Pharmacokinetics of Antibiotics in Pediatric Intensive Care

Subjects: Pediatrics

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Children show important developmental and maturational changes, which may contribute greatly to pharmacokinetic (PK) variability observed in pediatric patients. These PK alterations are further enhanced by disease-related, non-maturational factors. Specific to the intensive care setting, such factors include critical illness, inflammatory status, augmented renal clearance (ARC), as well as therapeutic interventions (e.g., extracorporeal organ support systems or whole body hypothermia [WBH]). This entry illustrates the relevance of both maturational and non-maturational changes in absorption, distribution, metabolism and excretion (ADME) applied to antibiotics.

Keywords: pediatric ; antibiotic ; critical illness ; pharmacokinetics ; augmented renal clearance ; extracorporeal membrane oxygenation ; continuous renal replacement therapy ; cardiopulmonary bypass ; whole body hypothermia ; therapeutic drug monitoring

1. Introduction

Antibiotics are commonly used in hospitalised children [1][2][3]. A one-day point-prevalence study reported antibiotic use in approximately 40% of all hospitalised children in European and non-European hospitals [1]. Another retrospective cohort study of 40 US children's hospitals found that 60% of all children received at least one antibiotic during their hospital stay, representing up to 601 antibiotic days per 1000 patient days [2]. The highest rates of antibiotics use have been reported in critically ill children and patients admitted to the hemato-oncology ward [1]. Up to 57–79% of all patients received antibiotics during their stay at the pediatric intensive care unit (PICU) [4]. Of the five drugs most commonly administered to neonates admitted in a neonatal ICU (NICU), three are antibiotics (ampicillin, gentamicin, and vancomycin) [5].

The decision on the timing of prescription (when), the choice of the antibiotic(s) (what), and appropriate dosing (how much) to achieve sufficient exposure are crucial determinants for successful antibiotic therapy [6]. Pharmacokinetics (PK) and its variability mainly relates to the 'how much' question. It is commonly accepted that adequate exposure above a critical target or within a given range is required for successful (effective and safe) antibiotic therapy [7]. Hence, knowledge of the processes that lead to drug exposure after its administration is essential to select the most appropriate dosing regimen. These processes consist of absorption, distribution, metabolism, and excretion to characterise the pharmacokinetics of a drug. In the setting of pediatric or neonatal intensive care and critical illness, these processes are modulated by both maturational (age, weight) as well as non-maturational (disease, therapeutic interventions) covariates.

Children show important developmental or maturational changes, which may contribute greatly to PK variability observed in pediatric patients [8][9]. Standard weight-based dosing regimens have been shown to lead to suboptimal exposure in certain pediatric patient populations [10][11], so that organ function should be taken into account to optimise pediatric drug dosing, also when the focus is on antibiotics [12][13]. These PK alterations are further enhanced by disease-related or non-maturational factors. Specific to the intensive care setting, such factors include critical illness, inflammatory status, augmented renal clearance (ARC), as well as therapeutic interventions (e.g., extracorporeal organ support systems or whole-body hypothermia [WBH]) (**Figure 1**) [14].

