Chapter 12
Antibiotic Dosing in Pediatric Critically Ill Patients

Pieter A.J.G. De Cock, Karel Allegaert, Matthew W. Linakis, and Catherine M.T. Sherwin

Abbreviations

ADME	Absorption, distribution, metabolism, elimination
AKI	Acute kidney injury
ARC	Augmented renal clearance
AUC	Area under the concentration time curve
Cmax	Maximal concentration, peak concentration
CPB	Cardiopulmonary bypass
CRRT	Continuous renal replacement therapy
ECMO	Extracorporeal membrane oxygenation

P.A.J.G. De Cock, Pharm.D, Ph.D.
Department of Pharmacy, Ghent University Hospital, Ghent, Belgium

Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium

Department of Paediatric Intensive Care, Ghent University Hospital, Ghent, Belgium

K. Allegaert, M.D, Ph.D.
Intensive Care and Department of Surgery, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands

Department of Development and Regeneration, KU Leuven, Leuven, Belgium

M.W. Linakis, B.S.
Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine, SLC, Utah 295 Chipeta Way, Salt Lake City, UT 84108, USA

C.M.T. Sherwin, Ph.D. (✉)
Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine, SLC, Utah 295 Chipeta Way, Salt Lake City, UT 84108, USA

Department of Pharmacology and Toxicology, College of Pharmacy, University of Utah, Salt Lake City, UT, USA
e-mail: Catherine.sherwin@hsc.utah.edu

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eGFR	Estimated glomerular filtration rate
F	Bioavailability
GA	Gestational age
GFR	Glomerular filtration rate
ICU	Intensive care unit
MIC	Minimal inhibitory concentration
NICU	Neonatal intensive care unit
PD	Pharmacodynamics
PICU	Pediatric intensive care unit
PK	Pharmacokinetics
PNA	Postnatal age
TDM	Therapeutic drug monitoring
Vd	Distribution volume

12.1 Introduction

12.1.1 Off-Label Practices

Antimicrobial agents are among the most commonly administered drugs in neonates, infants, and children during intensive care unit (ICU) admission. For instance, three of the top five most commonly administered drugs in the neonatal intensive care unit (NICU) are antibiotics (ampicillin, gentamicin, and vancomycin) [1]. Infections and sepsis are major concerns in this population because of the related mortality, morbidity, and costs.

Despite their frequent prescriptions, off-label prescription of antimicrobial agents is still very common. Though there is evidence to support the use of some off-label practices, in cases where evidence is lacking, off-label use of antibiotics can result in unpredictable responses related to either toxicity or therapeutic failure. Chloramphenicol with the associated "gray baby" syndrome is a historical illustration of toxicity related to maturation. Off-label practices have the potential to result in inadequate or inaccurate dosing, illustrated by the extensive variability in dosing regimens of off-label antibiotics within European NICUs [2]. In fact, older drugs such as vancomycin and penicillins were dosed below or above recommendations with extensive variability in daily dosing (e.g., *vancomycin*: −100% up to +60%; *cefotaxime*: −50% up to +120% compared to the mg/kg reference dose guideline) [2]. In contrast, newer antibiotics, such as meropenem, tend to have dosing guidelines built into their label, resulting in a much smaller variability in dosing regimens [2].

In those cases where a dosing regimen is not well established, caregivers will commonly have to prescribe antibiotics in neonates and children based on dosing regimens linearly extrapolated from adults. This situation arises because appropriate dosing studies have not been performed or because clinicians are not using existing pediatric PK models to obtain dose information. This becomes not only an issue

of science, but also an implementation and labeling issue. Although this practice is not limited to antibiotics, specific concerns related to dosing inaccuracy for antibiotics are treatment failure, antimicrobial resistance, and maturational toxicity [3, 4].

12.1.2 *Accurate Antibiotic Dosing in Critically Ill Children: A Complex Interplay Between Physiology and Pathophysiology*

Clinical pharmacology aims to predict drug-specific (side) effects based on pharmacokinetics and pharmacodynamics. Pharmacokinetics (PK, ***a***bsorption, ***d***istribution and **e**limination, through ***m***etabolism or primarily renal *excretion*, ***ADME***) describes the drug concentration over time (“*what the body does to the drug”*) at a specific site (e.g., blood, cerebrospinal fluid). Pharmacodynamics (PD) estimates the relationship between a drug concentration and effect over time (“*what the drug does to the body”*) and covers both intended effects, as well as side effects.

The regulatory framework (Fig. 12.1) for pediatric drug development in Europe and the United States provides guidance on how this should be addressed [5]. Governmental oversight bodies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) usually seek information regarding: (*1*) how similar disease progression is between adults and other patient populations, such as children; (*2*) how similar the response to intervention is between these populations; and (*3*) which valid and relevant pharmacodynamic measurements (biomarkers, outcome variables) are available, in order to decide on the type of product development program. When applying this decision tree to antibiotics, these regulatory bodies currently consider it to be reasonable to postulate similarities antimicro-

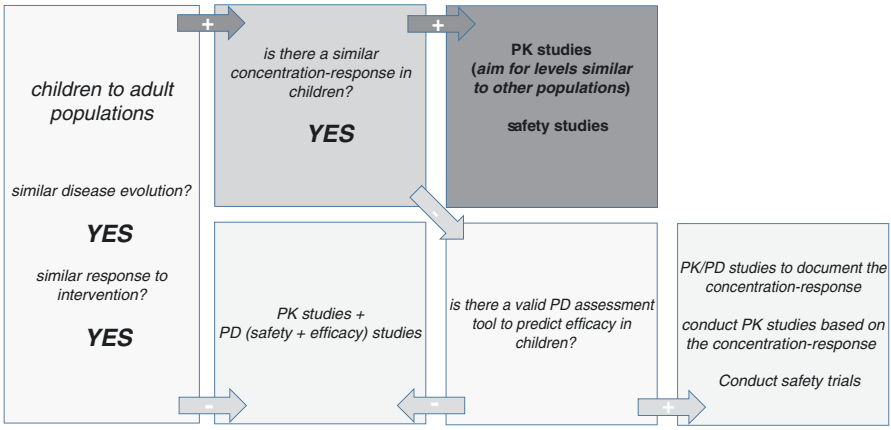

Fig. 12.1 The currently used pediatric decision tree to evaluate antibiotics in neonates. This is in general based on pharmacokinetics and safety data

bial pharmacodynamics between patient populations (concentration-response), because the treatment is aimed at the infectious organism (which is considered to behave the same between patient populations) and not the host per se. Consequently, differences in PK and safety aspects [6] are the primary focus for optimizing antibiotic utilization across populations. Three main PKPD targets, regardless the patient population, have been defined for maximum killing of the infecting pathogen depending on the properties of the antibiotic: peak plasma concentration > threshold, area under the concentration time curve > threshold, or time during which the concentration remains above a threshold.

