Pharmacokinetic considerations when prescribing in children

Before prescribing, the pediatrician typically considers recommended dosing guidelines and issues related to safety. Rarely does (s)he consider the impact of normal growth and development on drug disposition and by extension drug action. This paper reviews how the processes of absorption, distribution, metabolism and elimination differ between healthy children and adults and briefly discusses considerations for medication prescribing in children where these processes are altered secondary to comorbidities.

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Considerations for prescribing medications in pediatrics include: whether the drug is safe and approved for use in children; what the appropriate dose is for the child's age and weight; and, what key information about adverse reactions needs to be communicated to the parent or caregiver. At the time of prescribing, rarely does the clinician consider the processes of absorption, distribution, metabolism and elimination that the drug undergoes as it passes through the body or the impact of normal growth and development on the expected disposition and action of the drug. In this paper we discuss how selected pharmacokinetic processes differ between healthy children and adults, with their concomitant impact on dosing, and briefly review considerations for medication prescribing in children where pharmacokinetic processes are altered secondary to disease states.

Absorption

Absorption refers to the process by which a drug is taken up into the blood stream after administration by any one of several extravascular routes (e.g., oral, sublingual, buccal,

intramuscular, percutaneous, rectal). For nearly every route of administration, there are age dependent changes that can influence the rate and/or extent to which drugs are taken up by the body. These changes, which occur in the physical and/or chemical barriers a drug encounters, can diminish or augment the fraction of a dose that survives the absorption process and is thus available to interact with the therapeutic target [1].

Peroral administration

Oral administration is the most common route by which children are introduced to medicines. Before considering the impact of gastrointestinal development on drug absorption, however, one must contend with the factors that determine whether the drug will ever see the inside of the gastrointestinal tract. Children readily reject medications based on numerous factors including taste, smell and texture each of which has a unique developmental trajectory. The capacity to discriminate sweet and umami is present *in utero*, followed by texture, temperature and piquancy at 1–2 years of age and finally

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bitter, salty and sour around the age of 2 years [2–4]. Olfactory senses do not appear to fully mature until children are 5–7 years of age. Other adaptive behaviors, which typically manifest by 2–5 years of age, influence a child's willingness to accept novel foods, and by extension, medicines. The strongest teleological drivers of whether food will be rejected as harmful are sweetness and familiarity (influenced by exposure to foods and the context in which foods are offered). For example, infants extensively fed hydrolysate formulas, with their savory, sour and bitter components, demonstrate fewer expressions of distaste when compared to infants who have been fed cow milk formulas or human breast milk which is predominantly sweet [5,6]. The impact of unlearned behaviors are evidenced by the fact that children gravitate toward flavors that connote energy dense foods [2]. This may explain why sweeter tasting medicines are more likely to be accepted by children, though preferred flavors are still culturally informed [7].

Effectively masking aversive taste and trigeminal stimuli requires thoughtful consideration of the target age group being treated. For the prescriber this means having some knowledge of the various formulations that exist for a given drug and the likelihood that the formulation selected will be deemed palatable by the child. It also means recognizing that the acceptability of chronically administered medicines may change as the child matures. Ferrous sulfate, for example, is manufactured as an elixir, solution, syrup and tablet. It would not be surprising if at 1 year of age, a child being treated for anemia suddenly rejected the lemon-flavored liquid formulation. In this setting, knowledge of the various suppliers and their formulations would be imperative to successful continuation of treatment.

Once past the oropharynx, drugs first encounter the milieu of the stomach. It is well accepted that neonates experience a phase of relative achlohydria, with gastric contents demonstrating a neutral pH at birth which becomes acidic within the first 24 h of life and returns to neutral by 10 days post gestation [8]. However, the timeframe over which the gastric pH falls back to, and is maintained at, adult levels is still open to debate. Irrespective of this timeline, the frequency of feeds in the young infants (8- to 12-times per day) effectively buffers the gastric pH. At elevated pH, acid labile drugs such as β -lactam and macrolide antibiotics are protected from degradation and consequently generate higher systemic concentrations after oral administration in young infants than do comparable weight-based doses in older children and adults [9]. Conversely, some weakly basic drugs including ketaconazole, itraconazole, cefpodoxime and enoxacin experience reduced bioavailability at higher gastric pH [8]. Importantly, the

pH differences observed between children and adults is restricted to the stomach. Intestinal pH in neonates older than 2 weeks of age is similar to that of children and adults [10]. For the prescriber this means that some drugs require higher doses to achieve the desired clinical effect while others may pose a toxicity risk if dosed in excess of the labeled recommendations.

