Absorption and Bioavailability of Preterm Infants' Pharmacokinetics

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Contributor: Olga I. Butranova , Elena A. Ushkalova , Sergey K. Zyryanov , Mikhail S. Chenkurov

Drug absorption is the process of drug transportation from the site of administration to the systemic circulation and the fraction of unmetabolized drug that reaches the systemic blood flow is bioavailability. It is affected by multiple facrtors, including age. The process of maturation of organs and systems in newborns contributes to the changes in the drugs absorption, and variability is also seen between full term and preterm infants in this respect.

preterm pharmacokinetics antibiotics

1. Introduction

Absorption and bioavailability both depend on drug-related factors (formulation, rate of solubility, physicochemical properties, etc.) and patient-related factors. Patient-dependent factors affecting absorption and thus bioavailability in the oral route of drug administration include the value of pH in the stomach and intestine, the rate of motility of the gastrointestinal tract (GIT), GIT maturation rate, gastric emptying time, expression of transport proteins in GIT, the quality and quantity of gastric juices, the rate of bile production, pancreatic function, first-pass metabolism, gastric volume, and mucin production. The main sites of absorption of orally administered drugs in neonates include the stomach, small intestine, and colon. Absorption in the stomach is governed first by gastric pH and gastric emptying time. It is considered, that in neonates (both term and preterm) the colon can play a significant role in the absorption of some drugs and nutrients, which is not true for adults [1].

Neonates are characterized by different degrees of the structural and functional maturation of the GIT depending on the term or preterm birth mainly. The anatomical differentiation of the intestine happens within 20 weeks of gestation, while functional maturation demands more time and appears in general after 32–34 weeks of gestation [2]. Preterm newborns are characterized by a reduced intestinal surface area due to limited villi maturation (full maturation of villi is observed around 20 weeks of gestation), which may lead to impaired absorption of orally administered drugs compared to full-term neonates [3].

Gastric acid secretion emerges in the second trimester of pregnancy and is less in preterm babies compared with full-term; from the moment of birth in two months there is a doubling of the value of secretion [3]. Pepsinogen secretion starts after 17–18 weeks of gestation, and enterokinase—after 24 weeks (25% of the level of older infants). Lactase activity is decreased in preterm newborns, while activities of sucrase, maltase, and isomaltase have no differences with full-terms. Pancreatic lipase is decreased in preterm neonates, as well as bile production and bile ileal reabsorption. Concentrations of bile acids and bile salts in the intestinal lumen at birth are relatively

low, and insufficient functioning of transporter-mediated uptake and enterohepatic bile circulation is observed, though passive bile reuptake in the intestine and active transport in the distal ileum are presented [1].

An important factor in drug solubility and thus, absorption, is gastric volume. According to the Biopharmaceutics classification system (BCS), drugs can change their solubility class at different ages with the change in gastric volume. For example, antibacterials including chloramphenicol, erythromycin, and cefalexin alter from a low solubility classification in 6-month-old children to high solubility in adults [4]. Gastric motility is low in preterm newborns of 28–32 gestational weeks, while after 32 weeks, the value is close to full-terms. Gastric emptying is considered to be slower in infants than in older children and adults, with discussible factors affecting certain values [5]. A meta-analysis including 49 published studies of 1457 individuals proved the absence of effects of postnatal age or gestational age on the mean gastric emptying time. A significant effect of meal type was established. The fastest emptying time (mean simulated gastric residence time of 45 min) was determined for aqueous solutions, and the slowest (98 min) for solid food [6]. Published data state that the time of intestinal transit in preterm newborns is four times longer than in adults [7].