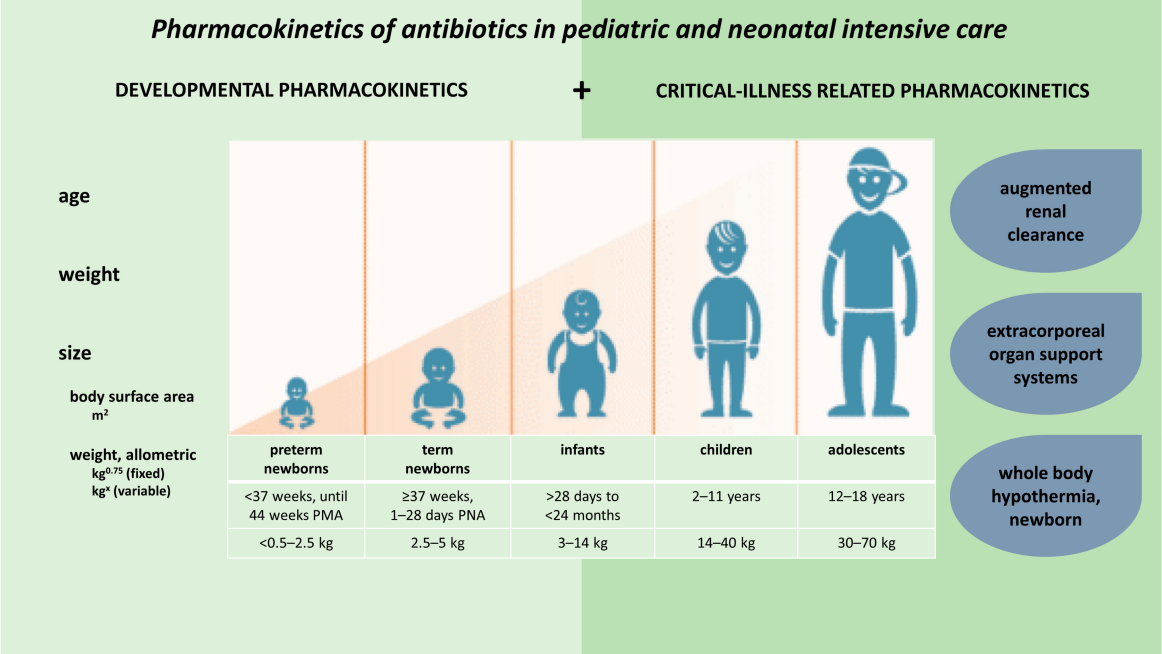


Figure 1. Illustration of developmental and critical-illness related pharmacokinetic alterations in children and neonates.

Most drugs—also antibiotics—have been developed in and for adults, with subsequent extrapolation of dosing regimens to children. Pediatric antibiotic trials are seldom performed due to ethical, practical, and economic considerations [8]. This is evidenced by a recent report of Thaden et al., who reviewed all pediatric trials registered in clinicaltrials.gov between October 2007 and September 2017 [15]. Less than 1% of all pediatric trials (122/17,495) were industry or US government-funded trials investigating systemic antibacterial or antifungal drugs. Consequently, off-label (dose, indication, formulation) prescription is very common, be it that recommendations on how health care professionals can handle this setting have recently been published [16][17]. It has been suggested that certain pediatric patient populations may benefit from individualised dosing to increase target attainment, while minimizing the risk of unnecessary toxicity, using model-informed precision dosing (MIPD) concepts in these populations [11][18].

2. Developmental Pharmacokinetics, Applied to Antibiotics

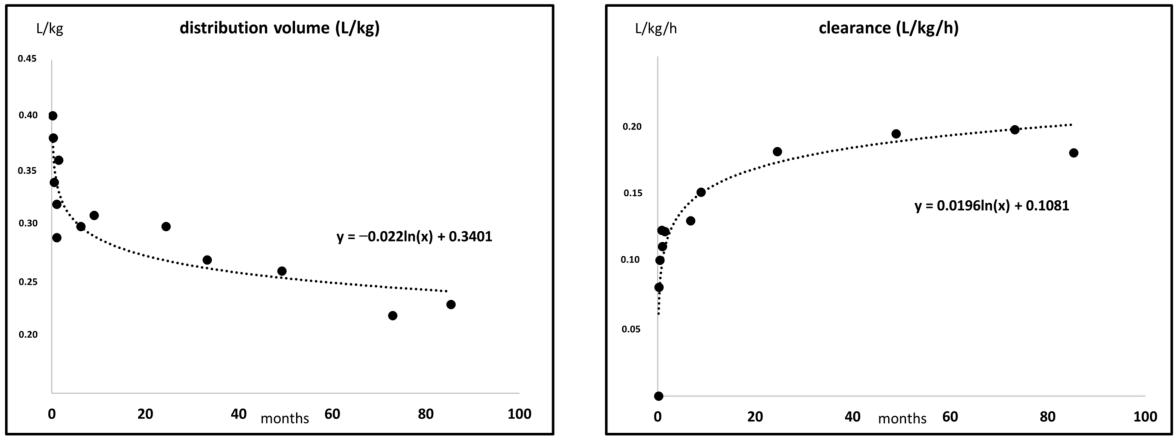
Developmental pharmacology describes the impact of maturation on drug disposition (PK) and drug effects (pharmacodynamics [PD]) throughout the pediatric age range (0–18 y) [19]. There is regulatory guidance to support pediatric drug development within a generic framework, also applicable to antibiotics [20]. This framework is based on 3 pillars, related to: (i) disease progression similarity between adults and children; (ii) the similarity in response to intervention between both, and (iii) the availability of relevant and valid PD markers (biomarkers, outcome variables). Applying this framework to antibiotics, regulatory bodies currently consider it to be reasonable to assume similarity on antimicrobial PD between patient populations (concentration-response) because the treatment is aimed at the infectious organism, not the host (adult or child) [19][20]. Consequently, differences in PK and safety are the primary focus to optimise drug development programs and antibiotic utilization in neonates and children.