Emptying of the gastric contents into, and subsequent motility of, the intestine influences the rate at which orally administered drugs are delivered to, and absorbed from, the primary absorptive site (i.e., the small intestine). Maturation of both processes entails integration and feedback via development of smooth muscle activity in combination with the enteric nervous system and humoral environment [11]. It was previously demonstrated that gastric emptying rates increase during the first 7 days of life [12]. Correspondingly, time to maximum blood concentrations (T_{max}) have been observed to decrease during the first few weeks of life for some drugs like cisapride where T_{max} at 42–54 weeks is nearly half-that observed at 28–36 weeks [13]. However, a recent meta-analysis challenges the theory that emptying matures as a function of age, proposing rather that the type of food administered to the child is more impactful [12,14].

Added to the influence of food type on gastric emptying rates are other pediatric comorbidities such as prematurity, gastroesophageal reflux disease and congenital heart disease [15]. Coincident with the maturation of gastric emptying are the age-dependent changes in intestinal motility. Though peristaltic activity is irregular at the time of birth, intestinal transit times mature rapidly and at 2 weeks of age are comparable to those of adults. Consequently, the physicochemical properties of a drug, specifically the rates of disintegration and dissolution, would be expected to influence the absorption profile of medicines more heavily than age after the first month of life. Continued study of the highly soluble, highly permeable Biopharmaceutics Classification System (BCS) Class I compounds in children may shed additional light on the topic of age-dependent differences in peroral drug absorption [10].

For drugs that require bile salts to facilitate their absorption (e.g., those that are highly lipophilic or formulated in lipid-based vehicles), absorption may be capacity limited during the first few months of life [16]. While young infants have no trouble synthesizing bile salts, the transporters responsible for carrying them across the biliary canaliculus appear to be immature [17–21]. This is the primary reason we deliver fat-soluble vitamins to young infants in a form that is slightly more water soluble (e.g., calcifediol vs cholcalciferol). It also explains why erratic and incomplete absorption profiles can be observed for selected lipo-

philic medications such as chloramphenicol palmitate and pleconaril during the newborn period [22,23].

Of equal importance to the hepatic bile salt transporters are the transporters directly responsible for the translocation of drugs across the intestinal epithelia (Table 1) [24,25]. These proteins carry drugs into the body (influx) or extrude them back into the intestinal lumen (efflux) highlighting the importance of understanding not only their ontogeny but the role of genetic polymorphisms on their expression and activity. Unfortunately, human studies exploring developmental changes in the expression and activity of these transporters are extremely limited. Most of our knowledge on the expression of these proteins is limited to data from animal models (Table 1), and despite the fact that we can equate developmental stages between species, there remain gaps in our understanding of the impact of age on transporter activity in the growing child [3,24,26].

The GI tract has other important features that influence the bioavailability of orally administered medicines. Phase I and Phase II drug metabolizing enzymes (DMEs) are heavily distributed along the intestine and play a large role in the bioactivation and detoxification of drugs (detailed further in the section titled 'metabolism'). As with transporters, however, data on the intestinal expression of DMEs in children is sparse [27]. A final, often overlooked, factor that can influence oral drug absorption (specifically low solubility and/or permeability BCS classes II–IV compounds) is the microbiome. Intestinal flora influence the biotransformation of drugs directly, via participa-

tion in processes such as deconjugation, nitro reduction and hydrolysis, and indirectly via regulation of host transporters and DMEs [28]. Examples include; bacterial β -glucuronidase participating in morphine clearance by cleaving the pharmacologically active morphine-6-glucuronide back into morphine which is then available for reabsorption [29,30], bacterial reduction of digoxin into pharmacologically inactive metabolites [31], *Bifidobacterium* spp. stimulating SLC26A3 *in vitro* thereby increasing anion exchange, and *Lactobacillus casei* decreasing the expression of CYP1A1 in the jejunum and colon [32]. Given that intestinal colonization is influenced by a multitude of factors including type of birth, age, disease, feeding, drug exposure etc., our ability to predict the impact of changes in the microbiome on oral bioavailability is limited at present.

