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Effect of Kidney Function on Drug Kinetics and Dosing in Neonates, Infants, and Children

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Abstract Neonates, infants, and children differ from adults in many aspects, not just in age, weight, and body composition. Growth, maturation and environmental factors affect drug kinetics, response and dosing in pediatric patients. Almost 80 % of drugs have not been studied in children, and dosing of these drugs is derived from adult doses by adjusting for body weight/size. As developmental and maturational changes are complex processes, such simplified methods may result in subtherapeutic effects or adverse events. Kidney function is impaired during the first 2 years of life as a result of normal growth and development. Reduced kidney function during childhood has an impact not only on renal clearance but also on absorption, distribution, metabolism and nonrenal clearance of drugs. ‘Omics’-based technologies, such as proteomics and metabolomics, can be leveraged to uncover novel markers for kidney function during normal development, acute kidney injury, and chronic diseases. Pharmacometric modeling and simulation can be applied to simplify the design of pediatric investigations, characterize the effects of kidney function on drug exposure and response, and fine-tune

dosing in pediatric patients, especially in those with impaired kidney function. One case study of amikacin dosing in neonates with reduced kidney function is presented. Collaborative efforts between clinicians and scientists in academia, industry, and regulatory agencies are required to evaluate new renal biomarkers, collect and share prospective pharmacokinetic, genetic and clinical data, build integrated pharmacometric models for key drugs, optimize and standardize dosing strategies, develop bedside decision tools, and enhance labels of drugs utilized in neonates, infants, and children.

Key Points

Changes in kidney function during childhood modify not only renal clearance but also absorption, distribution, metabolism and nonrenal clearance of drugs, affecting pharmacokinetics, response, and dosing of drugs.

New renal biomarkers are needed. ‘Omics’-based technologies, such as proteomics and metabolomics, can be leveraged to uncover novel markers for kidney function during normal development, acute kidney injury, and chronic diseases.

Pharmacometric modeling and simulation can be applied to simplify design of pediatric investigations, characterize effects of kidney function on drug exposure and response, and fine-tune dosing in pediatric patients, especially in those with impaired kidney function.

Collaborative efforts are required to evaluate new renal biomarkers, optimize and standardize dosing strategies, develop bedside decision tools, and enhance labels of drugs utilized in neonates, infants, and children.

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1 Introduction

Administering drugs in neonates, infants, and children is challenging. Up to 80 % of drugs prescribed in pediatric patients have not been formally tested in this population, and are therefore not labeled for use in neonates, infants, and children ('off-label use') [1, 2]. Clinical research involving children is more difficult than in adults for several reasons [3–6]: (1) a small number of pediatric patients are eligible for clinical trials; (2) the ethical hurdles of conducting studies with placebo/control arms in sick children; (3) cumbersome procedures for obtaining informed consent and, if appropriate, informed assent; (4) lack of suitable infrastructure to conduct pediatric clinical studies; (5) limited market size, and thus economically less attractive for pharmaceutical companies; and (6) technical challenges of collecting laboratory, imaging, or clinical data in pediatric patients.

A majority of drug dosing regimens for use in neonates, infants, and children are derived from adult data by adjusting for body weight/size. Such a simple extrapolation from adults to pediatric individuals may not be appropriate. Why? Children are not 'small adults'. They differ from adults in many aspects, not just in age and body weight: (1) body composition changes in neonates, infants, and children [7–9]; (2) organ maturation and development can affect pharmacokinetics and response of drugs, especially in children younger than 2 years of age [10, 11]; and (3) therapeutic window (TW), also called therapeutic index (i.e. exposure range with optimal efficacy/safety balance) may change over time in children. As a result of organ maturation and development, kidney function changes during the first 2 years of life, which in turn will affect both drug exposure and response in neonates and infants [12–14].

Various factors can affect kidney function in neonates, infants, and children: (1) development and maturation of kidneys as described earlier [10]; (2) underlying kidney diseases and comorbidities [15]; (3) medications and other therapeutic interventions, such as hypothermia in neonates [16–21]; and (4) environmental and genetic factors [22] (Fig. 1).

The focus of this article is to (1) review physiological differences between neonates, infants, children, and adults; (2) review markers for assessing and monitoring kidney function; (3) understand factors that affect kidney function and its impact on drug exposure and response in pediatric patients; (4) introduce quantitative approaches, such as pharmacometric modeling and simulation, to simplify designs of studies in pediatric patients, characterize effects of the kidney on drug exposure and response, and fine-tune dose strategies in pediatric patients, especially in those

with impaired kidney function; and (5) outline opportunities to facilitate development and optimize utilization of therapeutics in neonates, infants, and children. The majority of our examples and related discussion will focus on neonates and young infants, who are particularly subject to pharmacokinetic changes due to rapid growth, development, and maturation of organs, including the kidneys. Most studies using quantitative approaches such as pharmacometric modeling and simulation are conducted in this age range.

2 Method

Relevant articles in the PubMed and EMBASE databases were identified using the following keywords: 'neonates', 'infant', 'children', 'pediatric', 'drug development', 'pharmacokinetics', 'kidney function', 'modeling', 'simulation', 'drug dosing', and 'pharmacometrics'. Our search was limited to English-language studies published in peer-reviewed journals. Additional publications were identified from review articles.

3 Physiological Differences Between Adults and Children

Neonates, infants, and children differ from adults in many aspects, not just in age, body weight and composition: capacity of drug-metabolizing enzymes and kidney function change due to organ maturation and development, resulting in altered drug exposure and response, especially in children younger than 2 years of age. Stages of growth are illustrated in Fig. 2 [23].

3.1 How Does Body Size and Composition Change in Neonates, Infants, and Children?

Neonates, infants, and children represent a heterogeneous population with nonlinear growth in size and bodyweight from less than 500 g to more than 100 kg. Most changes in body composition take place during the first 2–3 years of life. Body weight doubles within 5 months, and triples within 1 year, while body length increases by 50 % during the first year, and doubles within 4 years. Proportions of body weight contributed by fat, protein, intracellular and extracellular water significantly change during childhood. Total body water (TBW) (i.e. the sum of intracellular and extracellular water) constitutes 80 % of body weight in preterm neonates and 75 % in term neonates. It decreases to adult values at 4 months and remains relatively constant from this age onwards [24] (Fig. 3).