The value of gastric pH in neonates, both full-term and preterm, is still a discussible question. Some works stated a nearly neutral pH at birth (6–8) with further change to acidic values [8]. In a study of 40 preterm infants (24–33 weeks of gestation) median gastric pH was found to be between 4.5 and 5.5 [9]. A study of 29 preterm neonates ≤28 weeks of gestational age with body weight ≤ 1000 g showed an acidic value of gastric pH on day 1 with nearly no change up to 4 weeks. For neonates ≥26 weeks, mean pH ± standard deviation on the first day was 5.25 ± 3.00, and on the 28th day, it was 4.56 ± 1.34. For neonates <26 weeks, the values were 5.33 ± 2.17 and 4.87 ± 1.06, correspondingly [10]. Research conducted in the earlier period with a smaller number of neonates revealed variable results with mean pH ranging from 1.3 up to 6.9 [11][12]. Postprandial pH in the infant stomach was shown to be on a level above 4.5 for about two hours [5]. In the intestinal lumen of infants, the range of pH was reported to vary between 5.8 and 7.0, based on limited data [1].

The rate of expression of transport proteins provides a great impact on drug absorption since it is generally low in neonates. There was proved a strong relationship between the age of neonate (mainly postmenstrual age) and expression of such transport proteins, as breast cancer resistant protein (BCRP), bile salt efflux pump (BSEP), glucose transporter 1 (GLUT1), P-glycoprotein (P-gp), multidrug-resistance like protein 1 (MRP1), 2 (MRP2), and 3 (MRP3), Na^+-taurocholate cotransporting polypeptide (NTCP), organic anion transporter polypeptides 1B1 (OATP1B1), and organic cation transporter 1 (OCT1) [13]. In preterm newborns, it is important to consider a high probability of insufficient levels of some transport proteins administering drugs orally. In the intestine, efflux transporters limiting drug absorption are P-gp, MRP2, and BCRP. Drug intestinal absorption is mainly performed with OATP1A2, OATP2B1, and peptide transporter 1 (PEPT1) [14].

Characteristics of the main transport proteins affecting drug absorption in the intestine are shown in **Table 1**.

Table 1. Time of expression, age-associated changes, and antibiotic-substrates for the main intestinal transport proteins.

Transport Protein	Time of Expression in Different Cells	Age-Dependent Change of Expression	Transported Antibiotics
BCRP	Intestinal epithelium—from 5.5 to 28 weeks of gestation. Hepatocytes—from 10 to 11 weeks [15]	Similar levels in preterm newborns, full-terms, and adults [13][16]	Delafloxacin, ciprofloxacin, enrofloxacin, nitrofurantoin, norfloxacin, ofloxacin [17][18]
P-gp	Enterocytes—from the 12 weeks of gestation [15]	Expression in fetus is lower than in adult samples [13]	Erythromycin, tetracycline [19] Azithromycin [20] Levofloxacin, sparfloxacin [21] Dicloxacillin [22][23]
MRP2	Appears in the liver of 14-week-old fetuses, strong expression at 19 weeks [24]	Lower protein expression in fetuses and term newborns than in adults [13] MRP2 mRNA was 30-fold lower in fetal, 200-fold lower in neonatal, and 100-fold lower in infant liver compared to adults [25]	Ampicillin, azithromycin, and ceftriaxone, cefodizime, ceftriaxone [14] [26]
OATP1A2	-	-	Levofloxacin [19] Ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, norfloxacin [27] Erythromycin [28] Tebipenem [29]
OATP1B1	-	High expression in the fetus and low expression in the term newborns, with stable protein levels further on [13] OATP1B1 expression was 20-fold lower in fetal, 500-fold lower in neonatal, and 90-fold lower in infant liver compared to adults [25]	Benzylpenicillin, rifampicin, rifampin, rifampicin [19] Cefazolin, cefditoren, cefoperazone, nafcillin [30]
OATP1B3	-	OATP1B3 mRNA was 30-fold lower in fetal, 600-fold lower in neonatal, and 100-fold lower in infant liver compared to adults [25] OATP1B3 exhibited high expression at birth, decline over the first months of life, and then increase in the preadolescent period [31].	Rifampicin, rifampin [19] Cefadroxil, cefazolin, cefditoren, cefmetazole, cefoperazone, cephalexin, nafcillin [30] Erythromycin [28]
OATP2B1	-	Similar levels in samples from all age groups [13]	Benzylpenicillin [32] Tebipenem pivoxil [33]