Extraoral administration

Although utilized to a lesser extent in otherwise 'healthy' pediatric patients, extraoral pharmacokinetics are also subject to age-dependent changes. For example, the absorption of erythromycin from rectally administered suppositories appears to be lowest in neonates (28%) when compared to infants (36%) and children (54%) despite the fact that intravenous administration of equivalent weight-based doses demonstrate comparable systemic exposure profiles [33]. This reduced absorption may reflect early expulsion of the suppository secondary to an increase in the number of pulsatile contractions that occur in the lower gastrointestinal tract of neonates or altered melting owing

Table 1. Developmental expression of intestinal transporters.

Transporter	Location	Expression (animal model)	Example drugs
P-gp (ABCB1)	Small and large intestines	~12 weeks gestation (human)	Morphine, cimetidine, omeprazole, ketoconazole, phenobarbital
BCRP(ABCG2)	Small intestines	5.5 weeks gestation (human)	Methotrexate, lamivudine
MRP1(ABCC1)	Small intestines	5.5 weeks gestation (adult distribution seen ~7 wks gestation; human)	Methotrexate, lamivudine
MRP2(ABCC2)	Ileum and jejunum	~12 weeks gestation (human)	Carbamazepine, codeine, morphine
OATP2B1(SLCO2B1)	Ileum and jejunum	Neonates > adult expression (human)	Atorvastatin, simvastatin
MRP3(ABCC3)	Distal ileum and colon	Adult > neonates expression (rabbit)	Lamivudine, methotrexate, codeine, morphine
OCT1(SLC22A1)	Small intestine and colon	No obvious neonatal expression (mouse)	Tramadol, metformin, lamivudine
PEPT1(SLC15A1)	Small intestine	Neonate > adult expression (rat and turkey)	Fluvastatin

Adapted with permission from [24].

to the temperature instability that can accompany illness in this population. Thus, the prescriber may elect to avoid rectal suppositories formulated in base with a higher melting point or delayed release characteristics.

For percutaneously and intramuscularly administered drugs, relevant age dependent factors that influence absorption include surface area, hydration status and capillary perfusion. Young infants demonstrate enhanced percutaneous absorption of topically administered compounds owing to a larger surface-to-mass ratio and an epidermal layer that is more well hydrated than is observed in adults. Providers should remain cognizant of the fact that percutaneous administration is a highly efficient mechanism for drug delivery when prescribing topicals in the young child and bear in mind the countless reports of systemic toxicity with drugs administered for local effect in this population [34–39]. For drugs administered by intramuscular injection (e.g., aminoglycosides, betalactams), the increase in capillary density observed in skeletal muscles of younger children results in effective systemic

delivery despite the fact that contractility may still be immature in these children [41,42].

Distribution

Distribution reflects the rate and extent to which drugs permeate various tissues within the body. Pediatric prescribers should note this process is governed primarily by the physicochemical properties of the drug and the physiologic constitution of the patient. In children, one of the most recognizable patient-specific factors that influences a drug's distribution volume is total body water stores. At birth, 80% of a newborn's weight is represented by water which steadily drops to adult values (~60%) during the first year of life [43]. For drugs that are hydrophilic (e.g., aminoglycosides, linezolid and the β -lactams), the corresponding volume of distribution will be larger, and circulating plasma concentrations lower, in the young infant administered comparable weight-based doses [26,43–45]. In contrast, body fat stores in the newborn and young infant are lower than those observed in older children and adults.