Drug disposition in healthy children is driven by the physiological processes of growth and development (common descriptors: weight and age). Maturational PK changes are most dynamic in infancy and early childhood [4]. However, among children that are critically ill, pathophysiological changes can occur that can also have a significant influence on PK. Finally, the impact of treatment modalities [e.g., interacting co-medication, whole body cooling, extracorporeal membrane oxygenation (ECMO), and renal replacement therapy] should not be neglected. Consequently, drug dosing in critically ill children should be based on integrated knowledge concerning all (patho)-physiological and treatment characteristics of the child receiving the drug, the specific diseases to be treated, and the pharmacokinetic and dynamic parameters of the compound [7].

In this chapter, we first discuss the impact of maturation and critical illness on PK among pediatric patients (Sect. 12.2.1–12.2.3). These aspects will subsequently be considered in the context of children with burns (Sect. 12.2.4.1) and the impact of certain invasive treatments on PK (ECMO, cardiopulmonary bypass, renal replacement) (Sect. 12.2.4.2). The section on PD focuses on the developmental safety of antibiotics (Sect. 12.3). This is followed by some compound-specific PK/PD observations (aminoglycosides, vancomycin, meropenem) in neonates and children to further highlight the complex interaction between normal physiology and disease-state changes (Sect. 12.4). In the final part of the chapter, we discuss approaches to improve knowledge and practices including population PK models, physiology-based models, therapeutic drug monitoring, and individualized dosing (Sect. 12.5).

12.2 Pharmacokinetics in the Critically Ill Pediatric Patient

12.2.1 Absorption

Absorption is the process of drug transport from the site of administration to systemic circulation. The extent of absorption is described by bioavailability (F), the fraction of the dose reaching the systemic circulation. If a drug is administered intravenously, F is 100%, for other routes, this is between 0 and 100%. Drug- and patient-specific factors are responsible for the rate and magnitude of absorption. Drug-specific factors include particle size, solubility, lipophilicity, ionization, and

dissociation constant of the drug [8]. For enteral drug administration, the main patient determinants for the rate and extent for absorption are gastric emptying time, gastrointestinal pH, intestinal motility, drug metabolism at the intestinal epithelium, and absorption surface area.

Gastric emptying matures over a period of 6–8 months to adult levels [8]. Furthermore, antral contractions and intestinal motor activity improve during the first weeks of life with possible consequences on enteral absorption. Delayed gastric emptying is estimated to appear in 50% of critically ill children, especially in the youngest ones where a developmental pattern further strengthens this phenomenon as described above [9, 10]. Gastroparesis may occur as a side effect of opioids, while the use of naso-duodenal gavage feeding will bypass gastric effects. Similarly, chronic kidney disease can also affect gastric emptying time through visceral neuropathy [11]. However, no studies specifically evaluated the effect of developmental and disease-related changes in gastric emptying and intestinal motility on absorption of antibiotics in infants and children. Generally speaking, one could suppose that delayed gastric emptying leads to a delayed intestinal appearance of the antibiotic and results in a more blunted peak concentration that is reached later compared to a patient without delayed emptying. The clinical relevance of it depends on the concentration-effect profile of the compound. If a minimum effective concentration has to be reached. this effect could be delayed [8]. Besides this, diarrhea is also common on the pediatric ICU with a reported incidence between 10 and 20%. One could expect that the faster passage of substances through the digestive tract could have possible effects on the absorption profile and absolute bioavailability of the compound [12].

Although there are no significant differences between neonates (a few hours after delivery), infants and older children in baseline pH, one should consider that gastric pH will rise postprandially as milk and feedings in general have a buffering effect. As a consequence, during the day, younger children and children on enteral feeding tend to have more often a basic gastric environment [13]. These changes in gastric pH are important for acid-labile drugs like penicillin G which can be absorbed more efficiently in a higher gastric pH environment. Huang et al. showed that neonates (less acidic stomach environment) tend to have a higher bioavailability of penicillin G as compared to older children [14]. Similar effects may occur in the case of stress ulcer prophylaxis with pH modulating agents, which is commonly prescribed at the PICU. Little is known about the age-related changes in intestinal pH.

Lipophilic antibiotics given enterally need biliary salts to be absorbed. One could speculate that due to maturation of conjugation and transport of bile salts up to the age of 4, absorption of these antibiotics can be age dependent. Other age-dependent factors are villi formation and absorptive surface and age-dependent increase of splanchnic blood flow [4, 13, 15].

Circulatory dysfunction in pediatric sepsis and septic shock leads to shunting of blood flow towards the vital organs like brain and heart and to a decreased peripheral tissue perfusion like muscles, skin, and splanchnic organs. Vasopressors and inotropes are very often used in hemodynamically unstable children and are known to alter splanchnic perfusion. Although several studies have assessed the gut-specific

effects of these vasoactive drugs in critically ill adult patients, it's not really known whether these effects are beneficial or detrimental in terms of gut perfusion and at what specific dose they occur [16]. This could be explained that "critically ill" is a term describing a very heterogeneous population in adults and maybe even more in children. King et al. evaluated in a retrospective manner the tolerance of enteral feeding in patients admitted to the pediatric intensive care unit receiving cardiovascular medication. Dopamine was the most commonly used vasopressor. 29% of patients had feedings held for a perceived gastrointestinal intolerance [17]. In another study [9], epinephrine at a dose more than 0.3 μg/kg/min was identified to be a significant factor for gastrointestinal complications in critically ill children receiving transpyloric enteral nutrition. One of the explanations for gastrointestinal intolerance could be a body's failure to meet the higher splanchnic metabolic demands when the gut is hypoperfused [18]. To our knowledge, there are no studies available investigating the impact of impaired peripheral perfusion on drug absorption specifically in children although it's hypothesized that drug absorption from these sites can be erratic. Cardiovascular failure in general can result in a reduced enteral absorption of drugs, not only due to the decreased organ perfusion but also due to an increased backward pressure (venous congestion) in the gut circulation.