Transport Protein	Time of Expression in Different Cells	Age-Dependent Change of Expression	Transported Antibiotics
		Intestinal OATP2B1 expression in neonates was significantly higher than in adults [25]	
PEPT1	Enterocytes—from 24.7 to 40th week of gestation (comparable level with full terms) [13]	The PEPT1 mRNA expression of the neonates/infants was only lightly lower (0.8-fold) than the older children ($p < 0.05$) [25]	Cefadroxil, ceftibuten, cefixime, cephradine, cephalexin [30]

Parameter	Age-Associated Change	Effect on Absorption and Bioavailability
pH	Value close to neutral at birth was described in some studies with rapid change to acidic values	High gastric pH may provide positive effect on the oral bioavailability of acid-labile drugs (e.g., ampicillin, amoxicillin, penicillin, nafcillin, erythromycin), it favors the ionization, and reduces the absorption of weak acids and may negatively affect absorption of weak bases by decreasing their solubility [34]
Gastric volume	Decreased	Solubility of some drugs can be decreased
Gastric emptying and intestinal transit	Some slowing is specific, intestinal transit in preterm newborns is 4 times longer than in adults [7]	Delay and decrease in absorption
Biliary function	Decreased compared with older children and adults [1]	Possible decrease in the intestinal absorption of lipid-soluble drugs
Pancreatic enzymes	Decrease at birth with further rise through the first year of life	Decreased intra-duodenal hydrolysis may result in incomplete absorption
Intestinal surface area	Reduced surface-to-volume ratio in children when compared with adults [34]	Reduced absorptive surface may influence absorption of some drugs
Intestinal permeability	In preterm infants (26–36 weeks gestation), intestinal permeability is higher than in healthy term infants only if measured within two days of birth [35]	Increase in absorption may by for drugs with paracellular route of absorption [36]
Transport proteins	Decreased p-gp, MRP1, MRP2—decreased efflux function	Possible increase in absorption of corresponding substrates
	Light decrease in PEPT1	Possible decrease in absorption of corresponding substrates
Intestinal wall drug-metabolizing enzymes	Possible decrease in cytochrome P450 isoenzime 3A4 (CYP3A4) in neonates at	Possible increase in absorption and bioavailability of CYP3A4 substrates

Pharmacokinetic (PK) parameters of orally administered antibiotics in neonates were studied mainly for beta-lactams, and for many of them, plasma concentration values high enough to exceed MIC were demonstrated.

Parameter	Age-Associated Change	Effect on Absorption and Bioavailability
	birth with further rise through childhood period [37]	[38][39]

the work by Hsieh EM et al. (2014) five drugs were reported (amoxicillin, oxacillin, nafcillin, penicillin G, and piperacillin tazobactam), in the work by Prusakov P et al. (2019)—nine (amoxicillin, and amoxicillin clavulanate, ampicillin sulbactam, penicillin G, cloxacillin, oxacillin, nafcillin, piperacillin, and piperacillin tazobactam) [38][39].

From the middle of XX century PK parameters of many penicillins were studied in neonates, and the results revealed differences between oral and parenteral routs of administration and age-dependent changes [40]. Oral penicillin was characterized by a lower C_{max} value compared with penicillin administered intramuscularly [41]. Studies revealed a better absorption of oral flucloxacillin in infants 0–1 month old compared with older children [42], especially for such formulations as mixtures [43], plasma concentrations after both intravenous (i.v.) and oral administration were well above the *MIC*-values generally reported for *Staphylococcus aureus* [44]. A review of the works dedicated to oral flucloxacillin in neonates revealed a T_{max} of 2 h in a majority of studies [40]. Studies of oral ampicillin and amoxicillin in neonates revealed a delay of T_{max} up to 4 h compared with 30 min in intramuscular administration with bioavailability values close to adults, C_{max} in preterm neonates was the highest compared with full-terms and older children [40][45].