A recent ‘throughout-life’ PK modelling effort on vancomycin hereby illustrated that the current dosing recommendations (Food and Drug Administration label) commonly resulted in underexposure, with the highest probability in children and adolescents (70%), except in newborns, while the label remains very descriptive on dosing in preterm neonates [21][22].

Absorption: the impact of gastrointestinal variability on oral drug absorption and the relevance of developmental changes (gastric pH, gastric emptying, gastric fluid composition, intestinal and colonic transit time, first-pass metabolism, pancreatic function) has recently been reviewed [23]. A systematic review recently reflected on these changes and assessed the available evidence on the switch from parenteral to oral antibiotics in neonates. Based on 31 studies and compared to parenteral administration, oral antibiotics generally reached maximum concentration later and had a lower bioavailability. However, in the majority of studies, adequate serum levels were reached, so that early switch could be beneficial when considering health economics and the burden to the patient and family [24].

Distribution: throughout infancy, the extracellular and total body water proportions are higher, and this results in higher volumes of distribution (Vd) and lower (peak) concentrations for water-soluble antibiotics (e.g., aminoglycosides, vancomycin, beta-lactams) when administered on an mg/kg basis. **Table 1** summarises maturational changes in body

water composition, while **Figure 2**A illustrates the impact of the body water composition on the Vd (L/kg) for a water-soluble antibiotic (amikacin) [25][26][27][28]. These patterns can be further affected by disease-related aspects, similar to those observed in adults, as, e.g., Lingvall et al. described that the Vd of gentamicin was significantly higher (+14%) in septic compared to non-septic neonates [29]. **Table 1** also summarises the maturational trends in plasma protein composition, as this determines the drug-binding capacity and free concentrations, as illustrated for, e.g., cefazolin or vancomycin [30][31][32]. Competitive binding of co-administered drugs or endogenous substances (indirect bilirubin) may occur and explains the contraindication for ceftriaxone in neonates [33].



(**A**) (**B**)

Figure 2. Illustration of maturational changes of (**A**) volume of distribution (Vd, L/kg) and (**B**) clearance (CL, L/kg/h) with the trend lines, based on amikacin pharmacokinetic data in 155 patients (body weight 1.35–33 kg) in the first 85 months of life [28].

Table 1. Maturational changes in physiologic variables relevant to the distribution of antibiotics [25][26][27].

Age	Total Body Water/Weight %	Extracellular Water/Weight %	Intracellular Water/Weight %	Plasma Albumin g/L	Plasma Total Protein d/L
Preterm, 2 kg	82	44	34	26	40
Term, at birth	78	40	32	28	43
7–30 days	74	32	43	29	53
1–3 months	73	30	42	29	54
3–6 months	70	30	42	29	54
6–12 months	60	27	35	29	54
1–3 year	58–63	27–21	38–34	31	59
>3–6 year	62	21	46	31	62

Age	Total Body Water/Weight %	Extracellular Water/Weight %	Intracellular Water/Weight %	Plasma Albumin g/L	Plasma Total Protein d/L
>6–18 year	61–57	22–18	43–42	32	59
Adult	59	19	40	40	63

