Pediatric Pharmacology

INSTRUCTOR: Joe B. Blumer, Ph.D.
OBJECTIVES: After studying this unit, you should be able to:

1. Describe the age-related factors that affect ***absorption*** of drugs in pediatric patients, including developmental changes in gastric pH, gastric emptying time and muscle mass.
2. Describe the age-related factors that affect drug ***distribution*** in pediatric patients, including developmental changes in total body water, adipose tissue and plasma protein binding.
3. Identify the age-related factors that affect drug ***metabolism*** in pediatric patients, including age-dependent expression of phase 1 and phase 2 metabolizing enzymes.
4. Describe the factors that affect drug excretion and ***elimination*** in pediatric patients, including age-dependent changes in kidney development and function, particularly glomerular filtration rate.
5. Identify the factors used to approximate safe dosing of medications in pediatric patients and the issues surrounding the relative paucity of information regarding the determination of safe pediatric drug dosing.
6. Describe the risk factors for adverse drug reactions in pediatric patients and drugs associated with unique toxicities in pediatric patients.

Prototype drugs: No specific drugs (several examples are discussed)

References:

1) Basic and Clinical Pharmacology, Ch. 59: Special Aspects of Perinatal & Pediatric Pharmacology, Katzung & Trevor, 14th edition (2018)
2) Pharmacotherapy: A Pathophysiologic Approach, Ch. 7: Pediatrics, DiPiro, 10th edition (2015)
3) Neonatal & Pediatric Pharmacology: Therapeutic Principles in Practice. Sumner Yaffe, Jacob Aranda. Wolters Kluwer (2010) https://ebookcentral.proquest.com/lib/musc/detail.action?docID=3418293
4) Aquifer Pediatrics, https://musc-md.meduapp.com/document_sets/5342
5) Lu, H. and Rosenbaum, S. Developmental pharmacokinetics in pediatric populations. *J Pediatr Pharmacol Ther* (2014);19(4):262–276
6) https://www.merckmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/overview-of-drug-treatment-in-children#v1085119
7) Hales CM, Kit BK, Gu Q, Ogden CL. Trends in Prescription Medication Use Among Children and Adolescents-United States, 1999-2014. *JAMA*. (2018) May 15;319(19):2009-2020.

I. Introduction

a. Significant progress has been made in diagnosis, management and treatment of pediatric diseases, particularly those of newborns; this is in part due to advances in the development of some of the medications used to treat these diseases.

i. However, this was not always the case. Historical issues regarding drug safety in pediatric pts include:

1. Sulfanilamide elixir

Elixir sulfanilamide

http://en.wikipedia.org/wiki/Elixir_Sulfanilamide_disaster

U. S. Races Death to Save 700 From Elixir

Recovery of Pint Bottles Sold to Patients Goal as Deaths From Poison Reach 36

By Associated Press.

CHICAGO, ILL., October 24.—A nation-wide race with death, its object recovery of more than 700 bottles, mostly pints, of a new liquid medicine, named Elixir of Sulfanilamide, which has already caused 36 verified deaths, was described today at the headquarters here of the American Medical Association.

Every agent of the United States Food and Drug Association, said Dr. Morris Fishbein, spokesman of the Medical Association, is scouring the country to recover the bottles. By some time on Monday, said J. G. Clarke of the Food and Drug Administration, it is hoped that all of the "outstanding" shipments will be recovered.

lies in the fact that large dosages are customary with sulfanilamide preparations.

The medicine stops the kidneys. At Medical Association headquarters its effects were said to be like those of bichloride of mercury. No antidote is known yet. The "Elixir" is made of sulfanilamide and diethylene glycol, a near relative of auto antifreeze fluid. The diethylene glycol is blamed for the lethal effect, although not itself classed as a poison.

The principal shipments, said Mr. Clarke, went to the South and Midwest. But in addition consignments have been traced to the Northern Peninsula of Michigan, to a distributing house in New York City and

https://www.the-scientist.com/foundations/the-elixir-tragedy-1937-39231

!!

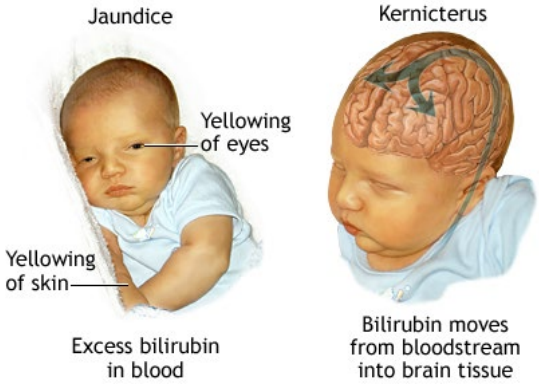
AGMA

Glycoaldehyde
↓
Glycolic acid
↓
Oxalic acid
↓
Calcium oxalate

MUDPILES	GOLDMARK
M – methanol	G – glycols
U – uremia	O – oxoproline
D – diabetes	L – L-lactate
P – paraldehyde	D – D-lactate
I – iron, isoniazid	M – methanol
L – lactate	A – aspirin
E – ethylene glycol	R – renal failure
S – salicylates	K - ketoacidosis

2. Sulfonamides – kernicterus (acute vs chronic bilirubin encephalopathy)

a. "**kern**" = nucleus; "**icterus**" = jaundice; initially used to describe the pathologic yellowing of the basal ganglia



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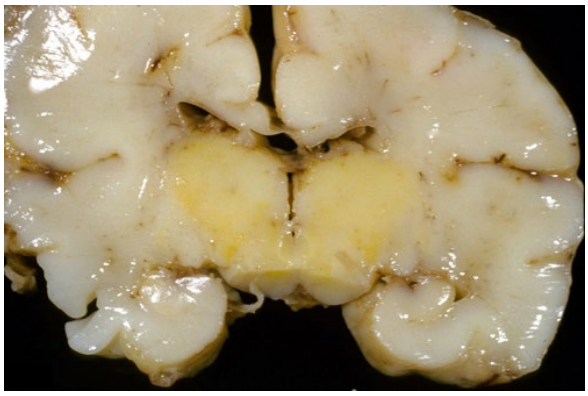
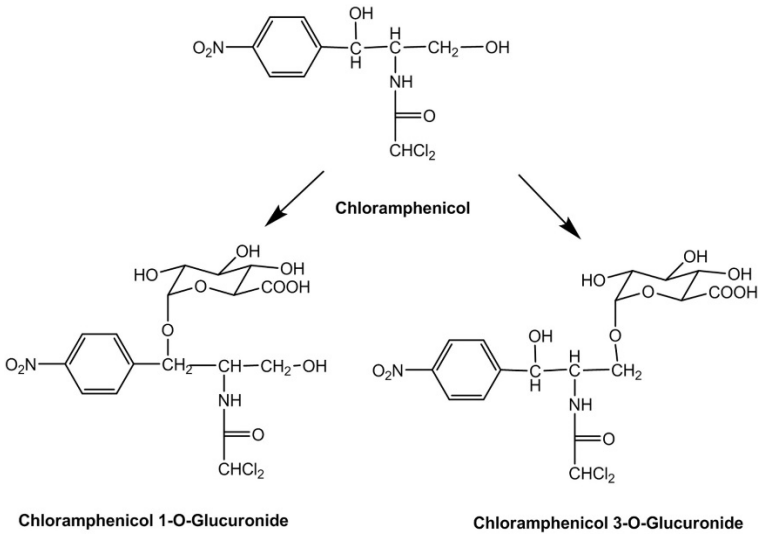