Fig. 1 Factors affecting kidney function in neonates, infants, and children

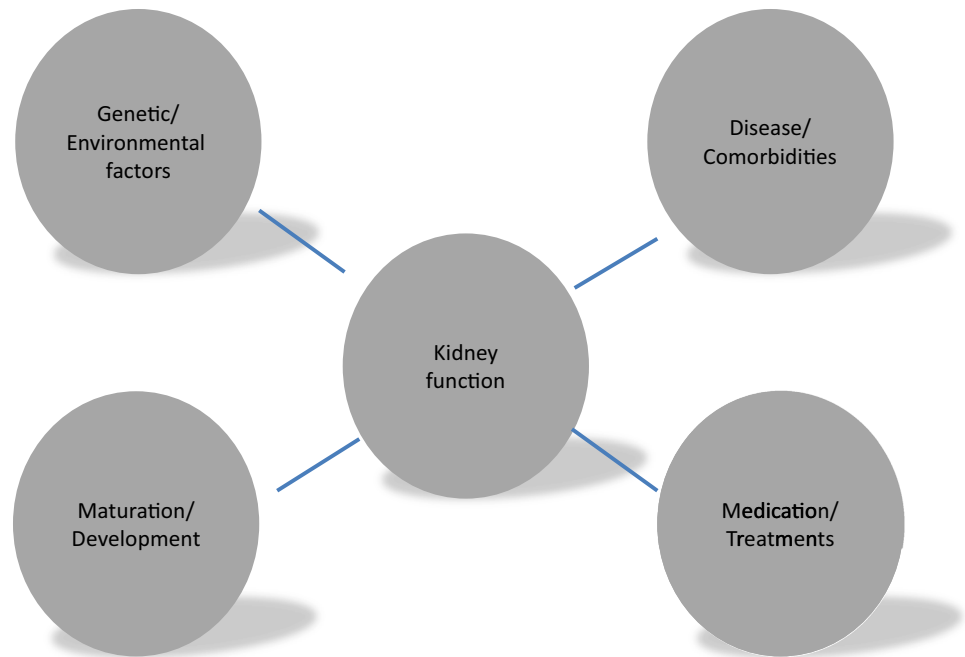
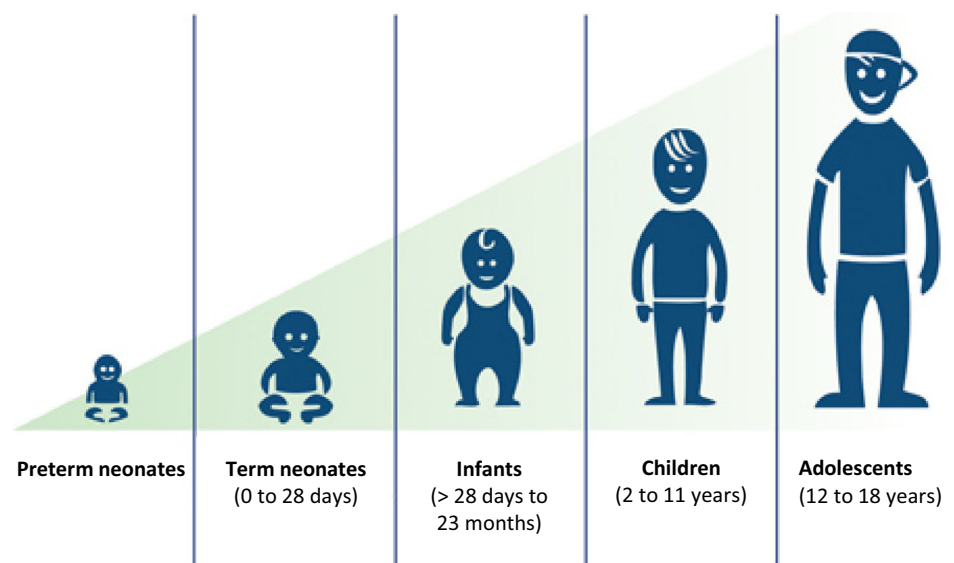


Fig. 2 Stages of growth. Modified from the National Heart, Lung, and Blood Institute [23]



3.2 How Does Development and Maturation of Organs Affect Drugs in Neonates, Infants, and Children?

Changes due to development and maturation of organs can affect various aspects of drug pharmacokinetics, especially in neonates and infants. Potential key changes in absorption, distribution, metabolism, and elimination of drugs during the first years of life are presented in Table 1 [10, 25–27].

Absorption is decreased in neonates and infants, and increases progressively during childhood, mainly due to

altered gastric pH, gastric emptying, and intestinal transit time [10, 28]. Colonization of the gastrointestinal tract by bacteria varies with age, route of delivery (vaginal vs. cesarean section), type of feeding, and concurrent drug therapy. This process influences metabolism of bile salts and drugs by intestinal cytochrome P450 (CYP) as well as intestinal motility and absorption [29]. An adult pattern of microbial products is established around 5–12 months of age [30, 31].

Distribution is modified essentially due to changes in body composition and protein-binding capacity. The amount of TBW is higher in neonates and infants [7].

Fig. 3 Body composition and growth. Adapted from Bechard et al. [24]

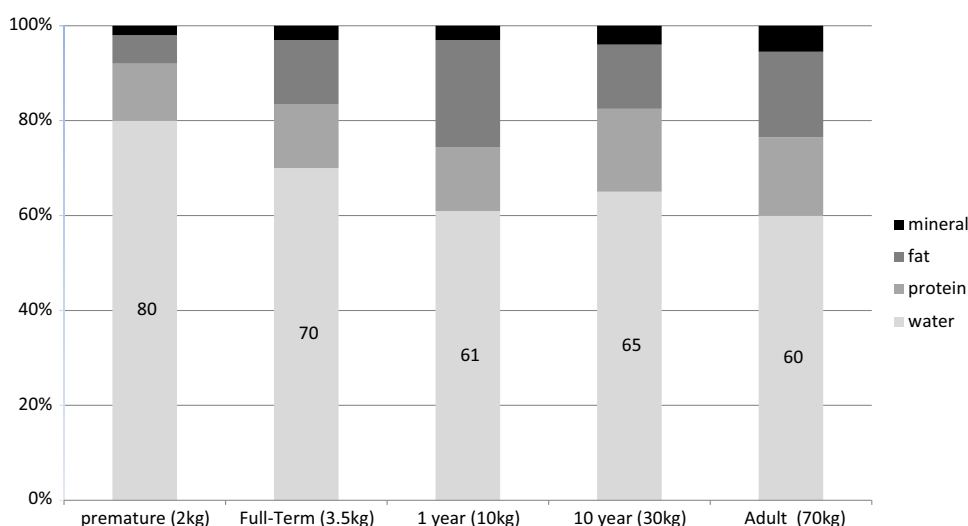


Table 1 Effects on drug pharmacokinetics related to organ maturation and development in children

	Neonate/infant	Effect on drug pharmacokinetics
Absorption	<ul style="list-style-type: none"> ↑ Gastric pH ↑ Gastric emptying ↑ GI transit time ↓ Gastric enzyme activity ↓ Bile salt Changes in intestinal flora Skin permeability 	<ul style="list-style-type: none"> Variable effect on rate and extent of absorption ↓ Absorption of some drugs ↑ Absorption of some drugs ↑ Absorption of some drugs
Distribution	<ul style="list-style-type: none"> ↑ TBW ↑ ECW ↓ Body fat ↓ Muscle mass ↓ Albumin levels ↓ α1-acid glycoprotein 	<ul style="list-style-type: none"> ↑ Apparent V_d for water-soluble drugs ↓ Apparent V_d for drugs that bind to muscle and/or fat ↓ Fraction bound for drugs highly bound to albumin ↓ Fraction bound for drugs highly bound to α1-acid glycoprotein, resulting in an increased apparent V_d and/or increased toxicity
Metabolism	<ul style="list-style-type: none"> ↓ Oxidative enzyme activity (CYP)^a ↓ Glucuronidation (UGT)^a 	<ul style="list-style-type: none"> ↓ Drug metabolism, plasma clearance with ↑ in apparent half-life in neonates and young infants ↑ Plasma drug clearance and ↓ in half-life of specific drugs
Elimination	<ul style="list-style-type: none"> ↓ Kidney function (filtration, reabsorption, secretion) 	<ul style="list-style-type: none"> ↓ Clearance and accumulation of renally excreted drugs