Elimination: the main route of elimination of most antibiotics is by renal excretion, determined by both glomerular filtration rate (GFR) and renal tubular activities (secretion, reabsorption) so that pharmacometric approaches to personalise the use of primarily renally eliminated antibiotics in a pediatric and neonatal ICU setting should focus on renal models and renal (patho)physiology [13]. A maturational human renal function with a sigmoid hyperbolic model has been described so that half of the adult value is reached at 48 weeks postmenstrual age to be at 90% of this value at the end of infancy, even when an allometric coefficient ($kg^{0.75}$) was used [34]. When based on body weight, the steep increase in clearance (CL) in infancy is even more pronounced. **Figure 2**B illustrates this maturational pattern in CL (L/kg/h), based on a published amikacin dataset [28]. Along the same line, and based on datasets of gentamicin, tobramycin, and/or vancomycin, semi-physiological functions for GFR maturation throughout human life have been constructed [21][35]. When scaling of CL was based on these GFR maturational models, maturational changes in plasma protein concentration only marginally affected renal clearance, except for drugs highly bound to alpha-1-acid glycoprotein [36]. In contrast, the contribution of active tubular secretion to overall renal clearance can range—depending on drug-specific PK properties—between 41 and 90%, so that ontogeny of tubular secretion cannot be ignored, not even in infants [37].

Such semi-physiological functions are relevant to truly assess the impact of non-maturational factors. Besides aspects related to the critical illness that will be discussed below, this also includes co-administration of nephrotoxic drugs, like non-steroidal anti-inflammatory drugs (ibuprofen, indomethacin), commonly administered to induce closure of a patent ductus arteriosus. Using the impact of those drugs on aminoglycoside or vancomycin CL, the transient reduction in GFR during ibuprofen or indomethacin administration is −20 and −40%, respectively, in the newborn [38][39].

3. Critical Illness Related Pharmacokinetic Alterations in Children and Infants

Pathophysiological changes and resulting PK alterations have been demonstrated for many antibiotics in critically ill children. Nevertheless, pediatric PK data remain relatively scarce and are lagging behind the plethora of PK studies reporting antibiotic PK in critically ill adults. Increased Vd is frequently observed due to fluid resuscitation and inflammation-induced capillary leak, further enhanced by hypoalbuminemia. Alterations in antibiotic CL have also been reported repeatedly in pediatric antibiotic studies, and have been related to both extremes of renal function (i.e., acute kidney injury necessitating renal replacement therapy [RRT] and ARC) [40][41]. Despite the similarity to patterns in critically ill adults, still, important differences in PK alterations have been reported in pediatric patients, as their phenotypic PK findings are the result of merged maturational (age- or weight-related) and non-maturational factors, like critical illness.

Higher Vd (L/kg) have been reported for most beta-lactam antibiotics in pediatric patients with severe bacterial infections compared with adult ICU patients. However, it should be noted that there is still large variability in PK between and within the different pediatric studies [40][41]. Bodyweight and age-related covariates are the most frequently retained predictors of interindividual PK variability on Vd and CL in pediatric ICU studies. Whereas renal function is the most frequently identified covariate for PK alterations in adult ICU studies, it is less frequently identified in pediatric ICU studies. This suggests that markers for renal function (which are mostly based on serum creatinine [SCr]) are less performant in predicting changes in the CL of antibiotics in pediatric vs. adult ICU patients. This is probably at least partly due to age-related changes in renal function. This maturational variability to a certain extent blurs non-maturational effects, which is a phenomenon that is most pronounced in early neonatal life and infancy [13][14]. Although renal function (GFR and tubular secretion) is lower in neonates and young infants, weight-corrected (per kg) GFR values are much higher (up to 70%) in young children (2–5 years), compared to adults [42].

Despite >50 published antibiotic PK studies in critically ill pediatric patients, PK data remain scarce and for most antibiotics, PK knowledge is based on only a few studies with small sample sizes [40][41]. For some commonly used antibiotics, there are even no PK data available in critically ill children (e.g., ceftazidime). Overall, PK studies show that the attainment of predefined PK/PD targets is suboptimal with standard dosing of many antibiotics in critically ill children