http://neuropathology-web.org/chapter3/chapter3eBilirubinencephalopathy.html

3. Chloramphenicol – grey baby syndrome, deficient glucuronidation



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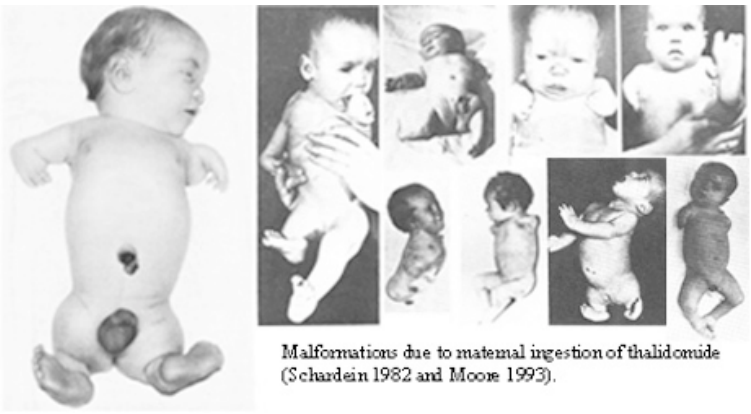
4. Thalidomide: phocomelia


Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

b. However, pharmacotherapeutic management of pediatric patients can be particularly challenging for a number of reasons, including:
    i. While most marketed medications are used in pediatric pts, only about 25% of them are actually FDA approved for use in peds pts; most are used "off-label"
    ii. Determining optimal dosing for peds pts is a critical concern
        1. Dosing for adult pts is typically based on body weight
        2. However, taking body weight-based dosing from adult pts and extrapolating them to peds pts has its limitations ("a child is not a miniature adult") – more below…
            a. Bioavailability, pharmacokinetics, pharmacodynamics, efficacy and safety data can be substantially different in peds pts due to differences in organ system development
    iii. There is comparatively very little data on pharmacokinetics, pharmacodynamics, efficacy, potency and safety of drugs in this pt population.
        1. This is somewhat understandable given practical and ethical issues regarding clinical trials and obtaining PK data in peds pts
            a. Consent?
            b. Safety?
            c. Sample collection?
        2. The NIH has recognized this issue and has begun to increase funding for obtaining drug safety and PK data in peds: developmental pharmacokinetics
c. Therapeutics in pediatric patients – important points to consider:
    i. How would the developmental and physiological differences in pediatric pts affect pharmacokinetics and drug therapy compared to adults?
    ii. How might this change over time? When do these organ systems mature enough to be considered comparable to an adult?

II. Absorption, Distribution, Metabolism and Excretion (ADME) of Drugs in Pediatric Pts

a. <u>Absorption</u>

i. Blood flow at the site of administration

1. Primarily effects IM and SC administration
    a. Muscle mass in preterm infants is minimal
        a. These issues can cause erratic and unpredictable absorption
        b. If perfusion rapidly increases, drug levels can quickly reach toxic levels
    b. For these reasons, IM administration in neonates is generally reserved for emergencies or inability to obtain IV access
2. Percutaneous absorption is generally increased in neonates due to underdeveloped epidermal barrier; infants are at increased risk of toxicity from topically applied drugs
    a. For example, topical corticosteroids are an extremely common, powerful and effective therapy for many dermatologic conditions. These corticosteroids vary greatly their potency and are categorized as such.

Potency Group	Example
Mild	Hydrocortisone acetate
Intermediate	Triamcinolone acetonide
Potent	Betamethasone dipropionate
Super-potent	Clobetasol propionate

Don't need to memorize these, just making the point these commonly used meds are quite varied in their potency & therefore risk…

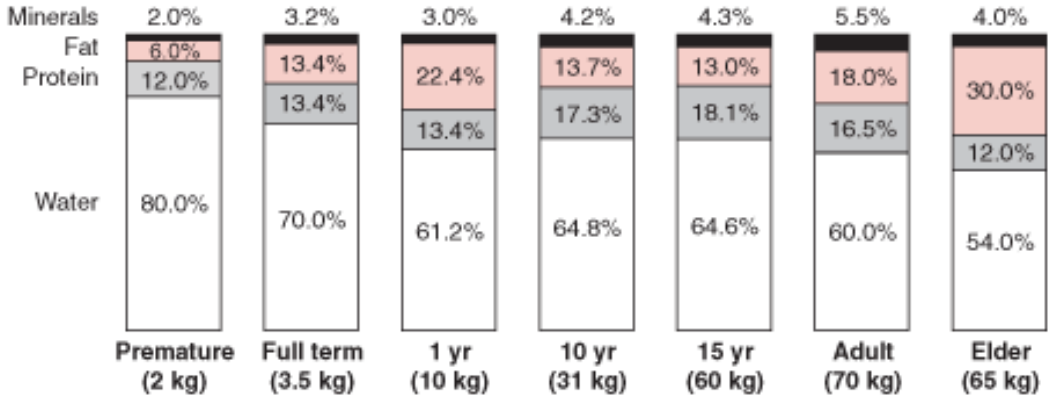
    a. These range from mild, low-potency preparations of 1% hydrocortisone to super-potent preparations of 0.05% clobetasol, which is 1000X more potent than 1% hydrocortisone
    b. Furthermore, the type of chemical formation also affects potency, e.g. hydrocortisone valerate is much more potent than hydrocortisone acetate
    c. In prescribing topical corticosteroids to peds pts, remember that neonates will absorb significantly more medication through their skin than adults. An occlusive dressing (e.g. diaper) will likely increase absorption.
    d. Side effects include:
        1. Skin atrophy
        2. Telangiectasias
        3. Hypopigmentation
        4. Suppression of the hypothalamic-pituitary axis
            a. Even low-potency topical steroids can cause these problems when used for long durations or over large areas of the body.
            b. Particular caution should be used when considering the use of steroids on the face or genitalia.

ii. GI tract
    1. pH-dependent passive diffusion
        a. Gastric pH in a full-term infant ranges from pH 6-8 at birth; gastric acid secretion begins soon after birth, resulting in a pH between 1-3 within 24 hours
        b. In preterm infants, this occurs much more slowly and lowering of gastric pH takes days
            a. Higher gastric pH in premature infants can cause higher serum concentrations of acid-labile drugs such as nafcillin
    2. Gastric emptying time is prolonged in the first 24-48 hours post-delivery and is particularly slow in premature infants
        a. Prolonged contact time with GI mucosa may increase drug absorption in infants compared to adults

b. <u>Distribution</u>

i. The volume of distribution of drugs in pediatric patient changes with age, particularly with respect to changes in **<u>body composition</u>** and **<u>plasma protein binding</u>**.

ii. Body composition: Neonates have a much higher percentage of total body water relative to body weight than adults.