GI gastrointestinal, TBW total body water, ECW extracellular water, V_d volume of distribution, UGT uridine diphosphate glucuronosyltransferase, CYP cytochrome P450, ↑ indicates increase, ↓ indicates decrease

^a Apparent increase in activity for selected drug-metabolizing enzymes in older children/adolescents

Although the percentage of TBW does not change considerably after 1 year of age, there is continuous decrease in extracellular water from infancy to young adulthood. It should be noted that drug-binding capacity to plasma proteins is decreased in neonates and infants, resulting in an increased volume of distribution of water-soluble drugs [32]. Other factors such as altered regional blood flow and immaturity of the blood-brain barrier can also affect distribution of drugs in neonates, infants, and children.

Metabolism of many drugs is dependent on hepatic blood flow and activity of drug-metabolizing enzymes and transporters. Hepatic blood flow is reduced in neonates, and increases with increasing cardiac output over time. Due to ontogeny, the capacity of drug-metabolizing enzymes and transporters changes in neonates and infants. Activity of phase I enzymes is reduced in neonates [11], increases progressively during the first 6 months of life, may exceed adult rates for a few years, slows during adolescence, and

approaches adult rates by late puberty [33]. Similar age-dependent changes are observed for the phase II enzymes, uridine diphosphate glucuronosyltransferase (UGT), sulfotransferase, glutathione-S-transferase (GST), and *N*-acetyltransferase (NAT) [10]. It is important to realize that different isoenzymes within a family of enzymes can mature at different rates during the first years of life.

Elimination of a majority of drugs from the body occurs primarily via the kidney. Nephrogenesis starts at weeks 5–6 of gestation and is completed around weeks 34–35 of gestation. This process of nephrogenesis is followed by postnatal changes in intrarenal blood flow, but kidney function is still impaired compared with that of adults. This is due to a combination of factors: (1) immature glomerular filtration and tubular function; (2) reduced kidney perfusion pressure; and (3) inadequate osmotic load to produce full counter-current effects. Glomerular filtration rate (GFR) increases rapidly in neonates because of a postnatal drop in kidney vascular resistance and an increase in renal blood flow. GFR continues to increase gradually, approaching adult levels by 12 months of age (Fig. 4), then exceeding adult rates during preschool years to finally reach adult values at prepubertal age [10, 34–39]. A transient increase has been explained by some authors to be based on a larger increase of kidney weight compared with body weight in preschool-age children. This might be explained by an augmented increase of glomerular and tubular cell size and an increased number of capillaries [40, 41].

Other factors influencing developmental changes in kidney excretion are prematurity, kidney/urologic fetal malformations, and concomitant medications. Preterm infants are particularly susceptible because of ongoing nephrogenesis [42]. A twofold increase of vancomycin clearance, a drug almost exclusively excreted by the kidney, from week 24 of postmenstrual age (PMA) to week 34

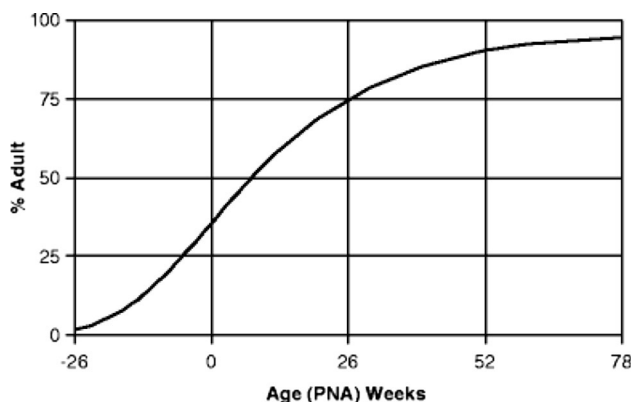


Fig. 4 Typical maturation of GFR as a function of PNA, expressed as a percentage of adult GFR. Adapted from Goyal [41]. *GFR* glomerular filtration rate, *PNA* postnatal age

is described [43]. Neonates born small for gestational age (SGA) were found to have a 16 % reduction in drug clearance compared with preterm neonates who are appropriate for gestational age (AGA) [44]. Drugs such as betamethasone or indomethacin have been shown to alter the normal pattern of postnatal kidney maturation in preterm neonates [45].

3.3 What Do We Know About the Therapeutic Window of Drugs in Pediatric Patients?

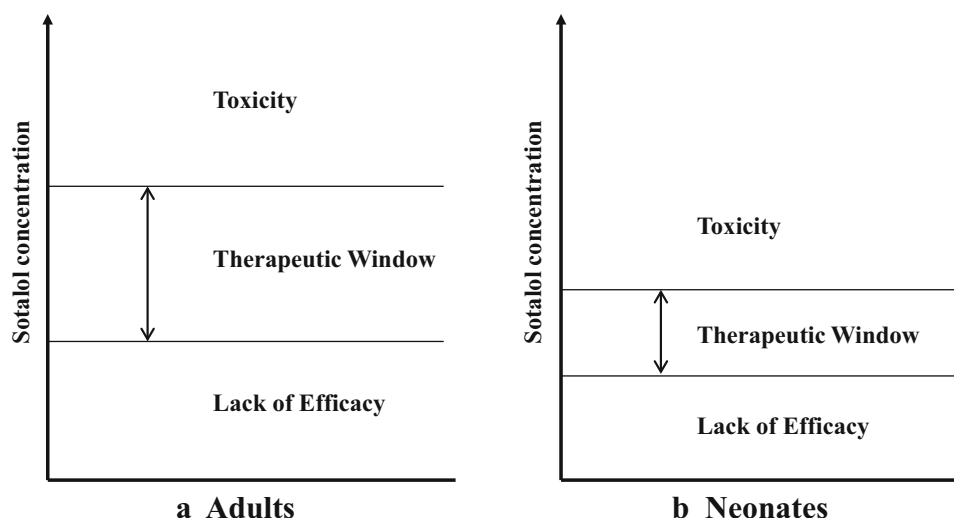
Developmental changes can modify pharmacokinetic profiles of drugs (e.g. increase high peak-to-trough ratios or variability in exposure), which may impact the efficacy/safety balance [46]. Developmental changes may also directly impact drug response without modifying pharmacokinetic profiles in children [11, 47–50]. Changing expression of receptors during the first years of life can affect efficacy/safety response of drugs in children [51]. A study of sotalol in the treatment of supraventricular tachycardia showed that neonates exhibited a higher sensitivity towards QTc interval prolongation compared with older children (Fig. 5) [52]. Augmented response to warfarin and cyclosporine in children [48, 49], increased sensitivity to d-tubocurarine, an antagonist of nicotinic neuromuscular acetylcholine receptors, in neonates and infants compared with children, adolescents, and adults [53], and different sensitivity to bronchodilators because of a lack of smooth muscles in the airways in neonates [54] are other examples that illustrate that developmental changes can impact the TW of drugs in neonates, infants, and children.