Table 2. Phase I and II enzymes and their transcript expression profiles.

Phase I enzymes	Phase II enzymes
CYP P450 1A	NAT
1A1 bladder	NAT1 prostate
1A2 hepatic ; adult activity after puberty	NAT2 hepatic; adult activity by 1–3 years old
1B1 gonads	NAT5 skeletal muscle
CYP P450 2A, 2B, 2C, 2D	UGT
2A6 hepatic	UGT1A1 hepatic
2B6 hepatic; adult activity after 12 months of age	UGT1A6 hepatic
2C9 hepatic; adult activity 6 months (may exceed adult activity in childhood by reaches adult levels again after puberty)	UGT1A9 extrahepatic (Renal)
2C19 hepatic; adult activity 6 months (may exceed adult activity in childhood by reaches adult levels again after puberty)	UGT2B7 hepatic
2D6 hepatic; adult activity 12 months	In general adult activity is reached between 6–24 months of age though expression appears to be isoform specific
CYP P450 3A	GST
3A4 hepatic tissue; adult activity at 6 month (may exceed adult activity between 1–4 yrs old, but returns to adult activity levels after puberty)	GSTA1 hepatic
3A5 extrahepatic tissue (intestines)	GSTA2 renal
Flavin-containing monooxygenases (FMOs)	SULT
Renal	SULT1A1 hepatic
	SULT1E1 hepatic
Epoxide hydrolase	TPMT
mEH adrenal	Thyroid gland; newborn activity is 50% higher than adults (adult activity in Korean children by 7–9 years)
sEH renal	

However, lipophilic drugs do not demonstrate strikingly different distribution volumes in this population as these drugs tend to associate with cellular components that are not restricted to adipose. By 36 months of age, fat stores are similar to adults [1,26].

Circulating proteins and displacers, such as bilirubin and fatty acids, represent additional physiologic factors that influence age-dependent differences in drug distribution. In newborns, α 1-acid glycoprotein stores are at concentrations half those of adults. Albumin stores are also lower in this population and constituted, in part, by fetal albumin which has a lower binding affinity for drugs. Finally, there are higher concentrations of displacers in the circulation of newborns that can interfere with drug binding [46,47]. Clinicians should recognize that the impact of these changes on the moderately bound drug are likely limited. However, what appears to be a small shift in binding, from 99 to 98%, for a highly protein bound drug may result in a significant increase in the unbound concentration of drug available to interact with the therapeutic targets (depending on the hepatic extraction ratio and apparent distribution volume of the drug).

Metabolism

Phase I and Phase II DMEs represent major routes of drug clearance in the body (Table 2) [27,48,49]. These enzymes are present in multiple tissues; however, the liver quantitatively plays the largest role in drug metabolism. Phase I enzymes covalently modify compounds by adding or uncovering functional groups to increase their polarity. Phase II enzymes enhance the water solubility of a compound via processes such as methylation, sulfation, acetylation and glucuronidation. Though pediatric prescribers may be aware of these processes, it's important to understand the impact of ontogeny on these enzymes given their critical role in drug disposition and consequently the dosing strategies employed.

Phase I enzymes

The CYP450 enzymes are a superfamily of proteins responsible for the oxidative metabolism of countless endogenous and exogenous compounds [24]. There are currently about 60 known CYP genes which are further divided into 18 separate families. The first three families (CYPs 1–3) are responsible for the majority (up to 80%) of xenobiotic metabolism while the higher number CYPs are preferentially involved with the metabolism of endogenous substrates [25].

The CYP450 1 family is divided into two main subfamilies (CYP1A and CYP1B) and 3 isoforms, CYP1A1, CYP1A2, and CYP1B1. CYP1A1 and 1B are primarily expressed in extrahepatic tissue while

CYP1A2 is primarily found in the liver [50]. Data accumulated to date support a role for CYPs 1A and 1B in the metabolism of hormones like estrogen and xenobiotics such as warfarin and the procarcinogen benzo[a]pyrene [51,52]. While dedicated investigations into the ontogeny of the CYP1A family are limited, there is evidence of CYP1A1 expression during embryogenesis and data to suggest that CYP1A2 activity is absent *in utero*, but gradually increase to almost half of that of adult activity by the age of 9 years [53]. Importantly, the CYPs 1A represent a family of highly inducible proteins that have been associated with different levels of expression or activity depending on gender, oral contraceptive use and diet [51,54].