Reduced skeletal muscle blood flow and inefficient muscular contractions may prevent or alter absorption from the site of intramuscular injection in neonates but can be counterbalanced by the relatively higher density of capillaries in skeletal muscles. Despite the known factors of variability in absorption, the intramuscular administration of benzyl penicillin and gentamicin have been evaluated as part of neonatal sepsis treatment (AFRINEST studies) due to the ease of administration in resource poor settings [19].

12.2.2 Distribution

The apparent volume of distribution is a theoretical measure of the extent to which a drug will migrate into extravascular tissues. It can be affected by normal developmental and pathophysiologic changes that influence cardiac output, regional blood flow, and tissue permeability. The latter depends on several factors including, the degree of drug binding in blood and tissues, presence of transporters (influx/efflux), tissue mass, and physicochemical properties of the drug. Of special note, the blood–brain barrier is less mature and more permeable in infancy or in the presence of inflammation and will have potential impact on antibiotic disposition when treating central nervous system infections.

In neonates and infants, the *extracellular and total body water* is higher compared to adults. This results in higher volumes of distribution and lower (peak) concentrations of water-soluble antibiotics (e.g., aminoglycosides, vancomycin, beta-lactam antibiotics, linezolid) when administered on an mg/kg basis. Increased capillary permeability, increased hydrostatic pressure, or decreased tissue oncotic pressure due to hypoproteinemia is commonly encountered in critically ill children

and may augment the distribution volume. These increases in volume of distribution may necessitate the use of a higher dose (mg/kg) to reach a given concentration. To illustrate this, Lingvall et al. documented that the gentamicin volume of distribution was significantly higher in blood culture confirmed septic neonates compared to non-septic cases [20]. In contrast, redistribution of blood during shock results in a reduced volume of distribution with decreased delivery of hydrophilic drugs to the capillary system and poor peripheral tissue penetration. In a study by Joukhadar et al., this resulted in a five to tenfold decrease of piperacillin distribution into fat and muscle tissues in adults [21]. We speculate that these patients with impaired tissue penetration would probably benefit from alternative dosing regimens (higher antibiotic doses or shortening the dosing interval).

Similarly, maturational changes in the overall plasma binding protein pool will have an impact on the unbound fraction of drug and, therefore, the ability of drug to migrate into tissues. The most important plasma proteins for drug binding are albumin and the acute phase reactant α-1 acid glycoprotein. Albumin preferentially binds acidic molecules whereas α-1 acid glycoprotein tends to bind compounds with basic moieties. Plasma albumin concentrations and binding capacity will reach adult levels around the end of infancy (~2 years of age) [4]. In states of severe illness, hypoproteinemia (<61 g/L) and hypoalbuminemia (<33 g/L) are frequently observed in children and are the result of a number of mechanisms such as increased protein catabolism, capillary permeability, and decreased production. In contrast, α-1 acid glycoprotein levels often increase during periods of critical illness [22, 23]. Smits et al. very recently evaluated protein binding of the highly protein-bound antibiotic cefazolin in postoperative neonates. As expected, the median unbound CFZ fraction was higher than in adults [24]. Besides protein concentration, the binding affinity of antibiotic to plasma proteins also depends on conformational changes. These conformational changes can be induced by fluctuations in pH and urea concentration, phenomena likely to occur in critical illness.

Competitive binding of co-administered drugs or endogenous substances may also have an impact on the degree of drug-protein binding. In neonates, competitive binding of antibiotics (e.g., ceftriaxone, cefazolin) and bilirubin to albumin has been described [24, 25]. As a clinical consequence, the highly albumin-bound antibiotic ceftriaxone is currently contraindicated because of displacement of unconjugated bilirubin which could potentially result in kernicterus [25, 26].

12.2.3 Elimination

Clearance of a drug generally occurs through metabolism and/or renal excretion. Drug metabolism is the process by which a drug undergoes biotransformation to a moiety that is more readily eliminated from the body. Typically, drug metabolites are more polar, water-soluble molecules than the parent drug molecule, and often they are biologically inactive. Drug excretion is the process by which parent drug and/or its metabolite(s) are removed from the body. This is mainly accomplished by

the kidneys (glomerular filtration and proximal renal tubular secretion) and hepatobiliary route. Both processes undergo maturational changes and can also be affected by critical illness. Out of scope for this chapter are maturational or critical illness-related changes in drug metabolism, since this only rarely applies to antibiotics (e.g., cefotaxime and desacetylcefotaxime) and we refer interested readers to recent reviews on this topic [3, 27–29].

Many of the commonly used antibiotics in critically ill children are subject to clearance by renal elimination. Glomerular integrity, physicochemical properties of the drug, and extent of protein binding determine the total amount to be filtered. Since only unbound drug can be filtered, the unbound fraction drives elimination of antibiotics excreted by glomerular filtration. In addition to glomerular filtration, drugs can be eliminated by active secretion in the proximal renal tubules, where transporters of cationic and anionic drugs are highly expressed. Weak acids and bases (i.e., most drugs) can be reabsorbed in non-ionized forms in the distal tubule. This applies to endogenous as well as exogenous compounds.

The glomerular filtration rate (GFR) matures starting from fetal organogenesis into late infancy. At birth, newborns experience profound hemodynamic changes. Among these changes, increased renal blood flow and decreased renal vascular resistance cause a rapid rise in GFR over the first weeks of life, with adult GFR typically attained by 12 months of age. Among preterm neonates, GFR is very low (2–4 mL/min) and can only be maintained due to a delicate balance between vasodilatory effects (regulated by prostaglandins) on the afferent and vasoconstrictor effects on the efferent glomerular arterioli [8]. The maturation of the active tubular secretion process is less well known but is assumed to reach adult capacity in early childhood [4, 30]. Evidently, all these maturation processes likely have a major impact on the dosing of renally cleared antibiotics in children below 1–2 years of age.

Besides maturation, disease characteristics also affect renal elimination capacity. Acute kidney injury (AKI) is common in the neonatal and pediatric ICU unit and may directly lead to impaired renal drug clearance [31, 32]. In critically ill neonates, co-administration of nephrotoxic drugs (e.g., indomethacin, ibuprofen) or peripartal asphyxia were covariates of decreased renal drug clearance of aminoglycosides [31–33]. In a prospective observational study on a tertiary care pediatric intensive care unit (PICU), the incidence of AKI was 27.4%. Risk factors included young age, lower weight, fluid overload, received inotropic support, diuretics, or aminoglycosides [34]. Also here, depending on the severity of renal insufficiency, antibiotic dosing reductions may be necessary.