[40][41][43]. Therefore, several studies suggest dose optimization strategies for these patients. Interestingly, the same PK/PD targets are commonly aimed for in pediatric and adult critically ill patients [11][41][44]. **Table 2** presents an overview of the three categories of PK/PD targets commonly used and the antibiotic classes falling into each category [11][44][45]. Next to the classic advice to increase the dose or dosing frequency, extended or continuous infusion strategies are regularly suggested to increase the probability of target attainment (PTA) with beta-lactam therapy in critically ill children. This strategy has been extrapolated from adult critically ill patients, however, until now, there is no conclusive evidence of its clinical benefit. Interestingly, a subgroup analysis of critically ill children included in a recent retrospective chart analysis revealed a potential mortality benefit (2.1% vs. 19.6%) of extended vs. intermittent beta-lactam infusion [43]. Additionally, therapeutic drug monitoring (TDM) is regularly suggested to overcome suboptimal exposure in critically ill children, also for beta-lactams. TDM is an interesting strategy for dose optimization considering the high inter-individual PK variability observed in these patients. Cies et al. found a relatively low mortality rate of 4.3–12.2% in pediatric ICU patients undergoing routine beta-lactam TDM and dose adjustments according to predefined PK/PD targets [46]. Compared to mortality rates of 25% or higher observed in septic pediatric patients [47][48][49], this study suggests a mortality benefit from beta-lactam TDM in these patients. Notwithstanding, confounding from baseline differences in patient characteristics cannot be excluded.

Table 2. Categories of antibiotics according to their pattern of antibacterial activity and their associated pharmacokinetic/pharmacodynamic (PK/PD) target.

Category Based on the In Vitro Pattern of Antibacterial Activity	Antibiotic Class	PK/PD Target for Efficacy
Time-dependent with minimal-to-no persistent effect	Beta-lactams, Lincosamides	% $fT_{>MIC}$
Time-dependent with moderate-to-persistent effect	Glycopeptides, Oxazolidinones, Macrolides, Tetracyclines, Glycylcyclines, Polymyxins	$AUC_{0–24}$/MIC % $fT_{>MIC}$ (erythromycin, linezolid)
Concentration-dependent with moderate-to-persistent effect	Aminoglycosides, Fluoroquinolones, Lipopeptides, Metronidazole, Ketolides	$AUC_{0–24}$/MIC C_{max}/MIC

% $fT_{>MIC}$: percentage of time during which the free concentration exceeds the minimum inhibitory concentration; $AUC_{0–24}$/MIC: ratio of the area under the curve over 24 h to the minimum inhibitory concentration; C_{max}/MIC: ratio of the peak concentration to the minimum inhibitory concentration.

It should be noted that most PK studies report antibiotics that are subjected to routine TDM in clinical practice (e.g., vancomycin and aminoglycosides). **Table 3** summarises all antibiotic PK studies performed in critically ill children. Studies performed only in neonates (or adults) were excluded from the general summary presented in **Table 3**, as these fell out of the scope of the current summary.

Table 3. Summary of all antibiotic PK studies performed in critically ill children.

Antibiotic	Number of Studies	Study Aspects	Age and Weight Range	Results and Clinical Implications
Vancomycin	19	4 prospective studies (*n* = 168) [50][51][52][53] 10 retrospective TDM studies (*n* = 1120) [54][55][56][57][58][59][60][61][62][63] 5 retrospective popPK studies (*n* = 704) [64][65][66][67][68]	0–18 y 0.68–108 kg	Conflicting results with regard to association between C_{min} and acute kidney injury [54][55][57][62] Eight studies reported CL and Vd. Mean Vd 0.44–1.04 L/kg. Mean CL 0.072–0.19 L/kg/h [51][52][53][56][64][65][67][68] Eight studies reported measured, simulated or estimated AUCs [50][51][52][56][62][66][67][68] Only two studies used continuous dosing [50][66] Substantial percentage of target non-attainment with standard dosing regimens (up to 92%, mostly subtherapeutic but also supratherapeutic concentrations) [50][51][52][54][55][56][59][64][66][67][68] Dosing of 60 mg/kg/day q8h advised if no renal impairment [61][67] One study advised lower doses for neonates (30 mg/kg/day), infants (35–40 mg/kg/day) and children (45 mg/kg/day) [59] Another study in neonates and infants <2m advised 14–18 mg/kg q8–12 h [68]
Teicoplanin	4	2 prospective cohort studies (*n* = 33) [69][70] 1 RCT (*n* = 20) [71] 1 prospective popPK study with dosing simulations (*n* = 42) [72]	7 d–15.6 y 3.74–56 kg	Three studies found that higher than standard dosing is needed to achieve Target attainment [70][71][72] One study found lower target attainment in older children (>1 y) compared to younger infants (<1 y) due to larger Vd and higher CL [71] Routine TDM of unbound concentrations was recommended due to highly variable unbound concentrations [72]

