-ICU hospital settings, because most of the infections are mild and the drug PK is predictable. However, this 'one dose fits all' strategy falls short in specific pediatric subpopulations, such as newborns or children in the PICU, who typically suffer from more severe infections and show significantly altered, highly variable PK. The TDM of β-lactams in these vulnerable patients, which is increasingly explored in critically ill adults today, could help to achieve PK/PD targets and optimize dosing. A limitation of conventional TDM, next to bioanalytical, technical, and practical challenges, is that TDM is often initiated in a post-steady state, which means that the critical 'golden hour' of early antimicrobial therapy is missed and dose adjustment is delayed. MIPD emerges as a promising frontier that combines patient-specific TDM, biochemical, microbiological, and clinical data with population PK models to provide timely recommendations for dose adaptations. Though current evidence supporting its impact on clinical success remains weak (non-RCT data) and restricted to adults, TDM/MIPD may present an opportunity for tailored β-lactam dosing to optimize therapeutic efficacy and safety in critically ill neonates and children in the future.

5. Expert opinion

As children show higher PK variability than adults for many drugs, including for β-lactam antibiotics, pediatric PK studies to identify the determinants that can explain inter- and intrapatient variability in drug exposure are essential to guide the design of optimal dosing regimens. We identified some significant shortcomings and gaps in currently available research, including small sample sizes, significant underrepresentation of (preterm) neonates and critically ill pediatric patients, and limited external validity of the available population PK models for β-lactams. As is the case in adults, the optimization of β-lactam therapy in children is also hampered by a lack of consensus about PK/PD targets linked to improved clinical outcomes and the absence of validated biomarkers to assess renal function, (nephro)toxicity, and efficacy. To address these gaps in current research, there is an urgent need for larger PK studies that pool data from multiple clinical centers. Such trials should include understudied pediatric populations (neonates, ARC, RI) and β-lactams (older ones such as flucloxacillin, cefuroxime, temocillin and aztreonam, but also novel agents under development-like ceftaroline and cefiderocol).

Depending on the specific β-lactam and the population, a relatively simple-dose stratification approach may be sufficient, for example depending on age (or gestational age because of prematurity), or by increasing the dose in patients with higher renal function and clearance. This could be the case in populations with predictable and stable PK (e.g. non-critically ill patients with common childhood infections, such as uncomplicated pneumonia or otitis media or toddlers, infants, and adolescents). Yet in patients with extensive and difficult-to-predict PK variability (e.g. critically ill patients with severe infections, or (premature) neonates) TDM or MIPD may be needed to guide dosing to achieve therapeutic drug exposure. Standard TDM will probably be inadequate in this context, as such patients will likely never reach a true steady-state, hence impeding a correct interpretation and its general usefulness. In contrast, MIPD can calculate the right dose for each patient early on during therapy (pre-steady state), which would be of the greatest benefit for the youngest and most severely ill pediatric patients. We believe piperacillin/tazobactam and meropenem would be interesting candidate drugs for this approach as they are frequently used in ICU settings for severe and difficult-to-treat infections.

To implement β-lactam TDM/MIPD in pediatric clinical practice, we have identified a number of barriers, solutions, and future perspectives for individualized dosing (see Figure 1). The primary and most fundamental obstacle is the lack of strong scientific evidence for their clinical benefit. Many TDM studies available today are retrospective or observational in design, or are performed in adults rather than in children. Prospective and long-term randomized clinical trials (RCTs) are needed that directly compare the clinical benefits in terms of both efficacy and toxicity of advanced-dose optimization (TDM/MIPD) over fixed dosing regimens and nomograms. New principles to improve RCT primary endpoints such as the Desirability of Outcome Ranking (DOOR) [151] may be useful in this context, yet questions remain about which exact end point should be measured. Options in this context include Sequential Organ Failure Assessment (SOFA) score, Pediatric Logistic Organ Dysfunction (PELOD) score, Length of Stay (LOS) or overall mortality. Related to this is the identification of the specific pediatric subpopulations that would benefit most from TMD/MIPD-optimized dosing. We believe this would be the groups with the highest PK variability: (preterm) neonates, patients in the pediatric ICU (potentially undergoing AKI, ECMO, CRRT) and children with unstable or altered renal function. Finally, the PK/PD targets required for efficacy that need to be attained in these clinical studies must be further elucidated and confirmed. Considering the ethical and practical difficulties to identify such targets in pediatric clinical trials, we see here a possible role for laboratory research, in particular for the 'Hollow Fiber System.' This preclinical tool is approved by the EMA for PK/PD research on new anti-tuberculosis drugs [152] and has already been used to simulate human pediatric PK profiles under *in vitro* conditions to evaluate antibacterial effects and propose dosing strategies for pyrazinamide in young children [153].