Augmented renal clearance (ARC) of antibiotics is frequently observed in critically ill adults. The exact pathophysiological mechanism remains unknown but an increased renal blood flow due to vasodilation and increased cardiac output during sepsis has been suggested [35]. Although the commonly used definition (estimated GFR > 130 ml/min) cannot be applied throughout the time span of renal maturation, the concept of supraphysiological, augmented renal clearance very likely also applies in children. However, the available observations are still very limited. De Cock et al. documented hyperfiltration in a cohort of 50 pediatric (range 4.1–65 kg)

cases exposed to amoxicillin-clavulanic acid during intensive care. Median clearance of amoxicillin and clavulanic acid were 17.9 and 12.2 L/70 kg, respectively, with the exposure to inotropics leading to a lower clearance (−18%). Due to the augmented renal clearance, the studied dosing regimen (25–35 mg/kg q6h, based on the amoxicillin compound) resulted in subtherapeutic concentrations in the early period of sepsis, and 25 mg/kg q4h was suggested [36]. Hirai et al. documented ARC (eGFR >160 mL/min 1.73 m^2) and increased vancomycin clearance in pediatric patients with febrile neutropenia, but not in pediatric patients after trauma with systemic inflammatory response syndrome or following surgery [37].

12.2.4 Specific Conditions in Pediatric Critically Ill Patients

12.2.4.1 Children with Burns

The mechanisms behind the alteration in PK remain poorly understood in burn wound patients. Physiological responses to severe burn wounds can be divided into two stages. The first is a resuscitative phase with increased capillary permeability leading to hypovolemia, hypoalbuminemia, tissue edema, and a decrease in cardiac output. The pharmacokinetic consequences of these physiological changes are typically a larger volume of distribution and lower drug clearance. The second phase consists of a hypermetabolic and hyper-inflammatory response with glomerular hyperfiltration, increased tissue perfusion and hypoalbuminemia. During this stage, changes in volume of distribution evolve over time and mainly relate to an increased unbound fraction of protein-bound antibiotics due to hypoalbuminemia. At this stage, patients also display augmented clearance.

Based on observations of vancomycin and amikacin PK in children, these phenomena have also been described in children with burn injuries. Both the distribution volume and clearance of vancomycin were increased in a dataset collected in 13 burned children with normal creatinine values [median age 6 (1–11) years, median weight 25 (12–45) kg], resulting in the recommendation to administer 90–100 mg/kg/day [38]. Amikacin PK were also altered in 70 burned children (median age 4.5 years, median weight 20 kg) with burn injury with an increased distribution volume [18.7–22.7 L, +21%] and clearance [5.36–7.22 L/h, +35%] compared to non-burned cases. The authors hereby suggested to use higher doses (25 mg/kg) to improve PD target attainment rates [39].

The burned skin, scars, and subcutaneous tissues are generally only poorly perfused and are a deep compartment. This matters since these tissues contain potential pathogens. Consequently, blood compartment PK do not necessarily reflect tissue kinetics. Following a distribution half-life, subeschar tissue fluid vancomycin and amikacin concentrations allowed confirmation that the elimination half-lives were significantly longer in the subeschar tissue fluid [40]. In a single dose study of teicoplanin PK in burn patients, including five children, the median teicoplanin concentrations in burn wound fluid were about 60% of the serum levels [41].

12.2.4.2 Use of Organ Support Equipment and the Consequences for Antibiotic Dosing in Children

In the absence of proper PK studies, basic PK principles guide dose selection in children with an extracorporeal circuit. In this circumstance, the initial dose is mainly driven by the distribution volume, while the maintenance dose is based on an estimated clearance. Even if data are available, we would like to suggest that PK observations also may depend on the specific equipment used and cannot simply be extrapolated to other equipment (e.g., priming volume, silicone membrane vs. hollow-fiber oxygenator, coating tubing, surface/flow rate, filter membrane).

Extracorporeal membrane oxygenation: Severe infection may be an indication to initiate ECMO, while the technique itself may also result in nosocomial infections. Consequently, optimal dosing of antibiotics is highly relevant for this specific subgroup of critically ill patients [42]. In an ECMO setting, PK of intravenous antibiotics may be affected by higher volumes of distribution through hemodilution with the additional volume of the extracorporeal circuit, and potential adsorption of antibiotics on ECMO component material, capillary leakage, and reduced drug clearance through secondary ECMO-related effects on elimination organs. The extent of extraction or sequestration, in part, depends on the lipophilicity of the drug (log P) and circuit material. This has been well illustrated using in vitro experiments [43].

Renal dysfunction is common in the ECMO setting, usually related to the underlying indication (e.g., shock, asphyxia, poor perfusion, and hypoxia). By initiating ECMO, there is a loss in the pulsatility of the blood flow and the intrusive equipment can induce an inflammatory state that may affect renal function [44]. Whenever renal function becomes erratic, ECMO is used in combination with renal replacement therapy (see below in renal replacement section).

Limited data are available on antibiotic disposition in children on ECMO [45]. For the aminoglycoside antibiotic gentamicin, it was described that distribution volume is higher and the clearance lower in comparison [45]. Using a contemporary extended dosing interval concept, it was appropriate to use 5 mg/kg of gentamicin in young infants and 9–10 mg/kg in 3–24 months, q24h with the option to prolong the dosing interval in neonates to 30–36 h, depending on therapeutic drug monitoring (TDM) results. Similar to the findings with gentamicin, a review of vancomycin PK in neonates and infants treated with ECMO, also documented that the distribution volume was consistently higher and clearance consistently lower relative to those not treated with ECMO [45]. Based on this pattern, the authors suggest using an initial 20 mg/kg dose of vancomcyin in neonates and children, with subsequent individualization using TDM (trough level target 15–20 μg/mL). Data on meropenem PK in children on ECMO are limited to two case reports from the same center. A first infant was treated with continuous meropenem administration (8-month-old infant, *Pseudomonas aeruginosa* pneumonia, estimated clearance 4.5 mL/kg/min) [46]. A second newborn was treated with both ECMO and renal replacement therapy (2.8 kg, term, 10 days). Following a positive blood culture with *Pseudomonas aeruginosa* (MIC 0.25 mg/L), meropenem (40 mg/kg bolus, 10 mg/kg/h continuous) was initiated and resulted in adequate concentrations (21 μg/mL) and clinical

recovery [47]. Sherwin et al. suggests a similar approach, with 40 mg/kg bolus dose, followed by 200 mg/kg/24 h continuous administration [45].