(adapted from Puig M: Body composition and growth. In Nutrition in Pediatrics, 2nd ed. BC Decker, 1996.)

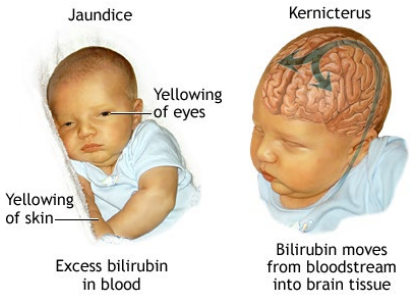
$$Loading\ dose = \frac{Cb_{ss}\ x\ Vd}{F}$$

$$t_2^1 = \frac{0.7\ x\ Vd}{CL}$$

1. Water-soluble drugs like aminoglycosides have much higher volumes of distribution in neonates and infants.
2. Higher doses per unit body weight of water-soluble drugs like aminoglycosides are typically required in neonates and infants.

iii. Binding of drugs to plasma proteins is generally lower in neonates:

1. Plasma protein concentration (e.g. albumin, alpha-1 acid glycoprotein, lipoproteins) in neonates is lower
2. Neonatal plasma proteins have lower drug-binding capacity
    a. Fetal albumin, for whatever reason, binds acidic drugs (e.g. penicillins, NSAIDs) rather poorly
3. Increased competition for protein binding sites by bilirubin and other endogenous compounds (e.g. sterol hormones, free fatty acids)
    a. Bilirubin binds to albumin and can displace some drugs, penicillins in particular
        a. However, some drugs can actually displace bilirubin binding to albumin, e.g. sulfa drugs, free fatty acids
            1. **This can lead to <u>kernicterus</u> and is the reason <u>sulfonamide/"sulfa" drugs</u> are generally avoided in neonates; also a concern for <u>ceftriaxone</u> (but only in neonates).**



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    b. Also, higher levels of unbound (free) drugs that are typically highly protein bound (e.g. highly lipophilic drugs) can affect drug bioavailability and can result in toxicities.
4. **Net result of lower protein binding in neonates (tl;dr)**:
    a. Increased free drug concentrations
    b. Greater availability of drug to bind receptors
    c. Increased pharmacologic effects at lower doses
    d. Increased risk of adverse effects at lower doses

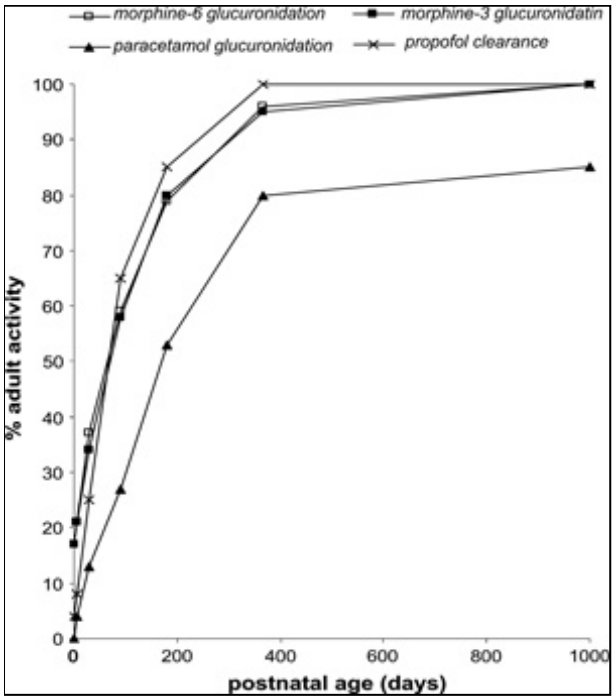
iv. Lower overall body fat in neonates compared to adults may also affect drug therapy

v. Drugs distributed in breast milk can also lead to accidental neonatal exposure
1. Most drugs do pass into breast milk, but often not in sufficient concentrations to be harmful/toxic to nursing infants.
2. However, some medications can reach concentrations that can result in pharmacological effects in infants. This is particularly true of small, lipid soluble medications, many of which are used for neurologic and psychiatric conditions (e.g. meds for anxiety, depression, bipolar disorder, seizures, opioids, etc.)

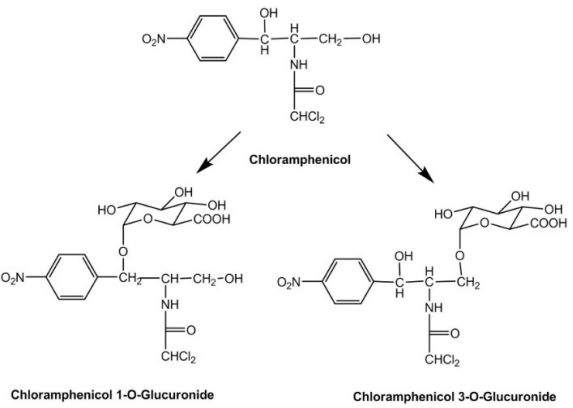
c. <u>Metabolism</u>

i. Drug metabolism varies considerably with age and is generally much slower in neonates and infants compared to children and older adults
1. Most drugs, e.g. phenytoin and barbiturates (used to treat seizures), some analgesics and digoxin have plasma half-lives 2-3X longer in neonates than adults

2. Drug metabolizing enzyme activities (e.g. many Phase I P450 enzymes and Phase II drug conjugating enzymes such as UGT1A) in neonates and infants vary greatly by substrate but are often ~50% lower than adults.
    a. Many enzymes reach near-adult levels within the first year



Age-dependent increase in glucuronidation activity compared with an adult level (100%) of activity. (Allegaert et al., *Therapeutic Drug Monitoring*. 31(4):411-415, August 2009.)