Antibiotic	Number of Studies	Study Aspects	Age and Weight Range	Results and Clinical Implications
Gentamicin	4	1 retrospective TDM study (*n* = 140) [73] 1 prospective popPK study with dosing simulations (*n* = 36) [74] 2 studies investigating application of a Bayesian forecasting program (*n* = 117) [75][76]	0 d–15 y Body weight not reported	Higher initial doses and/or extended dosing interval in neonates and (young) infants [74][75] Two studies found age and weight to be significant predictors for Vd and/or CL [73][74] One study also found serum creatinine to be a significant predictor for the elimination constant (k) [73]
Amikacin	3	1 RCT (*n* = 60) [77] 2 prospective popPK studies (*n* = 106) [78][79]	6 m–17 y 8–90 kg	Higher doses per kg needed for neonates and infants (<1 y) due to higher Vd and CL [77] Higher Vd and CL in burn patients [79]
Netilmicin	1	1 prospective study (*n* = 9) [80]	1 m–15.5 y 3.4–70 kg	Mainly neonates Once daily 6 mg/kg is sufficient
Piperacillin/tazobactam	5	4 popPK studies with dosing simulations (*n* = 139) [81][82][83][84] 1 prospective study (*n* = 14) [46]	0.1–18 y 2.7–53 kg	High median $eGFR_{Schwartz}$ in all studies (lowest median $eGFR_{Schwartz}$ 142 mL/min/1.73 m^2) [83] Median Vd: 0.24–0.444 L/kg (highest in neonates); Median CL: 0.19–0.299 L/kg/h [81][82][83][84] Insufficient target attainment with standard dosing. Extended infusion over >1 h needed for >90% probability of target attainment [46][81][82][83][84]
Cefotaxime	3	2 prospective studies (*n* = 39) [85][86] 1 prospective popPK study with dosing simulations (*n* = 49) [87]	0–19 y 2.5–70 kg	Neonates had longer elimination half-life [87] Continuous infusion needed for optimal target attainment and/or less susceptible microorganisms [85][87]

Antibiotic	Number of Studies	Study Aspects	Age and Weight Range	Results and Clinical Implications
Cefuroxime	1	1 prospective cohort study (*n* = 11) [88]	4 m–14 y 5.1 kg–45 kg	Vd and CL higher in children with mechanical ventilation vs. children without mechanical ventilation and controls The elimination half-life is longer in critically ill children vs. controls
Ceftriaxone	1	Prospective popPK study with dosing simulations (*n* = 45) [89]	0.1–16.7y	Vd and CL comparable to non-critically ill children aged 1–6 y Vd and CL higher than non-critically ill children with cystic fibrosis 100 mg/kg q24h sufficient for most critically ill children and neonates 50 mg/kg q12h if $eGFR_{Schwartz}$ > 80 mL/min/1.73 m^2 or increased MIC ≥0.5 mg/L
Ceftolozane/tazobactam	1	1 case series (*n* = 3) [90]	8–19 m 5.8–11 kg	Normal renal function: 35 mg/kg q8h appropriate for multidrug-resistent *Pseudomonas aeruginosa* Acute kidney injury: reduced dose 10 mg/kg q8h appropriate
Ceftaroline	1	1 prospective study (*n* = 7) [91]	1–13 y 12.6–40.1 kg	Higher median CL and Vd than reported in the package insert (non-critically ill children) Higher dosing and shorter dosing interval than package insert needed (15 mg/kg q6h)
Amoxicillin/clavulanic acid	3	1 prospective study (*n* = 15) [92] 1 prospective popPK study with dosing simulations (*n* = 50) [93] 1 meta-analytical modelling study (*n* = 44) [94]	1 d–15 y 1.7–65 kg	Higher amoxicillin CL than critically ill adults, comparable amoxicillin Vd and clavulanic acid CL and Vd [92][93] 25 mg/kg q4h as bolus or 1h infusion, depending on renal function, needed for optimal target attainment [93] Meta-modelling study (in neonates and young infants (<60 d) [94]: Sepsis is associated with lower amoxicillin concentrations and longer elimination half-life. Fixed dosing regimen: 125 mg and 250 mg q12h depending on body weight <4 kg or ≥4 kg