Cardiopulmonary bypass: While the cardiopulmonary bypass (CPB) equipment and its impact on PK are very similar to ECMO, the reasons for antibiotics mainly cover perioperative prophylaxis. In a cohort of 15 infants and children (3–34 months), cefuroxime (25 mg/kg) administration resulted in a median 8 h post dose simulated cefuroxime concentration of 16 mg/L [48]. A single dose of vancomycin (15 mg/kg) before CPB results in concentrations >5 mg/L throughout the CPB run, with subsequent dosing within 6 h after the initial vancomycin administration. A higher initial dose (20 mg/kg) can be considered if higher concentrations are necessary [49]. Amoxicillin and flucloxacillin (both 30 mg/kg) resulted in serum concentrations above the MIC throughout cardiac surgery, in part due to the reduced clearance [50]. A new dosing prophylactic regimen was proposed for cefazolin (40 mg/kg at induction, 20 mg/kg at start and end of CPB, and 40 mg/kg q8h after the third and fourth dose), based on a PK/PD model using the free fraction of cefazolin in serum from 56 neonates and infants [36]. A decreased tissue disposition into skeletal muscle during CPB with deep hypothermic circulatory arrest was observed in seven infants despite higher overall plasma exposure [51].

Renal replacement: The combination of sepsis and renal failure is common among critically ill patients, including children. While the PK of antibiotics in AKI are substantially different (commonly higher distribution volume and much lower clearance), renal clearance by artificial modes [intermittent hemodialysis or forms of continuous renal replacement therapy (CRRT), such as venovenous hemodialysis, venovenous hemodiafiltration, venovenous hemofiltration, or continuous peritoneal dialysis] necessitates additional considerations besides patient and drug characteristics that relate to the dialysis equipment itself. Dialysis membranes differ in pore size and may be subject to drug adsorption, which can have an effect on antibiotic clearance. Blood and dialysate/ultrafiltration flow rate also influence drug clearance since it affects renal clearance.

To date, guidance and knowledge in children on pediatric drug dosing during renal replacement therapy is scarce [52]. Moreover, polypharmacy in pediatric patients with acute renal failure managed with hemodialysis is common, potentially leading to cumulative drug exposure, complexity of drug interactions, and toxicity [53]. In a study of 2783 pediatric patients with acute renal failure treated with hemodialysis, longer courses of hemodialysis correlated with increasing drug exposure. Of the 50 most frequently prescribed drugs in this cohort, only 5 (10%) had accessible information on dosing adjustments. Overall, >75% received antibiotics (frequency of use: vancomycin > piperacillin/tazobactam > meropenem > trimethoprim/sulfamethoxazole > cefazolin > clindamycin > cefepime). Six out of seven of these drugs had dosing guidance for pediatric patients during pediatric renal dysfunction, but of these only three had guidance related to renal replacement therapy [52].

Compound-specific observations are available for cefazolin and vancomycin. Cefazolin PK data was collected in four children (1.9–17 years, 10.9–57.5 kg) during chronic hemodialysis (3–4 sessions/week) at a dose of 35 mg/kg post dialysis.

This regimen maintained adequate serum concentrations (>8 mg/L) until the next session [54]. Vancomycin is effectively removed by high-flux hemodialysis [55]. In a single case report of a child (6 years, anephric) on intermittent hemodialysis, the serum vancomycin half-life was found to decrease by more than 90% during each course [56]. There was no guidance on aminoglycosides, but its use in this clinical setting is not a first- or second-line treatment modality.

12.3 Pharmacodynamics: Developmental Safety of Antibiotics

As suggested in Fig. 12.1, evaluation of antibiotics in pediatric age categories should at least cover PK and safety since developmental aspects can also affect the safety profile of a given drug. To illustrate this, we use the example of meropenem which was recently labeled to treat abdominal infections in children less than 3 months of age. These labeling changes were based on PK as well as safety aspects collected in prospective studies [57, 58]. Adverse events included sepsis (6%), seizures (5%), elevated conjugated bilirubin (5%), or hypokalemia (5%) and none were judged to be probably or definitely related, while two serious adverse events (fungal sepsis, isolated ileal perforation) were judged to be possibly related. Seizures were of specific interest since this is explicitly mentioned as a warning in the label, independent of the age category. Clinical seizures were observed in 10 (pre)term neonates and 5/10 neonates were known to have an intracranial hemorrhage. Moreover, the predicted meropenem Cmax in subjects with seizures did not differ from those without seizures. In another retrospective analysis in 5566 infants treated with either meropenem or imipenem/cilastatin, the combined outcome of death or seizures was lower with meropenem (Odds Ratio = 0.77) [59].

Nephrotoxicity and ototoxicity related to aminoglycosides and/or vancomycin exposure is an example of the need to monitor safety in every subpopulation. Toxicity has limited the use of aminoglycosides but there is a consistently lower rate of oto- and nephrotoxicity in neonates when compared to adults. This suggests maturational toxicodynamics in favor of infancy [60]. The most recent Cochrane review on one dose per day compared to multiple doses per day for gentamicin in neonates suggests (pooled, all dosing regimens) that the incidence of ototoxicity was 1.4% (n = 3/214) with no cases (n = 0/348) of nephrotoxicity (increased creatinine or decreased creatinine clearance) [61]. Nestaas et al. also reported a pooled analysis (all aminoglycosides) in neonates, including nephrotoxicity (increased creatinine, urinary aminopeptidase, 50/589 events, 8.4%), and ototoxicity (1/210 events, 0.5%) [62]. Similarly, a recent review on the current evidence supports the favorable safety profile of vancomycin in neonates. However, observations on safety of high-dose intermittent dosing regimens are still very limited [63]. In an observational study on vancomycin-induced nephrotoxicity in children, admission

to the ICU and co-treatment with aminoglycosides were identified as predisposing factors [64].