Amoxicillin clavulanate is one of the most prescribed oral antibiotics for both adult and pediatric populations used in case of proved or strictly suspected beta-lactamase production. Evaluation of PK parameters of oral clavulanic acid in term neonates (*n*—15, dose of amoxicillin clavulanate 25/6.25 mg/kg, thrice a day administration) resulted in great variance in plasma concentrations (median: 1.4 mg/L; range: 0.20–4.82 mg/L) and extrapolation led to *AUC* of at least 8.4 mg·h/L, which is comparable to those of adults [46]. The conclusion of high variability of PK parameters of clavulanic acid in the pediatric population is supported by a systemic literature review of 18 studies, which did also state that C_{max}, for oral administration, was below that of the intravenous route [46], which is like it is in adults [47].

PK studies of penicillins in neonates with sepsis are limited. The results of the PK study of oral amoxicillin used together with parenteral gentamicin in 60 0–2 month infants with sepsis (final analysis included blood samples from 44 infants) revealed that amoxicillin concentrations exceed the susceptibility breakpoint for amoxicillin (2.0 mg/L) against resistant *S. pneumoniae* strains for >50% of a 12-h dosing interval [48].

3. Absorption of Oral Cephalosporines

In the list of most used drugs in neonatal ICU (for the period 2005–2010 years) among cephalosporins there are seven positions, and oral formulation is available only for the one—for cephalexin [38]. In the global point-prevalence survey of antimicrobial use in neonatal ICUs, there were eight cephalosporins with two available in oral form—cefadroxil and cephalexin [39].

The pharmacokinetics of oral cephalosporins are described in several studies including pediatric population. In children with osteoarticular infection, the achievement of optimal plasma exposure was demonstrated for oral cephalexin (median dose 40 mg/kg/dose every 8 h) [49]. Data on PK of oral cephalexin in newborns revealed that the serum levels achieved after a dosage of 15 mg/kg 8 hourly were lower than the average *MIC* for most of the Gram-negative organisms causing infections in neonates, while the levels achieved after 50 mg/kg 12-hourly were close to those in adults receiving 1 g. T_{max} was at about 2 h, demonstrating slower absorption than in adults [50]. PK studies performed in 70 s of XX century with cefadroxil and cephradine included infants and children with no inclusion of neonates. The results reported a decrease in C_{max} in the fed state, which can be true also for the neonatal population [51][52]. PK of cefaclor was studied in 10 newborns, a mean peak serum concentration of 7.7 µg/mL was achieved at 1 h after an oral dose of 7.5 mg/kg [53]. For plasma concentrations of cefaclor, the same effects of fed and fasting states were detected as those for cefadroxil and cephradine [54]. On the opposite side, for cefprozil, there were no food effects on PK [55]. PK of oral cefuroxime axetil was studied in the pediatric population (minimum age of participants—3 months). This research reported achievement of concentrations exceeding the MICs for common respiratory tract pathogens, including beta-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis*. Administration of 10 or 15 mg/kg doses resulted in serum cefuroxime concentrations similar to adult values following a 250 mg cefuroxime axetil tablet [56]. For oral cefixime pediatric data, supposed GIT absorption from 40 to 50% is more rapid and complete for oral suspension [57]. Oral ceftibuten (single oral dose of either 4.5 or 9.0 mg/kg) PK parameters were studied in infants and children. Rapid absorption was shown with mean T_{max}—140 min and C_{max} from 5.0 to 19.0 mg/L with no differences between dosing regimens [58]. Pediatric PK studies of cefpodoxime revealed T_{max} prolongation in the fed state (fed = 2.79 ± 1.10 h vs. fasted = 1.93 ± 0.54 h), but the extent of absorption was not affected by food [59]. Though this result was derived from the pediatric population, it can be also considered actual for neonates.