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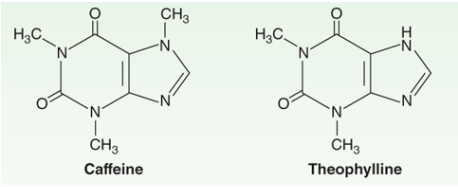
    b. This phenomenon of age-dependent expression of drug metabolizing enzymes underlies the cause of chloramphenicol-induced "grey baby syndrome" (fatal circulatory collapse) because of decreased metabolism of chloramphenicol by glucuronyltransferases (UGT)
        a. Instead of glucuronidating chloramphenicol and inactivating it, an alternative sulfation pathway forms a toxic, sulfated form of chloramphenicol
    c. **Bilirubin is also eliminated by glucuronide conjugation by UGT1A1; if bilirubin is displaced from plasma proteins by drugs such as sulfonamides or ceftriaxone in neonates, it cannot be efficiently metabolized because UGT1A1 expression is still low.** Significantly elevated bilirubin levels combined with a blood-brain barrier that is not fully intact in neonates can lead to **kernicterus**, which is essentially severe brain damage caused by hyperbilirubinemia. It is characterized by jaundice, lethargy, drowsiness, poor eating habits and fever as well as spasticity and opisthotonos. Kernicterus can cause cerebral palsy, intellectual disabilities and hearing and vision loss.

ii. Theophylline vs caffeine in apnea of prematurity (also BPD?)
    1. In the past, theophylline was commonly used to treat apnea of prematurity by stimulating respiration and increasing bronchodilation
        a. MOA: adenosine A1 and A2a receptor antagonist, indirect adrenergic agonist, inhibits cAMP phosphodiesterase
    2. However, it has a very narrow therapeutic window and is associated with toxicities (seizures, tachyarrhythmias); it must be dosed very carefully in neonates and levels need to be monitored
    3. In premature infants, theophylline is almost exclusively eliminated through renal excretion. Expression of enzymes that metabolize theophylline are developmentally regulated and increase with age. **Thus, decreased kidney function in neonates (see II. d., "Elimination and Excretion," below) combined with poor metabolism of theophylline can result in theophylline toxicity.**
    4. Caffeine, which is related to theophylline, is actually much safer to use than theophylline and has a much wider therapeutic window
        i. However, caffeine has a very long half-life in neonates due to delayed expression of CYP1A2, which demethylates and metabolizes caffeine
        ii. Caffeine is much safer than theophylline and adverse effects less likely than theophylline (tachycardia, seizures)
        iii. Long half-life of caffeine in neonates results in less frequent dosing



iii. **However, children may have higher basal metabolic rates, particularly <u>between the age of 1-2 years, and drug metabolism can actually be faster than adults</u>**, which then decreases over time to adult levels.
    1. Thus, in administering drugs that are metabolized by the liver to toddlers, an increase in dose or a decrease in dosing interval may be needed relative to the dose predicted by body weight/surface area.

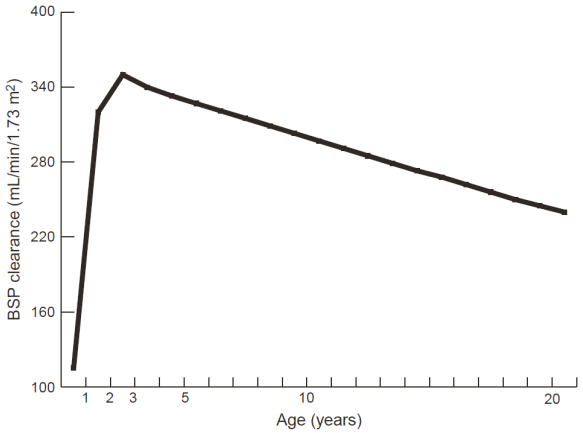


Figure 3.4. Change in hepatic clearance (expressed as mL/min/1.73 m^2) of Bromsulphalein (BSP) during childhood. (Adapted from Habersang RWO. Dosage. In: Shirkey HC, ed. *Pediatric therapy*, 6th ed. St. Louis, MO: Mosby, 1980:17–20, with permission.)

d. <u>Elimination and Excretion</u>

i. **GFR is very low in neonates and infants** – and takes several weeks and up to a year to fully develop kidney function.

Age	Mean GFR ± SD (mL/min/1.73 m²)
Preterm infants	
1–3 days	14.0 ± 5
1–7 days	18.7 ± 5.5
3–13 days	47.8 ± 10.7
1.5–4 months	67.4 ± 16.6
Term infants	
1–3 days	20.8 ± 5.0
4–14 days	36.8 ± 7.2
15–19 days	46.9 ± 12.5
1–3 months	85.3 ± 35.1
4–6 months	87.4 ± 22.3
7–12 months	96.2 ± 12.2

https://obgynkey.com/f-genito-urinary-tract/

ii. **Because of this slowed elimination/excretion, neonates (particularly premature neonates) require much lower daily doses of most drugs, which increases with age.**
   1. This is particularly true of penicillins, which are largely pumped into the renal tubule and excreted as unchanged drug.

iii. Interestingly, toddlers often have a higher GFR than adults and may require increased drug doses.

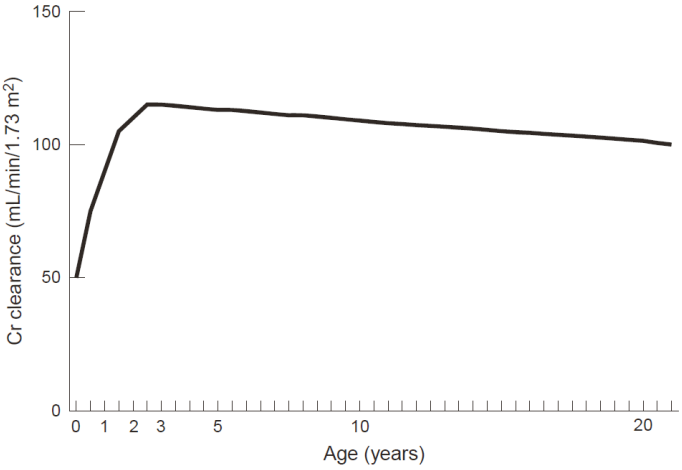


Figure 3.5. Change in endogenous creatinine (Cr) clearance during childhood. (Adapted from Habersang RWO. Dosage. In: Shirkey HC, ed. *Pediatric therapy*, 6th ed. St. Louis, MO: Mosby, 1980:17–20, with permission.)