There are three CYP2 subfamilies, each with coinciding clusters on three separate chromosomes; CYP2A, CYP2C and CYP2D. Collectively these genes contribute 25–73% of the hepatic CYP450 content. Within the CYP2A family, CYP2A6 is a major oxidative pathway for coumarin, nicotine, letrazole and aflatoxin B1 [55–57]. It is also responsible for the bioactivation of selected antineoplastics (e.g., tegafur) and antivirals (e.g., efavirenz) [57]. CYP2B6 accounts for approximately 5% of the total hepatic CYP content and metabolizes approximately 8% of clinically used drugs including; efaviranz, cyclophosphamide, ifosfamide, methadone, ketamine, bupropion and propofol. Expression of this isoform is inducible contributing to the large degree of interindividual variability in activity that has been observed for this enzyme [58]. With respect to ontogeny, CYP2B6 is expressed to a greater extent after infancy, and adult levels of activity occur after 12 months of age [59].

The CYP2C family is highly expressed in the liver and the clinically relevant isoforms include CYP2C8, 2C9 and 2C19. CYP2C8 accounts for approximately 7% of the CYP content in the liver and plays a significant role in Phase I metabolism of xenobiotics and endogenous substances including antidiabetics, antiarrhythmics and antimalarials. Like CYPs 1A2 and 2B6, CYP2C8 is expressed primarily in children over the age of 12 months. CYP2C9 accounts for approximately 20% of hepatic CYPs and is expressed perinatally. However, this enzyme is widely distributed throughout the body including the gut, kidneys, adrenal glands and nasopharynx [60]. Drugs that utilize the CYP2C9 pathway include warfarin, NSAIDs and sulfonyleureas. CYP2C19 is primarily expressed in hepatic tissue and, like CYP2C9, is expressed perinatally. However, genetics, more so than age, appear to influence the disposition and action of substrates for this gene including; proton pump inhibitors, antidepressants, anticoagulants and anti-infectives [61,62]. In the clinical setting, identification of individuals classified

as ultra rapid metabolizers may offer prescribers reassurance in support of dose-escalation above normally recommended doses and limit switching to other, possibly less effective, alternatives [25].

The CYP2D family is one of the most highly studied P450s and represents the major metabolic pathway for 15–25% of commercially used medications including; psychotropics (aripiprazole, fluoxetine, atomoxetine), opioids (codeine, oxycodone) and antiarrhythmics [25]. CYP2D6 is a polymorphically expressed liver enzyme that appears to be functional shortly after birth making genotype a better predictor of activity status than age even in children as young as 2 weeks of life [63]. Over 100 allelic variants of CYP2D6 have been described with measurable implications for therapeutic activity and adverse drug reactions. The role of CYP2D6 genotype in narcotic toxicity has gained a significant amount of attention with US regulatory agencies in recent months after reports of deaths in patients with duplications of the gene. These patients convert codeine to morphine in quantities more than twice that of wild-type extensive metabolizers [64,65]. In 2013, the US FDA issued a black box warning recommending against the use of codeine in postoperative pain management for tonsillectomy and adenoidectomy, or in breast feeding mothers, and most recently in 2016 an advisory committee to the FDA recommended that the drug be removed from the market [25,66].

The CYP3 family has only one subfamily (*CYP3A*) with 7 isoforms. CYP3A7 is expressed primarily during fetal life and accounts for up to 50% of hepatic CYP content; however, it is almost completely silenced by 24–36 months of age [67]. After birth, expression of CYP3A4 is evident maturing to adult levels around 1 year of life [68,69]. CYP3A4 and CYP3A5 are over 85% homologous and possess similar substrate specificity profiles. These enzymes participate in approximately 50% of all first pass metabolism that occurs in the intestines and liver including the immune modulators tacrolimus, sirolimus and cyclosporine. Though the functional consequences of CYP3A polymorphisms are less well studied than for CYP2D6, data suggest that CYP3A5*3 activity correlates with tacrolimus dosing wherein almost 50% of CYP3A5*3 homozygous patients receiving tacrolimus after kidney transplantation require lower doses due to toxicity [25,70].