4. Absorption of Oral Carbapenems

The first carbapenem with the oral route of administration approved for pediatric practice in Japan is tebipenem. Though there are no data on neonates, it is interesting to consider PK parameters derived from pediatric studies (*n*—217, minimum age of participant—6 months, dosing regimen—twice a day at 4 mg/kg or 6 mg/kg for 8 days). T_{max} values were 0.74 ± 0.26 and 0.69 ± 0.22 h (average + standard deviation) in 4 mg/kg and 6 mg/kg, C_{max} values were 3.48 ± 1.67 and 5.20 ± 2.84 mg/mL, and the $AUC_{0–24\ h}$ values were 11.00 ± 1.84 and 16.07 ± 3.35 mg·h/mL in the 4 and 6 mg/kg dosage groups, respectively [60]. Tebipenem pivoxil is characterized by remarkably high absorption in GIT due to its ability to be transported by OATP1A2 and OATP2B1 along with simple diffusion [33]. Interestingly to note, tebipenem pivoxil is the first beta-lactam demonstrated OATP-mediated transport in the process of intestinal absorption. Since there are some studies stating an increased intestinal OATP2B1 expression in neonates [25], there is a potential for variability in intestinal tebipenem pivoxil absorption in this population.

5. Absorption of Oral Macrolides

Macrolides are antibiotics used mainly in ambulatory practice, but in the list of 100 drugs most used in NICU erythromycin was ranked 24th being the 6th among most used antibiotics and the only macrolide [38]. In the global survey by Prusakov P et al. (2021), there were three macrolides used in neonatal ICU, erythromycin, azithromycin, and clarithromycin [39]. Erythromycin was the first macrolide studied in children. Comparison of absorption of erythromycin suspension in three age groups (0–1 month, 1–6 months, and 6 months to 6 years) revealed the lowest value for infants less than 1 month of age [61]. The value of absolute bioavailability of rectally administered erythromycin was 28% in neonates, 36% in infants, and 54% in children greater than 1 year [62].

PK parameters of orally administered azithromycin were studied in children after a single oral dose of 10 mg per kg of body weight on day 1 followed by single daily doses of 5 mg/kg on days 2 to 5. Mean values of PK parameters (±standard deviation) were estimated for C_{max}, T_{max}, and $AUC_{0–24}$: 383 + 142 ng/mL, 2.4 + 1.1 h, and 3109 + 1033 ng × h/mL, respectively. Concentrations in serum at 0 h (predose) and at 24, 48, and 72 h after the final dose were 67 + 31, 64 + 24, 41 + 17, and 29 + 14 ng/mL, respectively [63]. In the study of single (*n*—14) and multiple oral doses (*n*—9) of 12 mg/kg in 23 children, C_{max} and T_{max} of azithromycin were 318.2 + 174.5 µg/L, and 2.4 + 1.1 h, respectively, with no differences estimated between these doses groups [64]. Comparison between 30 mg/kg immediate-release (IR) and 60 mg/kg extended-release (ER) forms of azithromycin oral suspension in children revealed similar or greater systemic exposure in the case of ER form [65].

PK studies including clarithromycin revealed high rates of oral absorption both in children and adults not affected by food. In infants and children (6 months to 10 years), a brief delay in the onset of absorption was demonstrated for clarithromycin (suspension, 7.5 mg/kg). The mean C_{max} for clarithromycin was reached within about 3 h both under fasting and fed conditions with corresponding values of 3.59 and 4.58 micrograms/mL in a single-dose regimen. C_{max} values for 14-(R)-hydroxylated metabolite for fasting and fed conditions were 1.19 and 1.26 micrograms/mL, respectively [66]. Other studies reported a similar profiles of clarithromycin pharmacokinetics in the pediatric population [67].