3.4 What Do We Know About Pharmacogenetics in Pediatric Patients?

As in the adult population, polymorphism in drug-metabolizing enzymes, drug-transport systems, and drug targets can be associated with clinically relevant differences in drug disposition and/or efficacy/safety profile. Polymorphisms, also known as single nucleotide polymorphisms (SNPs), are defined as genetic variations occurring in at least 1 % of the population. An increasing number of studies are being published that describe differences in drug response as a result of individual genetic background, but most of these reports include only adult individuals [55, 56]. A few studies have shown the impact of pharmacogenomics in pediatric patients and highlighted differences between children and adults [55, 57].

In children with kidney or heart transplants, expression of CYP3A5 affects clearance, dose requirement, and immunosuppressive effects of tacrolimus. Children expressing CYP3A5 (those carrying the A nucleotide,

Fig. 5 Narrower therapeutic window can alter efficacy/safety balance of drugs in children/neonates (b) compared with that in adults (a). Example of sotalol [52]



defined as the *1 allele) have a higher dose requirement than non-expressers (those homozygous for the G nucleotide, defined as the *3 allele) [58, 59]. In children with asthma and the CYP3A4*22 allele, fluticasone treatment is associated with better asthma control than in those with the wild-type allele [60]. Pharmacogenetic effects on drug exposure and response can also impact efficacy/safety profiles of drugs in pediatric patients. Cisplatin ototoxicity has been associated with variants in the GST gene family [61, 62]. It is estimated that 10 % of the population have heterozygous mutations in the thiopurine *S*-methyltransferase (*TPMT*) gene, leading to decreased levels of the enzyme, while as many as 1 in 300 have homozygous mutations with very low levels of function of the enzyme [63]. SNPs in the *TPMT* gene are associated with an increased risk of developing severe and life-threatening *TPMT*-mediated myelotoxicity or hepatotoxicity in children treated with conventional dose of thiopurines [63, 64]. SNPs in the *TPMT* gene are also associated with a risk of developing severe, potentially life-threatening bone marrow toxicity when treated with conventional doses of azathioprine or mercaptopurine [65]. Studies have found a strong association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse reactions [66–68]. In such cases, drug labels should include treatment strategies based on pharmacogenetic factors; see example labels for 6-mercaptopurine [69], azathioprine (*TPMT* variants) [70], and carbamazepine (HLA-B*1502 allele) [71, 72]. Atomoxetine and pimozone are drugs with specific genotype-based dose recommendations for children [56, 73]. Other examples of dose recommendations can be found on the PharmGKB website (<http://www.pharmgkb.org>).

Pediatric patients present unique pharmacogenetic challenges as neonates, infants, and children have the

additional complexity of ontological phenotypes that impact their responses to drugs. Thus, the role and involvement of pharmacogenetics may differ between adult and pediatric patients, and dosing strategies developed in adults may be inaccurate in neonates, infants, and/or children. An example is the role of CYP2C9 and VKORC1 genetic variations in warfarin treatment [74]. In adult patients, such genetic variations are key contributors to intersubject variability in warfarin exposure, whereas in pediatric patients, age and body size have a more pronounced impact on intersubject variability in warfarin exposure than genetic variations [57, 74, 75].

4 Kidney Function and its Impact on Drugs in Pediatric Patients

This section reviews (1) factors that can alter kidney function; (2) effects of impaired kidney function on drug exposure (pharmacokinetics) and response; and (3) measures for assessing and monitoring kidney function and markers for detecting kidney injury/disease in pediatric patients.

4.1 Which Factors Affect Kidney Function in Pediatric Patients?

In neonates, infants, and children, multiple factors affect kidney function: (1) development and maturation of the kidneys as described earlier [10]; (2) acute kidney injury (AKI), underlying kidney diseases and comorbidities [15]; (3) medications, renal replacement therapy (RRT) and other therapeutic interventions, such as hypothermia in neonates [16–19, 76, 77]; and (4) environmental and genetic factors [22].

4.1.1 Chronic Kidney Disease (CKD)

Although CKD is seen less frequently in pediatric patients than in adult patients, it is not a rare disease as the overall prevalence is 75 cases per million children [78]. In adults, diabetic nephropathy and hypertension are the main causes of CKD, whereas in pediatric patients, congenital disease and glomerular disorders are frequent causes of CKD [79–81].

4.1.2 AKI

In ‘developed countries’ the most prevalent causes of an AKI associated with abrupt decrease in kidney function include sepsis, congenital heart disease, and renal ischemia [79, 82, 83]. Prospective studies report AKI incidence rates of 4.5 and 2.5 % in children admitted to intensive care units [82, 83]. In ‘less developed countries’, acute tubular necrosis secondary to gastroenteritis and primary kidney diseases such as hemolytic uremic syndrome and acute glomerulonephritis are more likely involved. Neonates, especially preterm newborns, are susceptible to acquiring a kidney disease due to immature function of their kidneys, rapid hemodynamic changes at birth, and increased risk of hypovolemia as a result of insensible water losses and exposure to nephrotoxic drugs [84].

4.1.3 Medications/Treatments

Nonsteroidal anti-inflammatory drugs (NSAIDs) [85–88], aminoglycosides (gentamicin, amikacin, tobramycin, netilmicin) [89–97] and glycopeptide antibiotics (vancomycin, teicoplanin) [98–101], amphotericin B [102, 103], antiviral agents [104, 105], angiotensin-converting enzyme (ACE) inhibitors [106, 107], calcineurin inhibitors [108], radiocontrast media [109], and cytostatic drugs [110–114] can be nephrotoxic and cause AKI in neonates, infants, and children [17, 115]. Direct pathophysiological mechanisms of nephrotoxicity include constriction of intrarenal vessels, acute tubular necrosis, acute interstitial nephritis, and, more infrequently, tubular obstruction [17]. Drugs without nephrotoxic effect may increase exposure to potentially nephrotoxic agents by exhibiting drug–drug interactions and altering drug-metabolizing enzymes or transporters.

RRT is a particular case of ‘acquired’ changes in the clearance of drugs. The use of RRT associated with AKI and CKD was 15 per million children in the US in 2008 [116]. Drugs can be removed during RRT by diffusion (hemodialysis) or convection (hemofiltration). Molecular weight and size, protein binding, volume of distribution and electrostatic charge are key characteristics affecting drug dialyzability [117–119]. Drugs with high protein binding

(>80 %), lipophilic drugs, cationic drugs (retained by anionic protein charges in blood), and drugs with high molecular weight are poorly dialyzable [117, 118, 120–124].