Phase II enzymes

Analogous to the Phase I enzymes, many of the Phase II DMEs possess multiple isoforms with tissue specific expression that differs at different stages of development [71]. However, these pathways have not received the same attention as the CYPs and their ontogeny is

less well characterized. Among the most well studied are the UGT enzymes. The isoform UGT1A1 plays a role in metabolism of medications such as acetaminophen, ibuprofen and warfarin [25]. Although its activity is not detected in the fetal liver, it appears shortly after birth and reaches adult levels between 3–6 months of age [72]. In contrast, UGT1A9, which also plays a role in metabolizing acetaminophen and ibuprofen, demonstrates activity that is only 64% that of an adult at 2 years of life [73]. UGT2B7 and UGT1A1 are responsible for morphine clearance which increases steadily during the first year of life, providing insight into the ontogenic profile of these isoforms [25,74].

The primary physiologic role of SULTs is to conjugate endogenous steroids, and contribute to the metabolism of catecholamines. However, these enzymes also metabolize acetaminophen, estrogen and aromatase inhibitors [27]. With respect to development, SULT1A1 is expressed in the fetal liver and has fairly consistent expression through adolescence while the expression of SULT1E1 progressively declines from birth into adulthood [75]. The GSTs are another family of Phase II enzymes with expression that varies as a function of age. There are two families of GSTs in humans, the first family divided into eight subfamilies. These soluble GSTs are significantly involved in the metabolism of toxic xenobiotics (e.g., azathioprine) and endogenous reactive oxygen species that result as a byproduct of normal cellular processes. GSTA1 and GSTA2 activity increases rapidly at birth (1.5–2-fold), whereas GST1 progressively increases during the first 18 months of life. There is no information on the MAPEG family [76].

Despite the wide array of ontogenic profiles for Phase I and Phase II DMEs, the child with immature DME pathways is not always disadvantaged when it comes to drug biotransformation. There is redundancy built into human detoxification pathways such that many drugs serve as substrates for multiple DMEs. For some drugs, compensatory mechanisms result in clearance rates that do not demonstrate appreciable age-dependence. For other drugs, minor pathways may be less efficient at processing the substrate resulting in delayed clearance until the primary pathway matures. Acetaminophen, for example, is metabolized by UGT1A6 and SULT1A1. Though glucuronide conjugation is the primary disposition pathway in adults, sulfation accounts for the majority of acetaminophen metabolites recovered in newborns [77]. Nevertheless, infants still exhibit lower total body clearance as compared with children and adults where UGT1A6 has matured. When in doubt, consultation of a pharmacology reference should provide guidance on any adjustments that might be necessary to a dosing regimen.

Table 3. Abbreviated comparison of neonate to adult kidney.

Kidney length	Doubles from birth to 12 years of age
Kidney weight	Parallels length development
Glomerular length	Newborn is 1/3 of adult length
Proximal tubule length	Newborn is 1/10th length of adult
Glomerular small pore radius	Increases 25% in first 3 months
Glomerular ratio large pores: small pores	Large pores ratio increases with development
Vascular resistance	Increased at birth
Renal bloodflow	Reduced at birth
Glomerular filtration rate	Increases until growth is completed (significantly decreased in preterm neonates)
Concentrating capacity	Significantly decreased at birth (300 mOsm/kg H ₂ O)