6. Absorption of Oral Oxazolidinones

Linezolid is used in neonates including preterm ones. Its bioavailability is extremely high in the oral route, reaching 100% with minimum decrease under the fed condition, T_{max} is about 1–2 h [68]. The PK study of oral linezolid suspension, 10 mg/kg used in 4-month-old infants (birth at 25 weeks) revealed that C_{max} and *AUC* were lower than in full-term infants who used linezolid intravenously [69]. Possible factors affecting the PK of linezolid in neonates may include incomplete absorption, faster clearance, or a smaller actual volume of distribution. PK study including extremely premature infants was performed for oral linezolid (dose 10 mg/kg every 8 h) and continuous intravenous infusion (dose 30 mg/kg). Analysis of 7 serum samples for oral linezolid revealed a mean C_{max} equal to 9.04 (0.69–32.9) mg/L, and 17 serum samples for intravenous linezolid revealed a mean C_{max} equal to 1723 (2.6–30.4) mg/L. Reported C_{max} values for both routes of administration were ≥*MIC* for causative microflora [70].

Another oxazolidinone, tedizolide, is also used in pediatric practice. The study of oral and intravenous tedizolid in infants (age—1 day to 24 months) started in the 2017 year (NCT03217565) and still has a recruitment status [71].

PK parameters of oral tedizolide (dose 3–6 mg/kg) were studied in children (2 to <12 years old), and results revealed high bioavailability value, compared with that of the intravenous route, median T_{max} was 2–3 h compared with 1–2 h after initiation of the 1 h intravenous infusion. C_{max} values were higher compared with adults (4.19 vs. ~2.5 mg/L) [72]. A study of oral and intravenous tedizolid in adolescents revealed no significant differences in PK parameters and the received results demonstrated similarity with adult PK parameters of tedizolid [73].

7. Absorption of Oral Fluoroquinolones

Fluoroquinolones are among the antibacterials prescribed for neonates with infections, including ICU practice [39]. Ciprofloxacin is used in the majority of clinical situations intravenously, though in some situations, oral route is available. Population pharmacokinetics of ciprofloxacin including oral form was derived using data from a mixed population, including 3 newborns, 17 infants and toddlers, 27 children, and 8 adolescents and young adults. For i.v. ciprofloxacin, sampling at a single point (12 h after the start of infusion) allowed the precise and accurate estimation of clearance (CL) and the elimination half-life, as well as the ciprofloxacin concentration at the end of the infusion, for oral ciprofloxacin the presence of a lag time after administration suggests a schedule based on two sampling times of 1 and 12 h [74]. Another population PK study was performed with data from 60 newborn infants who used intravenous ciprofloxacin (postmenstrual age [PMA] range, 24.9 to 47.9 weeks). The main covariates affecting ciprofloxacin pharmacokinetics were gestational age, postnatal age, current weight, serum creatinine concentration, and use of inotropes. Monte Carlo simulation demonstrated that 90% of hypothetical newborns with a PMA of <34 weeks treated with 7.5 mg/kg twice daily and 84% of newborns with a PMA ≥34 weeks and young infants receiving 12.5 mg/kg twice daily would reach the *AUC/MIC* target of 125, using the standard EUCAST *MIC* susceptibility breakpoint of 0.5 mg/L [75].

Levofloxacin also may be administered orally in pediatric practice. In the study 85 children (6 months to <2 years, 2 to <5 years, 5 to <10 years, 10 to <12 years, and 12 to 16 years) received a single 7 mg/kg dose of levofloxacin (intravenously or orally) absorption demonstrated no age-dependence and was close to adult values [76].