Developmental aspects may alter relative risks (exposure/toxicity), but some aspects are specific to the pediatric age category. The duration of antibiotic exposure is associated with an increased risk to develop necrotizing enterocolitis, a disease very specific to (pre)term neonates. Similarly, there is an association between antibiotic exposure in early life and the risk to subsequently develop obesity. Both phenomena are claimed to be due to the impact on the intestinal microflora [65, 66]. Another risk factor specific to neonates and young infants relates to the use of calcium containing perfusions to avoid hypocalcemia. Combined with low flow rates of perfusions to avoid fluid overload, co-administration of ceftriaxone with calcium-containing solutions holds a risk for intravascular precipitation and cardiovascular collapse [67]. Finally, because of potential competitive binding to plasma proteins with highly bound antibiotics, hyperbilirubinemia is another population-specific risk, since unconjugated hyperbilirubinemia is common in early neonatal life [24].

12.4 Compound-Specific Observations

12.4.1 Aminoglycosides

Aminoglycosides are frequently used (in combination with a penicillin) to treat suspected neonatal sepsis. Consequently, gentamicin is the most commonly administered drug in neonates. Other aminoglycosides commonly used are amikacin, netilmicin, or tobramycin [68].

The concentration-dependent response supports the use of high doses to attain peak concentrations for aminoglycosides. Aminoglycosides are hydrophilic, distribute to the extracellular water compartment, and are eliminated by glomerular filtration. In neonates, this means that higher doses (mg/kg, higher distribution volume) combined with extended dosing intervals (lower renal clearance) are needed [8]. In a pediatric meta-analysis comparing extended interval dosing with multiple daily doses for aminoglycosides, there were no significant differences in clinical failure rate, microbiologic failure rate, and combined clinical or microbiologic failure rates, but trends favored extended interval dosing consistently [69]. In neonates, extended interval dosing of aminoglycosides was safe and effective, with a reduced risk of serum drug concentrations outside the therapeutic range [61, 62].

Since elimination of aminoglycosides is exclusively by glomerular filtration, covariates of GFR will affect clearance [70]. In neonates, this means that gestational age (GA), birth weight, postnatal age (PNA), ibuprofen co-administration (−20%), and peripartal asphyxia (−40%) affect aminoglycoside clearance. To further illustrate this, the impact of ibuprofen on the elimination half-life of amikacin (+ 32%) in preterm neonates (<30 weeks, at birth) is provided in Fig. 12.2 [71]. Similarly, the impact

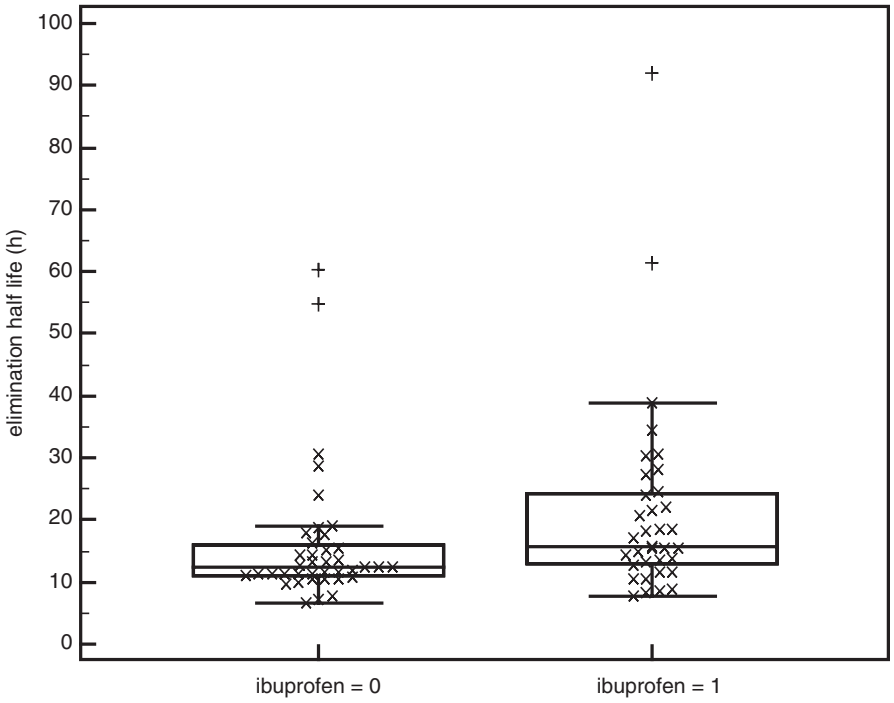

Fig. 12.2 The impact of ibuprofen exposure (yes/no) on the median amikacin elimination half-life in preterm neonates (<30 weeks, 16.4 instead of 12.4 h) in the first days of life [71]

of whole body cooling following perinatal asphyxia on amikacin clearance in early neonatal life (day 1, 2, 3, and 4) is compared to reference data in Fig. 12.3 [72, 73]. There is a 40% reduction in clearance on any of the consecutive days (day 1–4) [60].

12.4.2 Vancomycin

Vancomycin is commonly used in neonatal and pediatric intensive care units to treat Gram-positive infections. *Staphylococcus epidermidis and aureus*, including strains resistant to methicillin, are usually inhibited by concentrations of 1–4 μg/mL vancomycin (depending on the MIC). *Staphylococcus pyogenes*, *Streptococcus pneumoniae*, and *viridians* are susceptible to 2 μg/mL vancomycin. *Bacillus spp.* are inhibited by 2 μg/mL, *Corynebacterium spp*. by 0.04–3.1 and *Clostridium spp*. by 0.39–6 μg/mL vancomycin, respectively [3, 63]. Vancomycin is fairly water-soluble molecule with limited plasma protein binding (albumin, IgA) in adults and is mainly eliminated by the kidneys.