Yaffe, S. J. (2010). Neonatal and pediatric pharmacology : Therapeutic principles in practice. Retrieved from http://ebookcentral.proquest.com

e. ADME Summary for neonates and infants:

Table 1. Developmental Factors Affecting Drug Pharmacokinetics in Neonates and Infants

Physiologic Factors	Difference Compared to Adults	PK Implications	Example Drug
Oral absorption			
Gastric pH	↑	↓ Bioavailability (weak acids)	Phenytoin, phenobarbital, ganciclovir
		↑ Bioavailability (weak bases)	Penicillin G, ampicillin, nafcillin
Gastric emptying time	↑	Delayed absorption	Phenobarbital, digoxin and sulfonamides
Intestinal CYP3A4	↓	↑ Bioavailability	Midazolam
Intestinal GST	↑	↓ Bioavailability	Busulfan
Intestinal drug transporters	↓	↓ Bioavailability	Gabapentin
Percutaneous absorption			
Hydration of epidermis	↑	↑ Bioavailability	Steroids
Intramuscular absorption			
Skeletal muscle blood flow	Variable	Unknown	n.a.
Distribution			
Body water : fat ratio	↑	↑ Volume of distribution (hydrophilic drugs)	Gentamicin, linezolid, phenobarbital, propofol
		↓ Volume of d istribution (lipophilic drugs)	Diazepam, lorazepam
Protein binding	↓	↑ Free fraction of drugs	Sulfonamides
Hepatic metabolism			
Phase I enzyme activity	↓	↓ Hepatic clearance	Theophylline, caffeine, midazolam
Phase II UGT enzyme activity	↓	↓ Hepatic clearance	Morphine
Renal excretion			
Glomerular filtration rate	↓	↓ Renal clearance	Aminoglycosides
Renal tubular absorption and secretion	↓	↓ Renal clearance	Digoxin

↑, changes increased in values; ↓, changes decreased in values; GST, glutathione S-transferase; n.a., not available; PK, pharmacokinetic; UGT, UDP glucuronosyltransferase.

from Lu & Rosenbaum, *J Pediatr Pharmacol Ther* (2014);19(4):262–276

III. Pediatric drug administration, dosage forms and adherence issues

a. Because of the pharmacokinetic differences in infants and children described above, a simple proportional reduction based on the adult dose may not always be safe in pediatric patients.

b. Calculating doses for adolescents and large children can be challenging. Most drugs have limits for a maximum single dose and a maximum daily dose, **but be careful to note if this is listed for adults or children or infants**. Make sure that the dose you prescribe is not greater than the recommended single dose or daily dose.

c. Factors to consider for weight-based dosing of oral medications:
    i. Timing of doses: twice daily dosing is more convenient than 3 or 4 doses per day
    ii. Ease of measurement: whole numbers (e.g. 5 mL rather than 2.5 mL) may facilitate more accurate dosing
    iii. Volume per dose: smaller volumes may be better tolerated by some children, particularly for medications with a strong or unpleasant taste; **however**, smaller volumes are more prone to inaccurate dosing

d. Many drugs do not have reliable pediatric dosing information (sadly, manufacturers may not feel there is a large enough financial incentive to develop specific dosing guidelines)

e. That being said, most drugs do have recommended pediatric doses, typically listed as mg/kg.
    i. However, this assumes a linear relationship between weight and dose, which is not always accurate.

f. Another method for dose adjustment for pediatric pts is based on age, in which pts are divided into subcategories, e.g. preterm newborns, term newborns, infants, toddlers, children and adolescents.
    i. However, this does not take into account the changes due to developmental growth within each age group
        1. For example, dramatic changes in metabolism may occur between 1 and 6 months of age, but few if any changes exist between adolescents and adults

g. However, calculations of drug dosage based on age and/or weight are somewhat conservative and tend to underestimate the required dose. Doses based on surface area are more likely to be adequate and more accurate. (However, there are still caveats, as this assumes that metabolic processes are constant when expressed as a function of BSA.)

TABLE 59–6

Determination of drug dosage from surface area.[1]

Weight		Approximate Age	Surface Area (m^2)	Percent of Adult Dose
(kg)	(lb)			
3	6.6	Newborn	0.2	12
6	13.2	3 months	0.3	18
10	22	1 year	0.45	28
20	44	5.5 years	0.8	48
30	66	9 years	1	60
40	88	12 years	1.3	78
50	110	14 years	1.5	90
60	132	Adult	1.7	102
70	154	Adult	1.76	103

[1] For example, if adult dose is 1 mg/kg, dose for 3-month-old infant would be 0.18 mg/kg or 1.1 mg total.

h. Nonlinear relationships may be a more reliable way to establish how a dose relates to body weight, particularly those that scale dosing based on physiologic function in children; however, many of these scaling functions are not yet being adopted and are beyond the scope of this session.
i. Medication errors in pediatric cases commonly stem from the multiple calculations required for dose adjustments in younger patients. This is a particular risk in cases where drugs are only available in adult doses and must be prepared and compounded and labeled.
j. Wrong dose, wrong technique and wrong drug (!) are the three most common medication errors.

IV. Adverse Drug Reactions (ADRs) in Pediatric Patients

a. Many of the risk factors for ADRs relate to the ADME and dosage issues addressed above:

i. Greater pharmacokinetic variability in pediatric pts

1. Absorption: ↑ gastric pH, delayed gastric emptying
2. Distribution: ↑ total body water, decreased plasma protein binding
3. Metabolism: ↓ phase I & II enzyme activity in neonates; Δ's w/ age
4. Excretion: ↓ GFR & tubular secretion in neonates; ↑ w/ age

ii. Dependence on individualized dosage calculations based on age, body weight/surface area, organ function, underlying/comorbid dz

iii. Lack of ped-specific dosing forms – many peds pts cannot or will not take oral tablets, so meds often have to be compounded to oral solutions/suspensions

iv. Smaller doses (volumes) = increased risk for dosing errors

v. Most meds for peds pts do not have FDA-approved labeling

vi. Many pediatric pts cannot effectively communicate ADRs

b. Toxicities to look out for in pediatrics

i. Anticholinergic toxidromes: "big, hot, dry, fast"; seizures

1. This is not restricted to strict muscarinic antagonists like atropine or oxybutynin, but perhaps more common in meds that have anticholinergic properties – think diphenhydramine, tricyclic antidepressants (e.g. amitriptyline), cyclobenzaprine (Flexiril), antipsychotics (e.g. chlorpromazine).

ii. Cholinergic toxidromes: SLUGDE – think organophosphates (e.g., malathion)

iii. Sedative-hypnotics: sedation, apnea, bradycardia – benzodiazepines (e.g. alprazolam, diazepam, clonazepam)

iv. Sympathomimetics – tachycardia, diaphoresis, mydriasis, agitation/seizures

v. Opioids – respiratory depression, sedation, miosis, bradycardia

vi. Diabetes meds – hypoglycemia, AMS

TABLE Close

Drugs Manifesting Unusual Toxicity in Children

Drug	Clinical Syndrome	Mechanism	Comments
Anesthetics, topical (eg, benzocaine, mixture of lidocaine and prilocaine)	Cyanosis	Formation of methemoglobin (ferrous iron oxidized to ferric iron)	Incidence rare
Ceftriaxone	Jaundice Kernicterus	Bilirubin displaced from albumin	Affects only neonates
Codeine*	Respiratory depression Death	Ultrarapid metabolization of codeine to morphine	Genetic variant Deaths have occurred after surgery and in a breastfed infant whose mother took codeine
Diphenoxylate	Respiratory depression Death	CNS depression (in immature CNS)	Overdose syndrome, usually in children 2 yr
Fluoroquinolones	Cartilage toxicity	Unknown	Suspected based on animal studies, but adverse effects in humans unproved—short-term use may be safe
Lindane (topical)	Seizures CNS toxicity	Probably enhanced absorption in children	Should not be used in children 50 kg (alternative should be used)
Prochlorperazine	Altered CNS function Extrapyramidal effects Opisthotonus Bulging fontanelles	Actions via multiple CNS receptors	Febrile and dehydrated infants especially at risk
SSRIs	Suicidal ideation	Unknown	Increased incidence of suicidal ideation in children and adolescents
Tetracycline	Discoloration and pitting of tooth enamel	Chelation with calcium in growing teeth	Not given to children 8 yr