Elimination

With few exceptions, the primary routes of elimination for exogenously administered drugs and their metabolites are hepatic pathways that lead to clearance in the bile and renal pathways that eliminate compounds in the urine. Elimination via the liver is an active process involving transporters on both the basolateral surface of the hepatocyte (e.g., SLC-type transporters OATP, OATs) and the biliary canaliculi (e.g., ABC transporters MRP2, MDR1, BCRP) [27]. Notably, there remains a significant amount of research to be done with respect to elucidating the ontogeny of these transporters [78]. Though biliary transporter expression is believed to be reduced in the newborn (see section titled 'absorption'), these infants are able to compensate to some extent by using other clearance pathways. Cefoperazone, for example, demonstrates 55% renal clearance in the preterm neonate as compared with the full term newborn at 18% [79]. Similarly full-term newborns clear 70% of ceftriaxone via the kidney versus the adult which may be as low as 20%.

By contrast, the body of knowledge on kidney development and renal clearance capacity is vast. This organ remains one of the most well characterized along the continuum of age in children (Table 3) [1]. Kidney formation is completed by 36 weeks gestation, but even after birth, the collective function of the kidney does not reach maturity with regards to filtration, secretion and reabsorption until puberty [80–83]. Consequently, the capacity to eliminate drugs renally is markedly reduced in the newborn following a clear developmental trajectory through childhood (note: preterm infants follow a different trajectory than those born full term). For this reason, younger children often require less frequent drug dosing for renally cleared medications. Fluconazole, for example, demonstrates an elimination half-life of 88 h in premature infants compared with 19.5–25 h in the full term infant, 30–50 h in older children and

adults. The clinical implication is a dosing interval 72 h in infants <29 weeks of gestation and <14 days of age, 48 h in infants <29 weeks of gestation and >14 days of age or 30–36 weeks gestation and <14 days of age, and every 24 h in older children and adults [84].

Secondary factors influencing disposition

Though this paper focuses primarily on pharmacokinetics in the otherwise normal acutely ill pediatric patient, prescribers need to consider that chronic comorbid disease states can independently interfere with the processes that govern the disposition or action of the drugs we administer. Gastric emptying times are demonstrated to be slower in Type I diabetic patients and intestinal dysmotility is prominent in pediatric patients who've suffered from gastroschisis, Hirschsprung disease or infantile pyloric stenosis where there may be abnormal or altered expression of the interstitial 'pace-maker' cells [85–87]. Protein binding may be altered in children with higher levels of circulating displacers as in children with amino acid n-acyltransferase deficiency, which manifests with defects within the bile acid synthesis or patients on chronic total parenteral nutrition wherein cholestasis is a frequently encountered problem. Expectedly, renal filtration capacity would be compromised in the pediatric patient with focal segmental glomerulosclerosis. Children are also expected to experience the same challenges as adults when their genes encode a disposition protein that differs from the wild-type sequence. However, with Personalized Medicine on the horizon, genotyping for these DMEs should provide the prescriber with guidance on the best strategy for delivering substrate medications. The challenge will be ensuring that practitioners know how to interpret the results. By contrast, there is still little data to drive our understanding of the impact that alarming public health crises such as obesity and diabetes on pharmacokinetic processes [88,89].

Table 4. Example drug dosing altered by age.

Drug	Age, weight	Dosing and interval
Ampicillin (IV)*	<7 days old	
	- <2000 g	25–50 mg/kg/dose Q12 h
	- >2000 g	37.5–75 mg/kg/dose Q8 h
	>7 days	
	- <1200 g	25–50 mg/kg/dose Q12 h
	- 1200–2000 g	37.5–75 mg/kg/dose Q8 h
	- >2000 g	50–100 mg/kg/dose Q6 h
	Infant/child	
	- Mild–moderate infection	50–100 mg/kg/dose Q6 h
	- Severe infection	100–200 mg/kg/dose Q4–6 h
	Adult	500–3000 mg/dose Q4–6 h
Linezolid (oral/IV)*	Neonate – 11 years old	10 mg/kg/dose Q8–12 h
	12 years old adult	400–600 mg Q12 h
Zidovudine (oral-HIV treatment)*	<30 weeks gestation	2 mg/kg/dose Q12 h; increase to 3 mg/kg/dose Q12 h at 4 weeks of age
	>30–34 weeks gestation	2 mg/kg/dose Q12 h; increase to 3 mg/kg/dose Q12 h at 15 days of age
	>35 weeks gestation	4 mg/kg/dose Q12 h
	Child (>4 weeks–18 yrs)	
	- 4–9 kg	8–12 mg/kg/dose Q8–12 h
	- 9–30 kg	6–8 mg/kg/dose Q8–12 h
	- >30 kg	200–300 mg/dose Q8–12 h
	Adult	200–300 mg/dose Q8–12 h
Iron (oral) [‡] (iron-deficiency anemia treatment)	<37 weeks gestation (breastfed)	2–4 mg (elemental iron)/kg/day
	Term (>38 weeks gestation)	3–6 mg (elemental iron)/kg/day
	Adult	120–240 mg (elemental iron)/day