The rate of oral absorption of other fluoroquinolones, moxifloxacin, and gatifloxacin, were not studied in infants and only extrapolation of the results of PK studies made for an older category of patients is possible. For oral moxifloxacin data are available for the pediatric population suffering from multidrug-resistant tuberculosis (*n*—23, the median age—11.1 years, 6 out of 23 were human immunodeficiency virus (HIV)-infected). The median C_{max} was 3.08 (IQR, 2.85–3.82) µg/mL, *AUC* from 0–8 h ($AUC_{0–8}$)—17.24 (interquartile range, IQR, 14.47–21.99) µg × h/mL, T_{max}—2.0 (IQR, 1.0–8.0) h. In HIV-infected children, there was a decrease in $AUC_{0–8}$ and C_{max}. T_{max} was shorter with crushed vs. whole tablets [77]. PK parameters of oral gatifloxacin were studied for a single dose of suspension (doses—5, 10, or 15 mg/kg of body weight, 600 mg maximum; 76 patients with average age 6.7 ± 5.0 years) and for tablets (dose 10 mg/kg, 2 children >6 years of age). C_{max} and *AUC* increased in a manner approximately proportional to the dose, and at the 10 mg/kg dose, the bioavailability was similar between the suspension and tablet formulation [78].

8. Absorption of Other Oral Antibacterial Agents

Vancomycin is a glycopeptide administered intravenously to treat neonatal sepsis caused by resistant Gram-positive microflora. Oral vancomycin demonstrated effectiveness in the prophylaxis of necrotizing enterocolitis in preterm, very low birthweight infants, and no serious adverse effects were detected, with negligible serum drug concentrations suggesting the absence of systemic absorption [79]. The same results were revealed for older patients with colitis caused by *Clostridium dificile* (*n*—8, age from 2 to 18 years)—serum vancomycin levels were undetectable [80]. Published works reported increased rates of oral absorption of vancomycin in pediatric and adult patients with cancer and associated chemotherapy [81][82].

Trimethoprim sulfamethoxazole (TMPX) being a synthetic antimicrobial agent is found among drugs used in NICU in infants ≥3 days old [39]. Simulation of TMPX exposure (oral route of administration) revealed that for all dosing regimens steady-state area under the concentration-versus-time curve from time zero to τ ($AUC_{0-\tau,ss}$; where τ denotes the dosing interval) in subjects 0 to <2 years was similar with the group of 2 to <6 years of age (within 20%), but 29% less than in older children (6 to <21 years of age). Values of simulated $AUC_{0-\tau,ss}$ both for infants and children were generally lower than that for 70-kg adults [83].

Clindamycin is used in neonatal ICU including infants <3 days old [39]. Clindamycin exists in oral form, though due to negative organoleptic properties, it is not a common choice for the pediatric population. Since clindamycin is a highly lipophilic agent, its absorption is thought to be unaffected by age-associated changes specific to the pediatric population including neonates [84].

Fosfomycin (C3H7O4P) is a phosphonic acid derivative representing an epoxide class of antibiotics [85] proposed to treat NS in resistance to first-line antibiotics [86]. Fosomycin is hydrolyzed in the stomach and absorbed in the small intestine; factors affecting its bioavailability include gastric pH and gastric emptying rate [87]. In the PK study of fosfomycin in neonates with suspected sepsis (The NeoFosfo study (NCT03453177)) oral bioavailability was estimated to be 0.48 (dose was 100 mg/kg) [87] that is close to adult values [87].

Rifampin is a macrocyclic antibiotic effective mainly against resistant Staphylococcus aureus and Mycobacterium tuberculosis. Oral forms may contain only rifampicin, or its combination of isoniazid and pyrazinamide. The study included children with tuberculosis (age 3 months to 13 years, dosing for initial treatment, intensive phase—rifampicin 60 mg, isoniazid 30 mg, and pyrazinamide 150 mg; for continuation phase—rifampicin 60 mg and isoniazid 30 mg) the mean AUC_{0-6} on enrolment was 14.88 and 18.07 µg/hour/mL (p = 0.25) in HIV-infected and HIV-uninfected children, respectively, and after 4 months of treatment 16.52 and 17.94 µg/hour/mL (p = 0.59). The AUC_{0-6} of all 55 children was 16.81 (+10.82) µg/hour/mL on enrolment and 17.39 (+9.74) µg/hour/mL after 4 months of treatment [88]. Previous PK studies of oral rifampicin in children revealed Cmax three times less than that for the intravenous route [89]. Using PK data from preterm and term infants dosing simulation was performed based on weight and postnatal age, simulated regimens resulted in comparable exposures to adults receiving therapeutic doses of rifampin against staphylococcal infections and TB [90].