*See also the American Academy of Pediatrics' clinical report about codeine metabolism in children.

https://www.merckmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/overview-of-drug-treatment-in-children#v1085119

V. Trends in Prescription Medication Use in Pediatrics
   a. A recent (2018) study in JAMA indicated that overall use of prescription medications has declined slightly
   b. Among the most commonly prescribed medications for each age group (tables below):
      i. 0 to 23 months
         1. Antibiotics
         2. Asthma medications
         3. Topical agents (dermatological; topical steroids)
      ii. 2 to 5 years
         1. Antibiotics
         2. Asthma medications
         3. Topical agents (dermatological; nasal steroids)
         4. Antihistamines
      iii. 6 to 11 years
         1. ADHD medications
         2. Topical agents (dermatological; nasal steroids
         3. Antihistamines
         4. Antibiotics
   c. There has been a substantial decrease (~50%) in the use of antibiotics in children and adolescents. Largest decrease was in amoxicillin and cephalosporins.
   d. Use of prescription antihistamines has also significantly declined; studies have documented overuse of antihistamines in children with viral URIs that may explain why.
   e. Use of medications for asthma, attention-deficit/hyperactivity disorder (ADHD), and contraception have actually increased.
   f. Medications your peds clerkship directors think you should be more familiar with:
      i. ADHD meds – covered by FPC this block and will be revisited in Block 12 (Dr. Blumer)
      ii. Asthma meds – covered in Block 4
      iii. Seizure meds – will be covered in Block 12 (Dr. Blumer, Dr. Schmitt)
      iv. Topical meds, e.g. corticosteroids (see Section II. a. Absorption, page 3)
   g. Medications routinely administered to newborns:
      i. Intramuscular Vitamin K, to prevent hemorrhagic disease of the newborn (also referred to as Vitamin K deficiency bleeding)
      ii. Topical erythromycin (or tetracycline) to prevent gonococcal conjunctivitis (https://www.cdc.gov/conjunctivitis/newborns.html)
         1. Although ophthalmia neonatorum caused by N. gonorrhoeae is fairly uncommon, it can result in perforation of the globe of the eye and blindness; topical prophylaxis with erythromycin (or tetracycline) is standard.
         2. Chlamydial conjunctivitis is more common but would occur 1-2 weeks after birth and neonatal prophylaxis is not very effective.
      iii. Hepatitis B vaccine

V. Trends in Prescription Medication use in peds pts

Table 4. Trends in Prevalence of Prescription Medication Use in the Prior 30 Days Among Children Aged 0 to 23 Months, by Therapeutic Class: United States, 1999-2014[a]

Therapeutic Class	Prevalence, % (95% CI) 1999-2002 (n = 1646)	2003-2006 (n = 1699)	2007-2010 (n = 1539)	2011-2014 (n = 1288)	β (95% CI)[b]	*P* Value for Trend[b]
Antibiotics	15.5 (12.6 to 18.7)	10.9 (8.8 to 13.1)	11.7 (9.3 to 14.5)	7.6 (6.2 to 9.1)	−1.12 (−1.62 to −0.61)	<.001
Amoxicillin	8.9 (7.0 to 11.2)	5.7 (4.3 to 7.5)	6.6 (4.9 to 8.6)	4.9 (3.8 to 6.2)	−0.52 (−0.87 to −0.18)	.004
Amoxicillin/clavulanate	2.1 (1.3 to 3.1)	1.6 (0.7 to 3.1)[c]	0.7 (0.3 to 1.5)[c]	0.4 (0.0 to 1.6)[d,e]	−0.26 (−0.40 to −0.11)	<.001
Cephalosporins	2.6 (1.6 to 4.2)	2.4 (1.3 to 3.9)	2.4 (1.1 to 4.5)[c]	1.7 (0.8 to 3.1)	−0.15 (−0.41 to 0.11)	.27
Macrolides	1.7 (1.0 to 2.8)	1.6 (0.8 to 2.8)	1.7 (0.9 to 2.8)	0.9 (0.3 to 2.1)[f]	−0.13 (−0.31 to 0.05)	.16
Azithromycin	1.5 (0.8 to 2.5)	1.4 (0.7 to 2.6)	1.4 (0.7 to 2.6)	0.8 (0.2 to 2.1)[f]	−0.10 (−0.27 to 0.08)	.27
Antihistamines	1.6 (0.7 to 2.9)[c]	1.6 (0.9 to 2.5)	1.4 (0.8 to 2.4)	0.7 (0.3 to 1.3)[c]	−0.09 (−0.23 to 0.05)	.20
Asthma medications	4.1 (3.1 to 5.3)	4.5 (3.3 to 5.9)	5.1 (4.0 to 6.3)	2.8 (2.0 to 3.8)	−0.16 (−0.36 to 0.04)	.12
Bronchodilators	3.6 (2.7 to 4.8)	3.9 (2.7 to 5.4)	3.8 (2.6 to 5.4)	2.5 (1.7 to 3.5)	−0.18 (−0.38 to 0.02)	.09
Albuterol	2.8 (2.0 to 3.9)	3.8 (2.7 to 5.2)	3.1 (2.2 to 4.3)	2.3 (1.5 to 3.2)	−0.12 (−0.29 to 0.06)	.19
Inhaled corticosteroids	1.0 (0.4 to 1.8)[c]	1.8 (1.0 to 2.8)	1.8 (1.1 to 2.8)	0.6 (0.3 to 1.3)	−0.02 (−0.14 to 0.11)	.79
Glucocorticoids	1.6 (0.9 to 2.7)	2.2 (1.3 to 3.5)	2.2 (1.3 to 3.3)	1.1 (0.5 to 2.3)[c]	−0.05 (−0.23 to 0.13)	.56
H_2 antagonists	1.1 (0.5 to 2.1)[c]	1.3 (0.7 to 2.0)	1.9 (1.1 to 2.9)	2.1 (1.3 to 3.3)	0.18 (0.00 to 0.36)	.06
Topical agents	3.7 (2.6 to 5.1)	3.5 (2.4 to 5.0)	4.2 (2.7 to 6.0)	3.1 (2.0 to 4.5)	−0.03 (−0.27 to 0.21)	.78
Dermatological agents	1.3 (0.6 to 2.2)	1.6 (0.8 to 2.7)	1.6 (0.8 to 2.8)	1.0 (0.5 to 1.7)	−0.02 (−0.17 to 0.14)	.83
Topical steroids	0.8 (0.3 to 1.6)[c]	1.1 (0.5 to 2.1)[c]	0.8 (0.4 to 1.6)[c]	0.5 (0.2 to 1.1)[c,e]	−0.04 (−0.17 to 0.08)	.50
Upper respiratory combination medications	4.3 (2.6 to 6.7)	3.2 (2.0 to 4.8)	2.1 (1.2 to 3.5)	1.1 (0.5 to 2.1)[c]	−0.53 (−0.79 to −0.27)	<.001