*Source [90].

‡Source [91,92].

Conclusion

Fortunately, the general pediatrician typically encounters ‘otherwise healthy’ patients and prescribes medicines for which a basic understanding of pediatric disposition is available. In many cases, the practical impact of ontogeny on absorption, distribution, metabolism and elimination are already known (Table 4). However, when dosing guidelines are unclear, the challenge of pediatric prescribing is not insurmountable and can be rationally approached with knowledge of the anatomic and physiologic changes that occur during normal growth and development. When children experience an undesirable drug effect, it behooves the clinician to consider patient specific processes that may perturb the dose-exposure profile, before concluding that a drug or drug class should be avoided, if for no other reason

than to assure judicious medical management when these patients transition into adulthood.

Future perspective

Over the past two decades we have seen legislative support for pediatric drug development increase, and with it fiscal support for the conduct of pediatric clinical trials that elucidate age-specific dosing guidelines. However, much of this activity is centered around individual drugs. For prescribers to generalize this knowledge, a broad understanding of how it is that growth and development alters the pharmacokinetics of any new drug will be necessary. To some extent, predictions of dose-exposure relationships in children can be accomplished with *in silico* modeling software that examines the physicochemical characteristics of a drug and applies existing knowledge of disposition to inform

expectations of exposure at a given dose. However, there remain substantial gaps in the literature with respect to information on the activity and expression of various drug disposition proteins for which current pediatric models cannot presently account. Notably, this limitation may eventually be addressed by mining the ever expanding assembly of tissue repositories that pair histological and clinical data. Through a dedication to uncovering the roles of poorly characterized DMEs/transporters on drug disposition and examining the impact of ontogeny on their expression, we can refine these *in silico* modeling tools such that they can more robustly predict pediatric disposition. With this capability in hand, we can then turn to more thorough examinations of the perturbations in drug disposition that are introduced by pathologic conditions of vary-

ing degree when overlaid on the process of growth and development. Ultimately these tools should be able to assist providers with providing the highest level of care to the children they treat by individualizing dosing with the goal of maximizing efficacy and reducing unintended adverse events.

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Executive summary

- There are significant differences between children and adults when it comes to drug disposition which influence drug dosing regimens, some driven by changes in anatomy/physiology and others associated with disease. Prescribers should be aware of these differences when considering the unexpected drug responses they observe in their pediatric patients.
- Children are more likely than adults to reject oral medications due to many factors such as taste and texture.
- Neonates experience higher gastric pH and altered intestinal activity which can influence the stability and bioavailability of orally administered medications. Neonates are also uniquely susceptible to differences in extra oral drug absorption.
- Due to the larger extracellular and total body water stores, young infants are expected to experience lower plasma concentrations for hydrophilic drugs if administered at the same mg/kg dose as in older children and adults.
- Lower circulating protein stores and higher concentrations of bilirubin and fatty acids reduce protein binding in neonates.
- There are multiple drug metabolizing enzymes wherein altered expression and/or function confer different rates of clearance in children as compared with adults.
- Well defined changes in the anatomy of the kidney as a function of age permits robust prediction of changes in clearance for renally eliminated medicines.
- A prescriber's awareness of a patient's present and past medical history may provide clues to whether a drug dose or interval should be adjusted.

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