Studies in adults have shown that the advocated PK/PD index of favorable clinical outcome is an AUC over a 24 h period at steady-state divided by the minimum inhibitory concentration (MIC) of the suspected pathogen (AUC/MIC) of at least

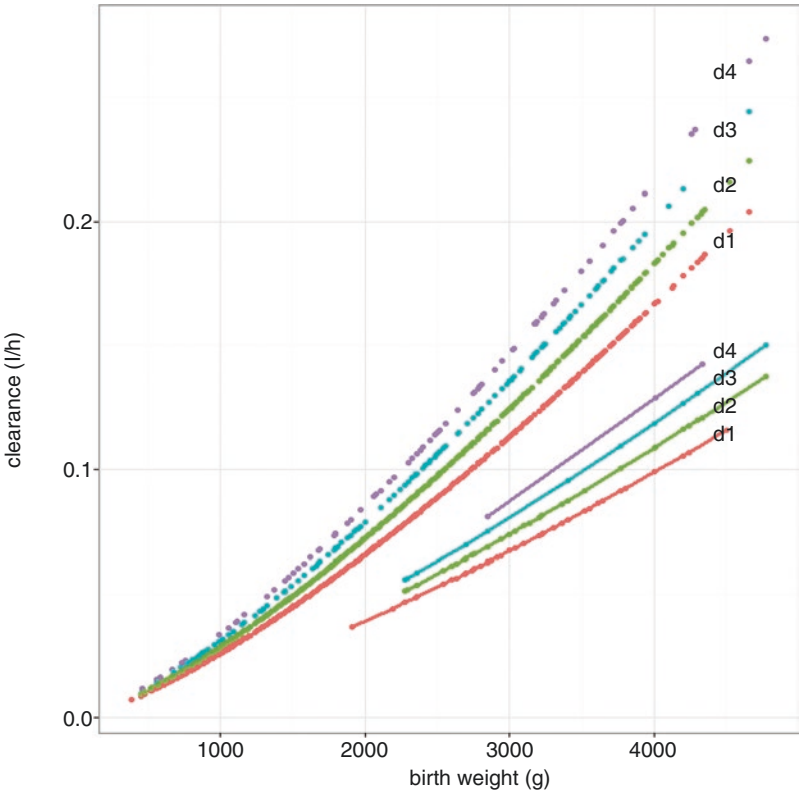

Fig. 12.3 Estimates of amikacin clearance trends in early neonatal life based on pooling of reported datasets. There is a maturational trend in clearance, related to birth weight and postnatal age (day 1, 2, 3, 4, as reflected by the colors) compared to a subgroup of term neonates undergoing whole body cooling as treatment for perinatal asphyxia. The lower group of lines are the "whole body cooled group" and the upper set of lines are those who were not "cooled" [72, 73]

400 [74]. In routine clinical practice, trough concentrations, which correlate well with AUC/MIC ratios, are used as a "surrogate" parameter to optimize vancomycin dosing regimens, because AUC/MIC calculations are labor- and cost-intensive.

Similar to the earlier mentioned findings on aminoglycosides, the maturational PK are mainly driven by changes in body water content and renal clearance. Based on an integrated analysis of gentamicin, tobramycin, and vancomycin, a semi-physiological function for GFR-mediated clearance from preterm neonates to adults was derived [75]. In critically ill children, altered PK was reported with around 50% of patients remaining below the AUC/MIC target of 400 [76]. However, lower protein binding (20–30%) has been suggested in two pediatric studies, when compared to non-critically ill adults (50%) [36, 77]. This lower protein binding had direct consequences on target attainment rates in critically ill children when using PK/PD indices based on unbound concentrations rather than those based on total concentrations [36]. Since unbound drug is pharmacologically active, these data support the need to assess protein binding in pediatric drug development of intermediate to highly bound antibiotics.

Table 12.1 Vancomycin dosing guidelines throughout pediatric life, depending on maturation and renal impairment [78]

Neonates, i.e., up to 28 days of postnatal life		
Initial dose	15 mg/kg	
Maintenance	10 mg/kg q12h, postnatal age < 8 days	
	10 mg/kg q8h, postnatal age 8–28 days	
Additional comment:		
In preterm neonates, vancomycin clearance decreases as postconceptional age decreases. Consequently, longer dosing intervals may be necessary and therapeutic drug monitoring is recommended		
Children		
10 mg/kg q6h		
Patients with impaired renal function		
(*Children not explicitly mentioned, nor excluded, but based on the reference creatinine clearance in adults*) Initial dose 15 mg/kg to achieve therapeutic drug concentrations In the anephric patient, the maintenance dose is 1.9 mg/kg/24 h		
Creatinine clearance mL/min	***Vancomycin dose mg/24 h***	***%, normal dose***
>100 mL/min	2000	100
100	1545	77
90	1390	70
80	1235	62
70	1090	55
60	925	46
50	770	38
40	620	31
30	465	23
20	310	16
10	155	8

These dosing regimen are different from the dosing regimens proposals based on PK study in specific NICU or PICU setting

All the above-mentioned dosing regimens differ substantially from the currently labeled dosing recommendations [78, 79], as summarized in Table 12.1, reflecting the paucity of evidence available to inform a uniform dosing regimen. Irrespective of the initial dose used, TDM is strongly recommended. Vancomycin is usually administered intermittently, with a target trough concentration of 10–15 μg/mL, but there is preliminary experience with continuous administration (after an initial loading dose) [80].

12.4.3 Carbapenems: Meropenem

Carbapenems are beta-lactam antimicrobial agents with an exceptionally broad spectrum, with activity against aerobic Gram-negative and Gram-positive and anaerobic pathogens. Older carbapenems like imipenem are susceptible to degradation and require co-administration of an inhibitor like cilastatin. More recently introduced carbapenems like meropenem, ertapenem, or doripenem demonstrated increased

stability. Meropenem is at present the most frequently administered carbapenem. It seems reasonable that other carbapenems will display similar patterns and impact of covariates since all are cleared by renal elimination (GFR + renal tubular).

Meropenem has recently been labeled for infants less than 3 months of age (30 mg/kg q8h for all neonates >32 weeks GA and >2 weeks PNA or 20 mg/kg, q12h when <32 weeks GA and <2 weeks PNA; q8h for <32 weeks GA and >2 weeks PNA or >32 weeks GA and <2 weeks) for abdominal infections (necrotizing enterocolitis). Complicated skin and skin structure infections, intra-abdominal infections and meningitis are dosed at 10 mg/kg (max 500 mg) q8h, 20 mg/kg (max 1000 mg) q8h, and 40 mg/kg (max 2000 mg) q8h, respectively, in children >3 months (weight based dosing), while 500 mg up to 1000 mg q8h is suggested in adults.

The SPC also provides guidance in the presence of renal impairment in adults [no adaptations >50 mL/min; 26–50 mL/min q12h instead of q8h; 10–26 mL/min q12h 50% recommended dose; <10 mL/min q24h 50% recommended dose]. These recommendations strongly support the fact that the main route of elimination is renal (GFR + renal tubular secretion).