4.1.4 Genetic Factors

The influence of variants in genes encoding for receptors, for example angiotensin II receptor 1 or toll-like receptor 9 (TLR-9), and peptides, for example vasopressin, involved in the pathogenesis of kidney disease have been discussed [22, 125–129]. Polymorphisms of genes encoding for proteins involved in drug elimination could predispose to drug nephrotoxicity. An association between *ABCB1* polymorphisms, encoding for the P-glycoprotein (P-gp), and tacrolimus-associated nephrotoxicity in pediatric patients following liver transplant is reported, suggesting that genotyping to find such polymorphisms may have the potential to individualize tacrolimus therapy and enhance drug safety [130]. SNPs in the genes encoding for CYP3A enzymes and the nicotinamide adenine dinucleotide phosphate–CYP oxidoreductase (POR), a protein that functions as an electron donor for CYP monooxygenase enzymes [131], have been shown to influence tacrolimus dose requirements. Individuals carrying the CYP3A4*22 T-variant allele have a lower tacrolimus dose requirement than individuals with the CYP3A4*22 CC genotype, and this effect appears to be independent of CYP3A5 genotype status [132–134]. Individuals carrying the POR*28 T-variant allele have a higher tacrolimus dose requirement than POR*28 CC homozygotes in CYP3A5-expressing individuals [135–137]. Their influence on the risk of nephrotoxicity is still inconsistent but they may also relate to tacrolimus-induced chronic nephrotoxicity [138]. Furthermore, the role of polymorphism in the organic cation transporter 2 (*OCT 2*) gene to cisplatin-induced nephrotoxicity has been reported [139].

4.2 How Does Impaired Kidney Function Impact Drug Pharmacokinetics and Response in Pediatric Patients?

Impaired kidney function affects not only renal clearance but also absorption, distribution, metabolism, and nonrenal clearance of drugs (Table 2) [122, 140–147].

Modification of distribution due to edema and decreased protein-binding capacity may be especially significant in children treated with highly hydrophilic drugs (such as aminoglycosides). An already large TBW compartment inherent of being a young child combined with a higher TBW due to kidney disease could result in a severe increased volume of distribution. The problem is often underestimated and may therefore go undetected. Even if a decrease in protein capacity induces an increase of the free

Table 2 Impact of impaired kidney function on absorption, distribution, metabolism and excretion (ADME) of drugs

	Pathophysiological changes	Effects on drugs	Impact
Absorption	Formation of ammonia in the presence of gastric urease/buffers/acid	Decreased absorption of drugs that are best absorbed in an acidic environment, prolonged gastric emptying, and delayed drug absorption [145–147]	Increased variability in bioavailability in subjects with kidney impairment compared with subjects with normal kidney function
	Increase in gastric pH	Increased amounts of active drugs in systemic circulation, higher bioavailability of acid-labile compounds and reduced bioavailability of weak acids [145–147]	
	Decrease in first-pass hepatic metabolism and biotransformation	Increased amount of drug removed during hepatic first-pass as more unbound drugs are available at the site of hepatic metabolism [145–147]	
	Bowel wall edema	Decreased absorption [145, 147, 148]	
Distribution	Formation of edema and ascites	Increases apparent volume of distribution of highly water-soluble or protein-bound drugs [145–147]	Lower plasma concentrations after a given dose
	Decrease in albumin concentration	Decreased affinity for drug reduces protein binding in patients with uremia, substantially increasing the unbound fraction of acidic drugs [149]	More abundant drug available at the site of drug action or toxicity
Metabolism	Accumulation of uremic toxins	Impaired glucuronidation to polar, water-soluble metabolites due to decreased clearance of glucuronide from plasma [150, 151]	Reduced removal of soluble metabolite
		Altered intestinal, hepatic, and renal transporters, intestinal P-gp, MRP-2 and OATP [143, 148, 152–154]	Accumulated active drug Higher incidence of adverse drug events
		Altered hepatic and renal metabolic enzymes such as CYP expression [148, 150, 151, 154–156]	
		The rate of reduction and hydrolysis reactions and microsomal oxidation are reduced	
		Altered disposition of drugs metabolized by liver through changes in plasma protein binding while unbound intrinsic/metabolic clearance declines with creatinine clearance [157]	
Elimination	Decrease in GFR	Reduced clearance of drugs eliminated primarily by glomerular filtration [141, 142, 144]	Increased plasma concentration and prolonged half-life in drugs that are eliminated primarily by glomerular filtration
	Decrease in protein binding	Decreased filtration of drugs, and this may result in an increased amount secreted by renal tubules [141, 142, 144, 157]	Prolonged excretion of drugs eliminated by active organic ion transport systems in renal tubules in patients with CKD; may become saturated upon multiple drug administrations

P-gp P-glycoprotein, *MRP-2* multidrug resistance protein 2, *OATP* organic anion-transporting polypeptide, *CYP* cytochrome P450, *GFR* glomerular filtration rate, *CKD* chronic kidney disease

fraction, the total drug concentration stays within the acceptable therapeutic range.

4.3 How to Assess Kidney Function and Detect Kidney Injury/Disease in Pediatric Patients?

Exact determination of kidney function is problematic in children. Measurement of GFR markers, such as inulin, iohexol, $^{51}\text{Cr-EDTA}$ or $^{99\text{m}}\text{Tc-diethylenetriaminepentaacetic acid}$ is difficult in pediatric patients due to ethical and practical reasons [158–161].

Equations based on serum creatinine measurements have been developed to estimate GFR. In adults, the most widely used equations for estimating GFR are the Cockcroft–Gault formula, the Modification of Diet in Renal Disease (MDRD), and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). These equations tend to overestimate GFR in children and should not be used in pediatric populations [162]. Several equations have been developed for pediatric patients: Schwartz, Counahan–Barratt, Leger, the Bedside Chronic Kidney Disease in Children (CkiD), Morris, Shull, Traub, Rudd, Dechaux,

Ghazali–Barratt and van den Anker formulas [163–170]. The most commonly used equations in children are the Schwartz formula, Leger, CkiD, and Counahan–Barrat formulas. The Schwartz formula, the most extensively validated formula, is based on serum creatinine and was first validated with data from 186 children, then with data from 2192 children in 14 subsequent validation studies. The Schwartz and Leger equations appear to overestimate GFR in children with decreasing kidney function when compared with measured inulin clearance [171–174]. The CKiD and Counahan–Barrat equations have been developed in children with a median GFR of 40–45 ml/min/1.73 m², and tend to underestimate kidney function in children with a GFR >60 ml/min [175]. It should be noted that serum creatinine is influenced by muscle mass, gender, diet, and tubular secretion. In children, serum creatinine may also be affected by diseases such as neuromuscular disease and anorexia nervosa [176]. At birth, the serum creatinine values measured in the neonate reflect maternal serum creatinine values because the placenta allows free transfer of creatinine between the mother and her unborn infant. Primarily in preterm infants the serum creatinine values increase during the first days of life, reaching a peak concentration around 5–7 days after birth before a gradual decrease in values are seen [177–179]. The highest values are seen in the most premature infants [180, 181]. As already shown in the rabbit kidney model, this increase in serum creatinine values is caused by an increased tubular reabsorption of creatinine in these preterm infants [182, 183]. Therefore, serum creatinine is a poor marker for GFR in neonates as it does not fulfill the assumptions of a purely filtered substance from which to calculate GFR. This underlines the need for, and evaluation of, newer, earlier markers for kidney function.