9. Effect of Food on Antibiotics Absorption

An important factor that may alter the rate of absorption of oral drugs is the presence of food in GIT. PK studies described above provide some data in this respect, and **Table 3** represents available information on food effects on the absorption of oral antibiotics.

Table 3. Food effects on absorption of oral antibiotics in pediatric and adult populations.

Drug (Oral Administration)	Food Effect on PK Parameters in Pediatric Population	Food Effect on PK Parameters in Adults
Penicillin V (phenoxymethylpenicillin)	C_{max} decreased	Penicillin V (phenoxymethylpenicillin)
Amoxicillin	C_{max} decreased at lower doses, unchanged at higher doses *AUC* unchanged at all doses	No effect
Ampicillin	C_{max} unchanged *AUC* unchanged	Some studies suggest reduction in C_{max} and *AUC* with food
Cefpodoxime proxetil	T_{max} prolonged C_{max} unchanged	C_{max} and *AUC* increase with any meal intake
Cephalexin	C_{max} lightly decreased *AUC* lightly increased	Delay in absorption *AUC* unchanged
Cefaclor	C_{max} decreased	T_{max} prolonged C_{max} decreased
Cefadroxil	C_{max} decreased	No effect
Cephradine	C_{max} decreased	No effect
Cefixime	No clinically significant changes in C_{max} and *AUC*	T_{max} prolonged C_{max} and *AUC* unchanged
Clarithromycin	C_{max} unchanged *AUC* unchanged	C_{max} unchanged *AUC* unchanged

10. Absorption in Non-Oral Routes of Administration

The data on age-associated change of absorption for non-oral routes of drug administration are given in **Table 4**.

Table 4. Age-associated change of absorption for non-oral routes of drugs administration.

Routes of Administration	Main Physiological Factors Affecting PK Parameters in Neonates	Change of Absorption
Intramuscular	Blood flow to muscle: variable decrease over the first 2–3 weeks of life. The ratio of muscle mass to body mass:	Possible variability in absorption, though for many antibiotics it nearly reaches adult values.

Routes of Administration	Main Physiological Factors Affecting PK Parameters in Neonates	Change of Absorption
	less in neonates than in adults Water content: higher proportion of water in neonates [91]	Hydrophilic drugs may have greater intramuscular absorption in neonates than children or adults due to high water content in muscles
Rectal	pH: decreased in neonates compared with older infants (mean pH 6.47 vs. 6.90) [92] and with adults (pH 7.2–7.4) [93]	Nearly no change in absorption of drugs (absorbable drugs should have *pKa* values near or above the physiological range)
Percutaneous	Skin thickness and keratinization: reduced Hydration of the stratum corneum: increased Surface area to bodyweight ratio: higher than in adults [8][94]	Increased absorption of drugs including some topical antibiotics with risk of overexposure, and potential toxic effects
Inhalation Intranasal	Stage of lung development: late preterm neonates (28–34 weeks of gestation) may have saccular stage of lung development, more preterm infants—just the stage of development of bronchioles and alveolar epithelium, both with surfactant deficiency and high risks for respiratory distress syndrome [95] Permeability of the mucosa of the nasal cavity: Increased in neonates [94]	Reduced absorption from the lower respiratory department and increased absorption from the upper respiratory department including nasal cavity (e.g., with facemask for inhalation)

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