The SPC states that there is no experience in pediatric patients with renal impairment. However, there is some guidance available in the literature in the setting of continuous renal replacement therapy in children. Goldstein et al. studied meropenem PK (single dose, 20 mg/kg, max 500 mg) in seven pediatric patients (age range 1.4–17 years) with end-stage renal disease and chronic renal replacement therapy [81]. Clinical trial simulations (in silico model predictions) demonstrated that children >5 years achieved target concentrations (>40 or 75% of time above MIC) with a dosing regimen of 20 mg/kg q12h, while in children <5 years, a dose of 20 mg/kg q8h was needed to optimize target attainment [82]. During hemodialysis (*intradialytic*), meropenem was cleared in a manner that correlated with the percent urea reduction. Median meropenem half-life was 1.3 (range 1.1–1.7) h while the meropenem half-life off dialysis (*interdialytic*) was 7.3 (range 4.9–11.7) h. Aiming for >70% of time a meropenem concentration > 4 μg/mL, dosing simulations revealed that either 25 mg/kg q24h or 40 mg/kg q48h between consecutive dialysis sessions is appropriate [82]. As mentioned earlier, there is—limited—experience with a loading dose (40 mg/kg), followed by a maintenance dose (200–240 mg/kg/24 h) in a newborn and an infant during CVVH. Finally, we want to mention a specific drug–drug interaction between meropenem and valproate of relevance in both adults and children since simultaneous administration results in a significant decrease in valproate levels with the potential of levels and seizures.

12.5 Approaches to Improve Knowledge and Clinical Practice

Traditionally, pharmacokinetic studies have involved intensive serial blood sampling performed in a limited number of healthy, male, adult volunteers [83–85]. These studies allow the investigator to estimate the variability in plasma drug concentrations between individuals following the administration of a certain dose. In

contrast, the population pharmacokinetic approach allows the investigator to characterize the pharmacokinetics of the drug of interest using fewer blood samples by treating all of the individuals in the study as a random sample from a larger population. From these data, it is then possible to estimate measures of central tendency for the pharmacokinetic parameters of the entire population, while simultaneously estimating within and between subject variability and quantifying the amount of residual, unexplained variability [86]. This improves the population mean and variance estimates and improves accuracy when selecting an initial dosing regimen or adjusting a dosing regimen in response to therapeutic drug monitoring data.

Population pharmacokinetic modeling is used to increase our understanding of the quantitative relationships between drug dosing regimens, patient characteristics, and drug pharmacokinetics. Today, the use of population pharmacokinetic modeling is actively encouraged by the FDA and the EMA [87, 88]. Despite the widespread acceptance of population pharmacokinetic methods in the drug approval process, relatively few population pharmacokinetics studies have been conducted among neonates [89].

Deriving the "optimal" individualized dose that is neither ineffective nor toxic is the ultimate goal of many physicians, pharmacologists, regulatory agencies, and pharmaceutical companies [90]. Achieving this goal is challenging for many drugs due to pharmacokinetic variability within and between patients. For drugs with narrow therapeutic windows (a small margin separates subtherapeutic from toxic concentrations), it is necessary to conduct population pharmacokinetic studies to determine whether predictable factors (covariates) can be identified that influence the extent and peak of drug exposure [91]. If substantial variability remains after such investigations and a target concentration range has been established, then it may be prudent to measure drug concentrations in each patient (a practice known as therapeutic drug monitoring) [92, 93]. Drug concentration measurements obtained from therapeutic drug monitoring can then be used to refine the model's pharmacokinetic parameter predictions for that patient in a Bayesian manner [23, 94].

The first step to improving the use of antibiotics in critically ill children is generating evidence of how a certain (critical) disease state affects a given drug. General trends have been discussed by Thakkar et al. and in this chapter, but additional clinical trials explicitly designed to monitor concentrations and compare pharmacokinetics of antibiotics in critically ill children to those who are not critically ill are needed [7]. One way by which this may be accomplished is through the collection and use of TDM and/or opportunistic sampling. For example, TDM is routinely performed as part of standard of care for certain antibiotics such as vancomycin to ensure that trough concentrations are in the desired range. Instead of simply discarding these sample concentrations, they could be used as part of a pharmacokinetic analysis. Alternately, if the antibiotic itself doesn't require TDM, collection of blood samples to monitor for endogenous markers and/or concomitant drugs (such as in burns patients) could also be salvaged and analyzed for the antibiotic. Interestingly, this process can also be useful in the opposite direction: Germosevek et al. presented a PK model that allows healthcare providers to take a gentamicin TDM sample at a time that is convenient (i.e., during a routine blood test) rather than needing to take a specific "trough" sample to determine whether drug levels are high enough [95].

Another potentially beneficial technique for facilitating PK studies in this protected population is microsampling. Microsampling, as the name implies, is the collection of smaller-than-normal plasma samples for bioanalysis. Use of microsampling in critically ill children would allow a significant reduction in the blood volume required, thereby reducing the risk of further upsetting fluid balance in patients whose fluid balance may already be compromised [95].

The next step is to then take the information available and utilize it to help improve predictions of antibiotic concentrations based on developmental status and disease state (in addition to other factors), which will in turn help inform dosing recommendations. A tool with great potential to help achieve this goal is pharmacokinetic analyses. Previous pharmacokinetic analyses of antibiotics have had a direct impact on care of critically ill pediatric patients. For example, current aminoglycoside dosing regimens have been driven by PK/PD analyses demonstrating improved efficacy and safety when dosing is once per day rather than multiple times a day [96, 97]. Two types of PK analyses in particular, population modeling (popPK) and physiologically based modeling (PBPK), could be at the forefront of antibiotic investigations in critically ill children moving forward. Population PK modeling leverages nonlinear curve fitting with fixed and random effects (error) to allow understanding of a drug's PK in both a population and an individual. One of the major benefits of popPK in this population is that it can effectively describe the PK of a drug even if patient plasma concentrations have only been sparsely sampled. As such, critically ill children, for whom taking more than two or three plasma samples is often impractical, could still provide valuable data to inform a popPK model. In fact, a number of PK models for antibiotics have been developed using only TDM samples [39, 43, 98], as described above. Conversely, a vetted and well-characterized PBPK model could help predict appropriate antibiotic doses and subsequent concentrations, thereby obviating the need for frequent TDM sampling [99]. Indeed, PBPK models, such as that developed by De Cock et al. could be used to establish evidence-based dosing regimens for renally excreted drugs (such as most antibiotics) in critically ill children [75].

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