Serum creatinine can be measured with different analytical methods: alkaline picrate method, Jaffe method classic and compensated, and an enzymatic method traceable to isotope dilution mass spectrometry (IDMS) [184, 185]. Interlaboratory variation is high with some of these methods [186, 187]; studies have reported median method group variation coefficients of 6.4 % at a concentration of 80 µmol/L [188]. Variation in serum creatinine values lead to variation in derived calculations of kidney function. Discrepancies are more pronounced in children aged 1–5 years [189]. Standardization initiatives have been launched to reduce interlaboratory variation in creatinine assay calibration [190].

In order to compensate for inaccuracy of existing equations based on serum creatinine, alternative equations utilizing cystatin C have been developed. Cystatin C is a nonglycosylated protein produced in cells, not influenced by gender, body habitus, or composition (Table 3) [191–195].

Table 3 Comparison between the kidney markers serum creatinine and cystatin C

Characteristics	Creatinine	Cystatin C
Excretion by kidney	Yes	No
Reabsorption/secretion by renal tubules	Yes	No
Level affected by GA	Yes	No
Level affected by muscle mass	Yes	No
Level affected by gender	Yes	No
Influence from maternal plasma level	Yes	No

GA gestational age

Cystatin C does not cross the placental barrier and no correlation was found between maternal and neonatal serum cystatin [196]. Its reference value obtained in children aged 4–19 years is 0.75 ± 0.09 mg/L [197]; cystatin C levels are higher at birth (up to 4.2 mg/L) [191], and decrease in neonates [196] and infants over time [193]. Cystatin C has not been shown to be superior to calculation of GFR through the Schwartz formula in neonates [198]. Data on cystatin C in children receiving RRT are scarce [199–202].

‘Omics’-based technologies, such as proteomics and metabolomics, are uncovering new markers for kidney injury/disease [203–212]. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) are promising candidates to detect kidney injuries in the early stages. These proteins are expressed by renal tubules, and clinical investigations have shown that they are massively expressed in cases of AKI in both adults and children [203, 205, 207, 208, 213–217]. NGAL concentrations seem to correlate with the severity/stage of CKD [204]. The ability to measure these newer markers noninvasively in urine represents an advantage over current serum markers, especially in children. Other new biomarkers are evaluated for (1) AKI: interleukin (IL)-18, liver-type fatty acid-binding protein (L-FABP), urinary insulin-like growth factor-binding protein 7 (IGFBP7), and tissue inhibitor of metalloproteinases-2 (TIMP-2) [206, 218–222]; (2) CKD: β-trace protein (BTP), L-FABP, and asymmetric dimethylarginine (ADMA) [223–227]; and (3) nephrotoxicity: *N*-acetyl-glucosaminidase (NAG), GST, gamma-glutamyl transpeptidase (GGT), alanine aminopeptidase (AAP), and lactate dehydrogenase (LDH) [228–231].

Animal studies have shown modifications of the metabolome in plasma and kidney tissues in renal ischemia/reperfusion injury. Increase in prostaglandins, higher catabolism of tryptophan and accumulation of citrulline in the kidney could be metabolic signatures of intrarenal inflammation associated with ischemia/reperfusion injury [209]. Clinical studies in neonates, infants, and older children are warranted to (1) evaluate potential measures

for kidney function, especially during the first days of life; (2) test new markers such as NGAL and KIM-1 [232]; and (3) explore ‘omics’-based methods in order to improve detection and management of kidney injury/disease in neonates, infants, and children [233].

5 Quantitative Approaches and Opportunities in Pediatric Patients with Impaired Kidney Function

This section introduces quantitative approaches, such as pharmacometric modeling and simulation, to (1) simplify designs of studies in pediatric patients; (2) characterize effects of the kidney on drug exposure/response; (3) fine-tune dosing in pediatric patients with impaired kidney function; and (4) facilitate development and optimize utilization of therapeutics in neonates, infants, and children.

5.1 What is Pharmacometrics?

Pharmacometrics is an emerging science of developing and applying mathematical and statistical methods for characterizing, understanding, and predicting a drug’s pharmacokinetics, and its effects on biomarker and clinical responses over time [234, 235]. With pharmacometric approaches, biological knowledge can be translated into compartmental models with mathematical and statistical components [236]. ‘Population approaches’, introduced by Sheiner in the 1970s, can be utilized to quantify intersubject variability, at the population level, and test covariate effects on model parameters such as impact of body weight or kidney function on drug clearance. Such population models can also be applied to (1) project individual pharmacokinetic, biomarker and clinical responses, e.g. by Bayesian-inference [237–241]; (2) evaluate the impact of alternative doses on pharmacokinetics, biomarker and clinical responses; and (3) provide a scientific rationale for individualized dosing strategies [242–245]. Quantitative approaches such as pharmacometrics have been suggested to quantify the impact of kidney function on drugs and the impact of drugs on kidney function [246–248].

In pediatric patients, body weight reflecting growth, and age describing maturation, are key covariates. As described in Fig. 6, different age descriptors need to be considered in pediatric patients, especially in neonates, including PMA, gestational age (GA) and postnatal age (PNA), also called chronological age [249].

Pharmacometric approaches include pharmacostatistical, exposure-response, and disease progression models [236, 250, 251]. Systems pharmacology approaches may represent more complex models, such as physiology-based pharmacokinetic models (PBPK) consisting of a large

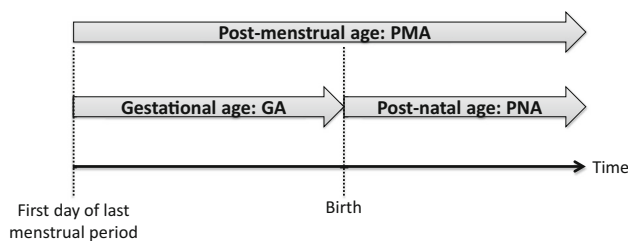


Fig. 6 Age terminology during the perinatal period

number of compartments to represent different organs or tissues in the human body [235, 252]. PBPK models may contain enzyme information from tissues, such as CYPs, involved in the metabolism of drugs [253–255].

Both pharmacometrics and systems pharmacology have been successfully applied in adults with impaired kidney function to (1) evaluate and simplify sampling designs of studies; (2) characterize and quantify the relationships between kidney function and drug exposure or effect; (3) fine-tune dosing strategies; and (4) enhance drug labels leveraging model-based simulations [148, 256–259]. Such quantitative approaches have the potential to facilitate development and optimize utilization of drugs in neonates, infants, and children, especially those with impaired kidney function.

5.2 How to Simplify Sampling Designs of Studies in Pediatric Patients?

Design and conduct of clinical studies in pediatric patients are difficult due to enrollment constraints (especially children <6 years of age), blood volume constraints (especially in neonates and young infants), and other practical challenges of collecting pharmacokinetic or other samples [243, 260]. Pharmacometric and systems pharmacology approaches, including PBPK-based simulations, can be leveraged to (1) identify starting dose in first-in-children pharmacokinetic studies and provide rationale for dose regimen optimization; (2) simplify pharmacokinetic–pharmacodynamic (PK–PD) sampling scheme (number and timing of blood collections for pharmacokinetic and/or PK–PD analyses); and (3) optimize sample size of studies in neonates, infants, and children [243, 261–267].