Other, secondary barriers currently hinder the use of TDM/MIPD for β-lactams in children. One is technical and financial in nature: as few commercial (immuno)assays for β-lactam

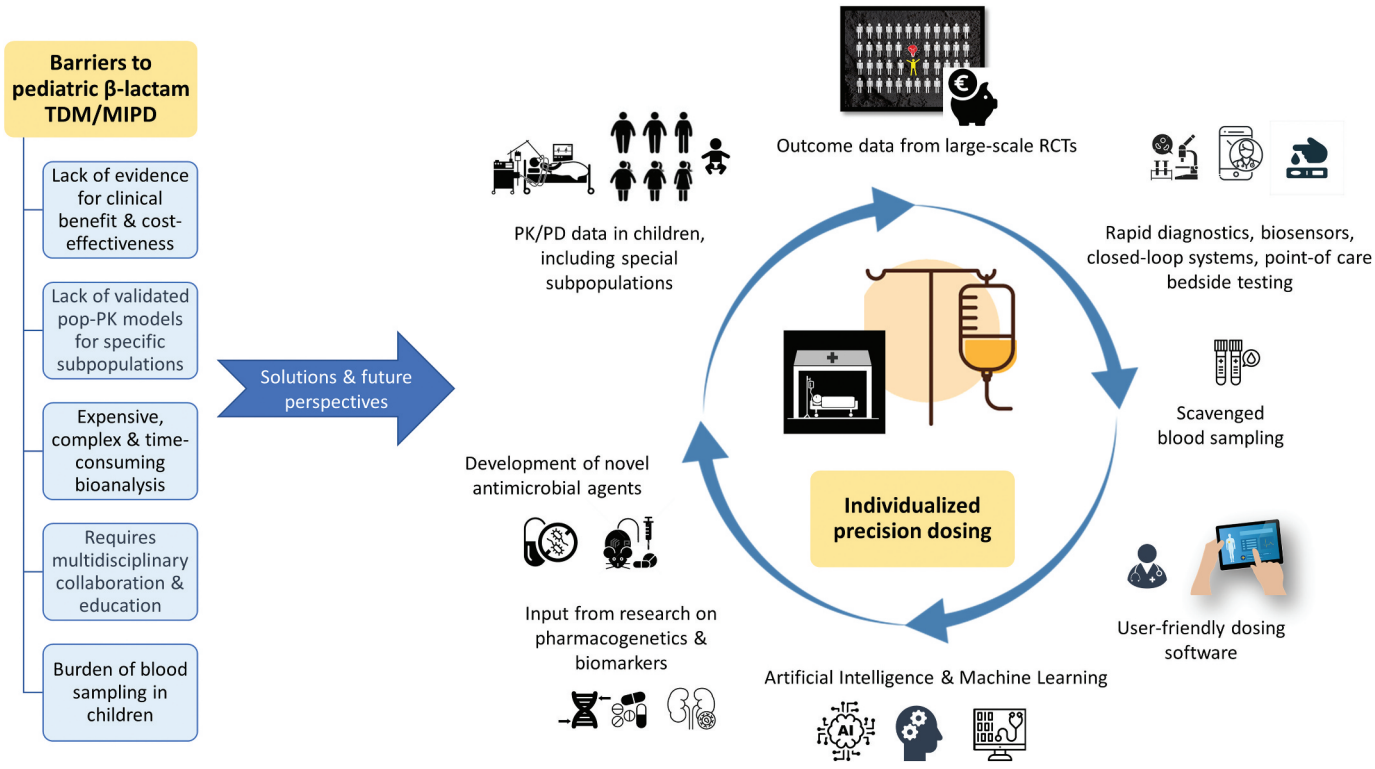

Figure 1. Barriers and future perspectives for pediatric β-lactam Therapeutic Drug Monitoring (TDM) and Model-Informed Precision Dosing (MIPD). Pop-pk: population pharmacokinetics; PK: pharmacokinetics; PD: pharmacodynamics; RCT: randomized controlled trial.

bioanalysis are currently available, chromatography methods are most commonly used. Such methods have prolonged turnover times, rely on specialized equipment and expertise to operate and require additional quality control and cross-validation efforts as many are developed in-house. In the absence of clinical benefit and cost-effectiveness data, such costs further hamper the implementation of TDM, in particular in resource-limited settings where other compounds for which more solid and clear evidence is available (e.g. cytostatics). Another challenge is education. Compared to other drugs such as cytostatics and vancomycin, TDM for β-lactams is a relatively new concept and guidelines are still under development and discussion. The multidisciplinary nature of TDM, involving physicians, clinical pharmacists, microbiologists, nurses, pharmacometricians, and IT support, adds complexity for TDM implementation in routine care. A final challenge, specific to the pediatric population, is the difficulties in blood sampling. This could potentially be mitigated by scavenged blood sampling methods.

So, how do we see the field of β-lactam dose optimization in children evolving in the next 5 years? We foremost hope for the availability of robust prospective data from large-scale RCTs, providing clinical evidence for optimized dosing using TDM/MIPD, for β-lactams but also for other antibiotic classes. Such studies are currently ongoing in adults; evidence will also need to be generated in the pediatric population. Alongside, novel data PK and PK/PD data for β-lactams in neonates remain needed. In this context, new and improved markers of renal function in critically ill young children and neonates (e.g. Cystatin C [154]) to timely detect changes in glomerular filtration rate and adequately adapt β-lactam dosing would also be most welcomed. From the pharmacometrics perspective, model averaging and continuous learning approaches could further improve existing pop-PK models and guide the selection of the 'best' model (or combination of models) for MIPD [155,156]. New antibiotic PK/PD targets and indices that could overcome the limitations of the current MIC-based approaches [157] are under experimental investigation [158] but still require clinical validation. Mechanism-based models (that describe the relation between bacterial killing kinetics and varying drug exposure) could be integrated with pop-PK models and other patient-specific factors in another step toward antibiotic precision dosing in patients [159].

Looking further into the future, MIPD for *a priori* dosage recommendations may become the norm for a number of drugs. Whether the β-lactam class will be included will depend on evidence generation on the clinical benefit from RCTs in the adult and pediatric population, implementation and ongoing legal/regulatory hurdles (i.e. MIPD software and tools as a medical device and/or clinical decision support system [160]). As digital tools rise, artificial intelligence and machine learning will increasingly assist in real time dose adjustment. Drawing insights from precision dosing in fields like oncology, biomarkers, and pharmacogenetics may also come to play an increasingly important role in antimicrobial therapy in general. We express hopes for fully integrated precision dosing within electronic patient records, closed-loop systems where biosensors measure drug exposure in real-time to guide β-lactam dosing at the bedside, novel antimicrobial agents to combat bacterial strains that have become resistant to current β-lactams, and rapid diagnostics to guide

therapeutic decisions. Such precision medical tools can pave the way for a future where individualized dosing stands as a cornerstone to optimize clinical outcomes of β-lactam and other antibiotic therapy in the most vulnerable pediatric populations.

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