Antibiotic	Number of Studies	Study Aspects	Age and Weight Range	Results and Clinical Implications
Meropenem	5	1 retrospective popPK study (*n* = 9) [95] 1 case report (*n* = 1) [96] 1 prospective popPK study with dosing simulations (*n* = 23) [97] 1 retrospective popPK study with dosing simulations (*n* = 26) [98] 1 prospective study in children with sepsis (*n* = 15) [99]	0.03–15.6 y 2.7–59 kg	CL is slightly lower [99], within [97], or higher [95][96][98] than the CL range observed in non-critically ill children, depending on the study population Increased dosing and extended infusion needed [95][96][97][98][99]
Imipenem	1	1 prospective study (*n* = 19) [100]	9 d–12 y Body weight not reported	Vd and CL comparable to non-critically ill children At least 100 mg/kg/day to avoid subtherapeutic concentrations
Aztreonam	1	1 case report (*n* = 1) [101]	16 y	CL double than reported in the package insert 2g q6h over 4h infusion achieved 40% $fT_{>MIC}$
Linezolid	1	1 prospective popPK study with dosing simulations (*n* = 63) [102]	0.1–15.3 y 4.2–70 kg	Recommended age-differentiated dosing regimens lead to adequate attainment of the target AUC/MIC (>80) for sensitive pathogens Dose increase needed if MIC >1 mg/L Dose reduction needed if liver impairment (aspartate aminotransferase)
Ciprofloxacin	1	1 prospective study (*n* = 20) [103]	3 m–4.75 y 4.2–21.2 kg	No difference in CL and Vd between children aged <1 y and older. 20 mg/kg/day sufficient to cover pathogens with an MIC up to 0.8 mg/L 30 mg/kg/day in 3 doses needed in patients with normal renal function infected by pathogens with an MIC > 0.8 mg/L

Antibiotic	Number of Studies	Study Aspects	Age and Weight Range	Results and Clinical Implications
Daptomycin	3	1 popPK study (n = 4) [104] 2 case reports (n = 2) [105][106]	8–14 y 17–45 kg	Higher Vd and CL in sepsis patients vs. the patient without sepsis [104] CL in sepsis patients is double the CL in non-critically ill children [104] Children with sepsis showed suboptimal AUC values, even with increased dosing. This was even more pronounced in the burn patient. Increased dosing and TDM is recommended [104].

AUC: area under the curve; CL: clearance; C_{min}: trough concentration; $eGFR_{Schwartz}$: estimated glomerular filtration rate according to the Schwartz equation; $fT_{>MIC}$: time during which the free concentration exceeds the minimum inhibitory concentration; MIC: minimum inhibitory concentration; popPK: population pharmacokinetic; RCT: randomised controlled trial; TDM: therapeutic drug monitoring; Vd: distribution volume.

Vancomycin is by far the most frequently reported antibiotic in critically ill children, with studies covering its PK over the whole pediatric age range in more than 1000 critically ill children [50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68]. Teicoplanin, another antibiotic belonging to the same antibiotic class as vancomycin, has been described in four studies [69][70][71][72]. Three of these four studies reported insufficient target attainment with standard dosing regimens [70][71][72]. Furthermore, the most recent study reported highly variable unbound teicoplanin concentrations, highlighting the need for TDM of unbound teicoplanin [72].

Aminoglycosides are also commonly monitored in clinical practice, which is reflected by several studies describing the PK of gentamicin [73][74][75][76] and amikacin [77][78][79]. For gentamicin, higher initial doses and longer dosing intervals have been suggested for neonates and (young) infants in two studies to compensate for an (age-related) increase in Vd and decrease in CL, respectively [74][75]. Similar findings have been reported for amikacin [77][79].

Beta-lactam PK studies in critically ill children show diverse results and are mostly limited to a few studies or cases reports for a specific beta-lactam antibiotic [46][81][82][83][84][85][86][87][88][89][90][91][92][93][94][95][96][97][98][99][100][101]. In general, studies found suboptimal exposure with standard beta-lactam dosing regimens, due to an increased beta-lactam CL rate. Several studies recommended increased dosing and/or prolonged infusion to achieve target attainment [81][82][83][84][87][91][93][95][97][98][99][101].

Finally, we also found a few PK studies describing linezolid [102], ciprofloxacin [103], and daptomycin [104][105][106] PK in critically ill children (**Table 3**).

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