Furthermore, PBPK models can also be applied in neonates, infants, and children to (1) characterize pharmacokinetic behavior of drugs; (2) identify genetic factors that influence exposure/response of drugs; (3) assess risk of drug–drug interactions; and (4) quantify the impact of impaired kidney function on drugs [268–270]. PBPK models validated in adults may be expanded to pediatric patients by incorporating identified differences in drug pharmacokinetics and response between children and adults [267, 271].

5.3 How to Characterize Drug Exposure–Response and Enhance Drug Labels?

Pharmacometric and systems pharmacology approaches, utilizing pharmacokinetic, biomarker and/or disease progression data, can be useful to (1) identify factors that influence disease progression and responses to interventions; (2) facilitate comparison of concentration–response relationships across age groups; (3) link PD/biomarker endpoints to (longer term) clinical outcome measures, which may then be used as surrogate markers for assessing efficacy in various age groups; (4) simulate treatment-related responses in pediatric patients with and without impaired kidney function [259, 264, 272–274]; and (4) enhance drug labels for pediatric patients, such as atazanavir [275], busulfan [276, 277], levofloxacin [278], argatroban [279], piperacillin-tazobactam [280], etanercept [281], and subcutaneous immunoglobulin [282–284].

5.4 How to Fine-Tune Dosing Strategies for Drugs in Pediatric Patients with Impaired Kidney Function?

In the absence of specific dosing recommendations for children with changing kidney function, pediatric doses are extrapolated from adult data [1]. A priori dosing (prior to any measurement) in neonates, infants, and children is viewed as a scaling exercise, assuming a simple linear relationship between body weight and drug pharmacokinetics. Since developmental and maturational processes in pediatric subjects are mostly nonlinear, empirical dosing recommendations may result in over- or underdosing, resulting in toxicity or therapeutic failure. After initiating therapy, an adjusted a posteriori dose, based on therapeutic drug monitoring (TDM), can be identified [285–289]. A limitation of TDM in pediatric patients is that, for a majority of drugs, target concentrations are derived from adult patients rather than defined based on pediatric data, assuming similar exposure/response and TW across age groups [290–294]. Pharmacometric approaches can be leveraged to identify

predictive covariates, characterize exposure/response and TW of drugs, and provide a scientific basis for individualized dosing strategies, including Bayesian-based TDM, in neonates, infants, and children [242–245, 289, 295, 296]. Model-based approaches can also be applied to fine-tune RRT strategies in pediatric patients [296–298].

5.5 What are the Opportunities to Facilitate Development and Optimize Utilization of Drugs in Pediatric Patients?

Strategic applications of pharmacometrics and systems pharmacology have the potential to streamline development and optimize utilization of drugs in pediatric patients with and without impaired kidney function. An overview of opportunities is provided in Table 4.

6 Case Study: How to Fine-Tune Amikacin Dosing in Neonates with Impaired Kidney Function?

Neonates are known to be at high risk of infection and are exposed to antibiotic-resistant bacterial pathogens; thus, antibiotics are the class of medicines most frequently prescribed in neonates. Early appropriate antimicrobial treatment is imperative to optimize response and limit the spread of resistance [300–302]. In addition, there is an important lack of uniformity in dosing information to ensure consistent drug exposure in neonates, leading to inappropriate prescription of most antibiotics [303]. Pharmacometric approaches can be used to (1) identify and quantify covariate effects on pharmacokinetic parameters; and (2) fine-tune dosing of antibiotics in neonates with and without impaired kidney function.

In this section, we focus on the application of pharmacometrics to evaluate and fine-tune dose strategies of amikacin in neonates. After penicillins, aminoglycosides are the most commonly used drugs in the neonatal intensive care unit [304]. Amikacin is used as a short-term treatment of serious infections caused by strains of

Table 4 Quantitative approaches to enhance development and utilization of drugs in pediatric patients

	Opportunity for pharmacometrics and systems pharmacology
Streamline development of therapeutics for pediatric patients	Simplify design of PK–PD studies by performing model-based trial simulations [243, 261, 264] Quantify impact of kidney function and RRT on drug exposure/response by applying pharmacometric and PBPK models [259, 264, 272–274, 299] Facilitate key development decisions by applying pharmacometric modeling and simulation [240, 264, 272–274]
Optimize utilization of therapeutics in pediatric patients	Adjust/individualize dosing strategies by applying Bayesian-based TDM [243–245] Provide scientific rationale for pediatric drug labels applying pharmacometric modeling and simulation [281–284]

PK–PD pharmacokinetic–pharmacodynamic, *RRT* renal replacement therapy, *PBPK* physiology-based pharmacokinetic, *TDM* therapeutic drug monitoring

Pseudomonas sp., *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia* sp., and *Staphylococcus* species [305–307]. This drug is almost exclusively eliminated by kidneys (90 %) and its clearance reflects GFR [308]. There is huge variability in the choice of neonatal dosing regimen used across the world [309]. Leroux et al. found 19 different neonatal dosing regimens proposed in the literature [44, 303, 310–323]. Amikacin use is difficult because of its toxicity and pharmacokinetic variability, and no study or specific recommendations in cases of changing kidney function were described. Potential kidney effects on pharmacokinetic parameters were tested by incorporating age and weight as indirect measures for maturation and growth, and serum creatinine as a measure of kidney function in a population pharmacokinetic model [313, 324].

Sherwin et al. recently developed a population-based pharmacokinetic model based on 70 pediatric burn patients (6 months to 17 years) receiving amikacin, and found that weight had a significant influence on amikacin clearance [325].

De Cock et al. conducted a large population pharmacokinetic modeling study using data from 874 preterm and term neonates treated with amikacin (range: GA 24–43 weeks; PNA 1–30 days) [311]. Amikacin clearance was found to be related to PNA and birth weight, with children with higher age and weight having a faster maturation of clearance. Furthermore, coadministration of ibuprofen appeared to reduce amikacin clearance, likely (at least in part) due to negative effect on kidney function [311, 326, 327]. The individual amikacin clearance can be predicted using Eq. 1, with CL_i being amikacin clearance in the i th individual, CL_p being the population value of amikacin clearance, and bBW being birth body weight and PNA corresponding to PNA:

$$CL_i = CL_p \times \left(\frac{bBW}{bBW_{\text{median}}} \right)^{1.34} \times \left(1 + \left(0.213 \times \frac{PNA}{PNA_{\text{median}}} \right) \right) \times 0.838_{\text{ibuprofen}} \quad (1)$$

Table 5 Amikacin dosing regimen according to De Cock et al. [311]. The dosing interval is prolonged by 10 h when ibuprofen is coadministered

Postnatal age (days)	Current bodyweight (g)	Dose (mg kg ⁻¹)	Dosing interval (h)
<14	0–800	16	48
	800–1200	16	42
	1200–2000	15	36
	2000–2800	13	30
	≥2800	12	24
≥14	0–800	20	42
	800–1200	20	36
	1200–2000	19	30
	2000–2800	18	24
	≥2800	17	20