Table 5. Trends in Prevalence of Prescription Medication Use in the Prior 30 Days Among Children Aged 2 to 5 Years, by Therapeutic Class: United States, 1999-2014[a]

Therapeutic Class	Prevalence, % (95% CI) 1999-2002 (n = 1807)	2003-2006 (n = 1977)	2007-2010 (n = 1898)	2011-2014 (n = 1910)	β (95% CI)[b]	*P* Value for Trend[b]
Antibiotics	9.1 (7.0 to 11.5)	7.3 (5.0 to 10.1)	7.1 (5.2 to 9.5)	5.9 (3.7 to 8.9)	−0.43 (−0.88 to 0.02)	.07
Amoxicillin	5.0 (3.4 to 7.0)	2.9 (1.7 to 4.7)	4.1 (2.9 to 5.6)	4.0 (1.8 to 7.6)[c]	−0.06 (−0.46 to 0.34)	.77
Cephalosporins	0.9 (0.4 to 1.9)[c]	1.8 (0.8 to 3.3)[c]	1.0 (0.5 to 1.8)[c]	0.8 (0.3 to 1.6)[c]	−0.07 (−0.20 to 0.07)	.34
Macrolides	1.4 (0.7 to 2.5)	1.0 (0.5 to 1.8)	0.6 (0.3 to 1.2)[c]	0.9 (0.2 to 2.4)[d]	−0.10 (−0.26 to 0.06)	.23
Azithromycin	1.1 (0.5 to 2.1)[c]	0.8 (0.3 to 1.7)[c]	0.6 (0.3 to 1.2)[c]	0.9 (0.2 to 2.4)[d]	−0.04 (−0.19 to 0.11)	.60
Antihistamines	3.1 (2.0 to 4.6)	3.8 (2.3 to 5.9)	1.1 (0.7 to 1.7)	2.3 (1.4 to 3.6)	−0.25 (−0.49 to −0.01)	.04
Asthma medications	4.5 (3.2 to 6.1)	6.5 (5.1 to 8.1)	6.9 (5.3 to 8.8)	5.4 (4.1 to 6.9)	0.09 (−0.20 to 0.39)	.54
Bronchodilators	3.6 (2.5 to 5.1)	4.7 (3.6 to 6.1)	5.2 (4.1 to 6.5)	3.8 (2.8 to 5.0)	0.03 (−0.22 to 0.27)	.84
Albuterol	3.2 (2.2 to 4.4)	3.8 (2.7 to 5.0)	4.6 (3.6 to 5.7)	3.5 (2.5 to 4.7)	0.05 (−0.18 to 0.28)	.66
Inhaled corticosteroids	1.2 (0.5 to 2.3)[c]	2.0 (1.1 to 3.2)	2.7 (1.8 to 3.8)	2.1 (1.2 to 3.4)	0.20 (0.02 to 0.39)	.03
Montelukast	0.8 (0.4 to 1.6)[c]	2.0 (1.2 to 3.0)	2.4 (1.4 to 3.8)	1.2 (0.7 to 2.0)	0.04 (−0.09 to 0.17)	.55
Glucocorticoids	1.1 (0.6 to 1.9)	1.4 (0.8 to 2.3)	2.5 (1.8 to 3.4)	1.3 (0.6 to 2.4)	0.06 (−0.09 to 0.21)	.44
Topical agents	2.8 (1.9 to 3.9)	3.2 (2.1 to 4.5)	3.0 (1.9 to 4.4)	2.5 (1.4 to 4.2)	−0.05 (−0.27 to 0.17)	.64
Dermatological agents	0.6 (0.2 to 1.1)[c]	1.2 (0.6 to 2.1)	1.3 (0.8 to 2.1)	0.7 (0.3 to 1.2)	0.02 (−0.07 to 0.11)	.61
Nasal steroids	1.0 (0.5 to 2.0)[c]	1.6 (0.8 to 2.7)	0.4 (0.1 to 1.0)[e]	1.1 (0.5 to 2.0)[c]	−0.04 (−0.17 to 0.09)	.52
Upper respiratory combination medications	2.5 (1.5 to 3.9)	3.1 (2.0 to 4.5)	1.6 (1.0 to 2.4)	0.4 (0.1 to 0.8)[c,f]	−0.39 (−0.54 to −0.23)	<.001

from Hales et al., *JAMA*. 2018;319(19):2009-2020.

Table 6. Trends in Prevalence of Prescription Medication Use in the Prior 30 Days Among Children Aged 6 to 11 Years, by Therapeutic Class: United States, 1999-2014[a]