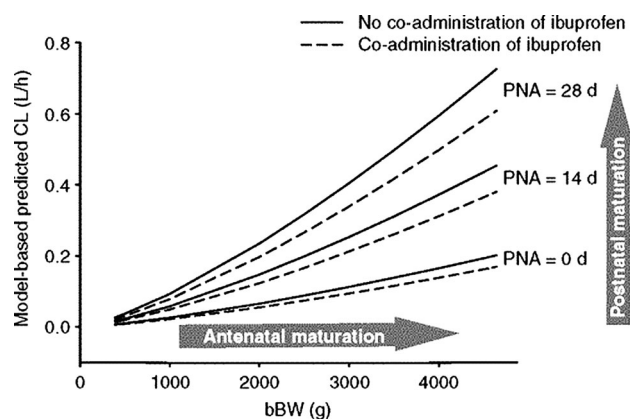


Fig. 7 Model-based predicted amikacin clearance values versus bBW for PNA of 0, 14, or 28 days with and without coadministration of ibuprofen, according to De Cock et al. [311]. bBW Birth body weight, PNA postnatal age, CL clearance

Figure 7 illustrates how the predicted clearance of amikacin increases with birth body weight (representing antenatal maturation) and PNA (representing postnatal maturation), taking into account coadministration of ibuprofen.

Predictive performance of this model was externally validated in 239 neonates. An evidence-based dosing regimen, summarized in Table 5, was proposed by performing simulations with the developed model. They demonstrated that the currently used dosing regimens for amikacin, based on reference handbooks, may increase the risk of toxicities, and should be revised [311].

The authors also performed a study to extrapolate the amikacin model to other drug compounds almost entirely eliminated through glomerular filtration and with similar physicochemical properties (netilmicin, tobramycin, vancomycin, and gentamicin). They showed that pediatric covariate models may represent physiological information on developmental changes in glomerular filtration that may be leveraged to describe kinetics of other antibiotics that are primarily eliminated by kidneys [328].

7 Discussion and Outlook

Growth, maturation, and environmental factors affect drug kinetics, response, and dosing in pediatric patients. Changes in kidney function, as a result of normal growth and development as well as underlying kidney diseases, comorbidities, medications, and environmental and genetic factors, will not only have an impact on renal clearance but also on the absorption, distribution, metabolism, and non-renal clearance of drugs [141, 142]. Both drug exposure and response may change during childhood and impact the TW and efficacy/safety balance of drugs in neonates, infants, and children. Current markers of kidney function provide limited value in assessing and monitoring kidney function in children, especially during the first days of life and in cases of AKI [172, 173]. Therefore, new renal biomarkers are needed. ‘Omics’-based technologies, such as proteomics and metabolomics, can be leveraged to uncover novel markers in plasma and urine for kidney function during normal development, AKI, and CKD.

Motivated by challenges in conducting clinical studies in pediatric subjects, supported by regulatory agencies such as the European Medicines Agency (EMA) and the US FDA, pharmacometric and systems pharmacology have been suggested to facilitate the design and conduct of studies in pediatric subjects [329]. Strategic use of model-based quantitative approaches and biomarkers [240, 330] has the potential to streamline development and optimize utilization of drugs in pediatric patients with and without impaired kidney function by (1) informing the design of pediatric clinical trials, including sample size and first dose selection, providing rationale for the dose range to be studied, and simplifying PK–PD sampling; (2) characterizing disease progression to project long-term clinical outcomes; (3) quantifying the effects of impaired kidney

function (and RRT) on drug pharmacokinetics and/or response; (4) facilitating key development decisions; and (5) providing a scientific rationale for pediatric drug labels.

The recently formed Drug Disease Model Resources (DDMoRe) consortium facilitates collaborations between pharmaceutical industries and academic partners [331]. They aim to address the lack of common tools, languages, and standards for modeling and simulation to improve model-based knowledge integration. A public drug and disease model library, supported by an open source and universally applicable framework, provides access to disease modeling tools [331, 332]. It should also be noted that online tools have been developed to facilitate evaluation and optimization of study designs in adult and pediatric subjects. For example, Mentré et al. developed a software tool known as PFIM, which is a set of *R* functions that evaluates and/or optimizes study designs based on the expression of the Fisher information matrix (FIM) in nonlinear mixed effects models (<http://www.pfim.biostat.fr/>) [333, 334].

In clinical practice, pharmacometric approaches can be applied to identify predictive covariates, such as the impact of kidney function changes on drugs, and provide a scientific basis for optimizing dosing in pediatric patients [242, 244, 245]. Bayesian-based TDM methods can leverage patient characteristics, physiological differences between adults and children, genetic and environmental factors and pharmacokinetic properties of drugs, and individualize dosing strategies in neonates, infants, and children. Decision support tools are emerging to assist clinicians at the bedside in personalized dosing of pediatric patients, including neonates, such as the EzeCHiel (<http://www.ezechieel.ch/>) [244, 289] and DoseMe software packages (<http://www.doseme.com.au/>) [335].

Table 6 outlines opportunities to overcome challenges in further streamlining development and optimizing

Table 6 Challenges and opportunities to facilitate development and optimize utilization of drugs in pediatric patients

Challenges in pediatric patients	Opportunities for innovative and collaborative approaches
Lack of markers for assessing kidney function or detecting AKI and CKD	Leverage proteomics and metabolomics to identify new renal markers for kidney injury/disease
Lack of large pharmacokinetic, biomarker and clinical outcomes datasets	Create and share integrated large databases
Lack of common tools, languages, and standards for modeling and simulation	Develop platforms with standardized modeling tools
Lack of consensus, rationale on dosing strategies	Collaborate between clinicians and scientists in academia and industry to optimize and standardize dosing strategies
Lack of individualized dosing in children	Apply model-based Bayesian TDM to leverage patient characteristics and fine-tune personalized dosing
Lack of application of model-based approaches by clinicians	Develop user-friendly bedside decision tools for clinicians
Lack of specific drug labels	Collaborate between clinicians and scientists in academia, industry and regulatory agencies to enhance drug labels

AKI acute kidney injury, CKD chronic kidney disease, TDM therapeutic drug monitoring

utilization of therapeutics in neonates, infants, and children, especially those with impaired kidney function.

Collaborative efforts between clinicians and scientists in academia, industry, and regulatory agencies are required to (1) identify new renal biomarkers for early detection and enhanced monitoring of kidney injury and disease; (2) collect and share prospective pharmacokinetic, genetic, and clinical data with the goal of creating large clinical outcome databases; (3) build and evaluate integrated pharmacometric models for key diseases and therapeutics; (4) optimize and standardize dosing strategies; (5) develop user-friendly bedside decision tools for clinicians; and (6) enhance drug labels for neonates, infants, and children.

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Compliance with Ethical Standards

Conflicts of interest Frederique Rodieux, Melanie Wilbaux, Johannes N. van den Anker and Marc Pfister have no conflicts of interest to declare.

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