Therapeutic Class	Prevalence, % (95% CI) 1999-2002 (n = 2353)	2003-2006 (n = 2178)	2007-2010 (n = 2519)	2011-2014 (n = 2698)	β (95% CI)[b]	*P* Value for Trend[b]
ADHD medications	4.8 (3.7 to 5.9)	4.6 (3.4 to 6.0)	6.0 (4.9 to 7.3)	6.2 (4.8 to 7.8)	0.32 (0.04 to 0.59)	.03
Antiadrenergic agents (centrally acting)	1.1 (0.5 to 2.0)[c]	0.8 (0.4 to 1.3)	0.6 (0.2 to 1.4)[d]	1.6 (0.9 to 2.6)	0.11 (−0.03 to 0.24)	.14
CNS stimulants	4.3 (3.4 to 5.5)	3.6 (2.6 to 4.9)	5.3 (4.3 to 6.5)	5.3 (4.0 to 7.0)	0.25 (−0.03 to 0.52)	.08
Amphetamines	1.3 (0.7 to 2.3)	1.2 (0.6 to 2.2)	2.8 (2.0 to 4.0)	2.1 (1.5 to 2.7)	0.21 (0.07 to 0.35)	.005
Methylphenidate or dexmethylphenidate	3.0 (2.0 to 4.3)	2.4 (1.4 to 3.7)	2.5 (1.6 to 3.6)	3.3 (2.2 to 4.9)	0.05 (−0.22 to 0.31)	.73
SNRI (atomoxetine)	NA[e]	0.8 (0.5 to 1.3)	0.8 (0.3 to 1.4)[c]	0.6 (0.2 to 1.3)[d]	NA[e]	NA[e]
Antibiotics	6.1 (4.1 to 8.6)	5.8 (4.1 to 7.9)	4.8 (3.5 to 6.3)	2.7 (1.8 to 4.0)	−0.52 (−0.91 to −0.14)	.009
Amoxicillin	3.7 (2.6 to 5.0)	2.5 (1.5 to 3.9)	2.5 (1.7 to 3.4)	1.0 (0.6 to 1.5)	−0.39 (−0.58 to −0.19)	<.001
Cephalosporins	0.7 (0.3 to 1.5)[c]	1.2 (0.5 to 2.3)[c]	1.1 (0.6 to 1.8)	0.4 (0.1 to 1.1)[f,g]	−0.04 (−0.14 to 0.06)	.41
Macrolides	0.7 (0.3 to 1.6)[c]	0.6 (0.2 to 1.5)[d,g]	0.7 (0.3 to 1.3)[c]	0.8 (0.3 to 1.5)[c]	0.04 (−0.08 to 0.15)	.56
Azithromycin	0.5 (0.1 to 1.5)[f,g]	0.4 (0.1 to 1.1)[f,g]	0.6 (0.3 to 1.2)[c]	0.7 (0.3 to 1.4)[c]	0.07 (−0.04 to 0.18)	.21
Anticonvulsants	0.2 (0.1 to 0.6)[d,g]	0.8 (0.3 to 1.6)[c]	0.6 (0.3 to 1.2)[c]	0.8 (0.3 to 1.5)[c]	0.06 (−0.02 to 0.15)	.16
Antidepressants	1.5 (0.8 to 2.4)	0.6 (0.2 to 1.4)[c,g]	0.9 (0.4 to 1.6)	0.5 (0.2 to 1.2)[c]	−0.12 (−0.26 to 0.02)	.10
SSRIs	0.8 (0.4 to 1.4)	0.4 (0.1 to 1.0)[f,g]	0.5 (0.2 to 0.9)[c]	0.4 (0.2 to 0.9)[c,g]	−0.04 (−0.14 to 0.05)	.33
Antihistamines	4.8 (3.5 to 6.5)	3.3 (2.4 to 4.5)	2.6 (1.8 to 3.7)	3.0 (2.1 to 4.1)	−0.27 (−0.51 to −0.02)	.04
Antipsychotics	0.5 (0.2 to 1.1)[d,g]	0.4 (0.2 to 0.8)[c]	0.9 (0.4 to 1.7)[c]	1.2 (0.8 to 1.7)	0.13 (0.04 to 0.22)	.006
Anxiolytics, sedatives, and hypnotics	0.5 (0.2 to 1.1)[c]	0.4 (0.2 to 0.9)[c]	0.5 (0.3 to 1.0)[c]	0.6 (0.3 to 1.2)[c]	0.02 (−0.07 to 0.11)	.69
Asthma medications	4.6 (3.2 to 6.4)	6.5 (5.0 to 8.2)	8.2 (6.6 to 10.1)	7.6 (6.4 to 9.0)	0.50 (0.16 to 0.83)	.004
Bronchodilators	4.2 (2.8 to 6.0)	5.1 (3.7 to 6.7)	6.0 (4.9 to 7.3)	4.8 (3.9 to 5.7)	0.11 (−0.19 to 0.41)	.47
Albuterol	4.1 (2.7 to 5.9)	4.3 (3.4 to 5.5)	5.1 (4.1 to 6.2)	4.0 (3.3 to 4.9)	0.01 (−0.28 to 0.30)	.95
Inhaled corticosteroids	0.9 (0.4 to 1.7)[c]	1.0 (0.6 to 1.6)	2.2 (1.6 to 3.0)	2.4 (1.7 to 3.3)	0.30 (0.16 to 0.44)	<.001
Montelukast	0.7 (0.3 to 1.4)[c]	2.7 (1.5 to 4.2)	3.8 (2.5 to 5.5)	3.0 (2.1 to 4.0)	0.38 (0.23 to 0.53)	<.001
Glucocorticoids	0.6 (0.3 to 1.0)	1.5 (1.0 to 2.1)	1.4 (0.9 to 2.0)	0.8 (0.5 to 1.3)	0.02 (−0.07 to 0.11)	.70
Proton pump inhibitors	0.1 (0.0 to 0.6)[f,g]	0.4 (0.1 to 0.9)[d,g]	0.9 (0.4 to 1.6)	0.7 (0.2 to 1.5)[d]	0.10 (0.02 to 0.19)	.02
Topical agents	2.6 (1.7 to 3.6)	4.2 (3.0 to 5.7)	3.3 (2.4 to 4.4)	3.7 (2.8 to 4.9)	0.15 (−0.05 to 0.36)	.14
Dermatological agents	0.5 (0.2 to 1.0)[c]	0.8 (0.3 to 1.8)[c]	0.7 (0.4 to 1.3)	1.2 (0.8 to 1.7)	0.11 (0.03 to 0.20)	.009
Nasal steroids	1.5 (0.7 to 2.7)[c]	2.7 (1.8 to 4.0)	1.9 (1.4 to 2.5)	2.0 (1.3 to 2.9)	0.06 (−0.13 to 0.25)	.55
Mometasone nasal	0.2 (0.0 to 0.6)[f,g]	1.2 (0.6 to 2.1)	0.6 (0.3 to 1.1)	0.8 (0.4 to 1.5)[c]	0.07 (−0.03 to 0.17)	.16
Upper respiratory combination medications	1.8 (1.0 to 3.0)	1.8 (1.0 to 2.9)	1.2 (0.6 to 2.0)	0.6 (0.2 to 1.5)[d]	−0.21 (−0.36 to −0.06)	.007

from Hales et al., *JAMA*. 2018;319(19):2009-2020.

VI. Absolute Facts

a. There is great pharmacokinetic variability in pediatric pts
    i. Absorption: ↑ gastric pH, delayed gastric emptying, ↓ muscle mass, ↑ percutaneous absorption of topically applied drugs particularly in neonates
    ii. Distribution: ↑ total body water, ↓ plasma protein binding, drug distribution into breast milk, particularly in neonates
        1. ↑ Vd of water-soluble drugs; ↑ doses of water-soluble drugs required
        2. Some drugs can affect bilirubin binding to plasma proteins and vice-versa
    iii. Metabolism: ↓ phase I & II enzyme activity in neonates; ↑ at 1-2 years of age; normalizes over time to adult levels
    iv. Excretion: ↓ GFR & tubular secretion in neonates; normalizes to adult levels over time

b. While drug doses for pediatric patients are often expressed as mg/kg, they are more likely to be adequate if calculated based on surface area
    i. Calculation errors for dose adjustments are a common cause of medication errors

c. Risk factors for adverse drug reactions in pediatric pts are commonly related to:
    i. ADME
    ii. Manifold dosage calculation issues
    iii. Lack of drugs with specific FDA-approved drug labels
    iv. Inability of many peds pts to self-report ADRs