كليّة الصيدلة – جامعة بغداد
وحدة التعليم المستمرّ

SAFE AND EFFECTIVE MEDICATION USE IN CHILDREN

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INTRODUCTION

Providing care for children can be one of the most challenging, but rewarding, aspects of pharmacy practice.

Patients range in age from premature neonates to adolescents and can vary in weight by 300-fold, from a 0.5-kg premature neonate to a 150-kg 16-year-old.

INTRODUCTION

60% of all prescriptions written by pediatricians are for “off-label” uses.

Health care providers caring for children must be capable of assessing the appropriateness of drug doses for this diverse population and providing recommendations for dosage adjustments and patient monitoring with limited resources.

GROWTH & DEVELOPMENT

As an example: The appropriate analgesic for a 4-month-old infant who started teething is acetaminophen.

Aspirin is no longer used as an analgesic in children because of its association with Reye syndrome.

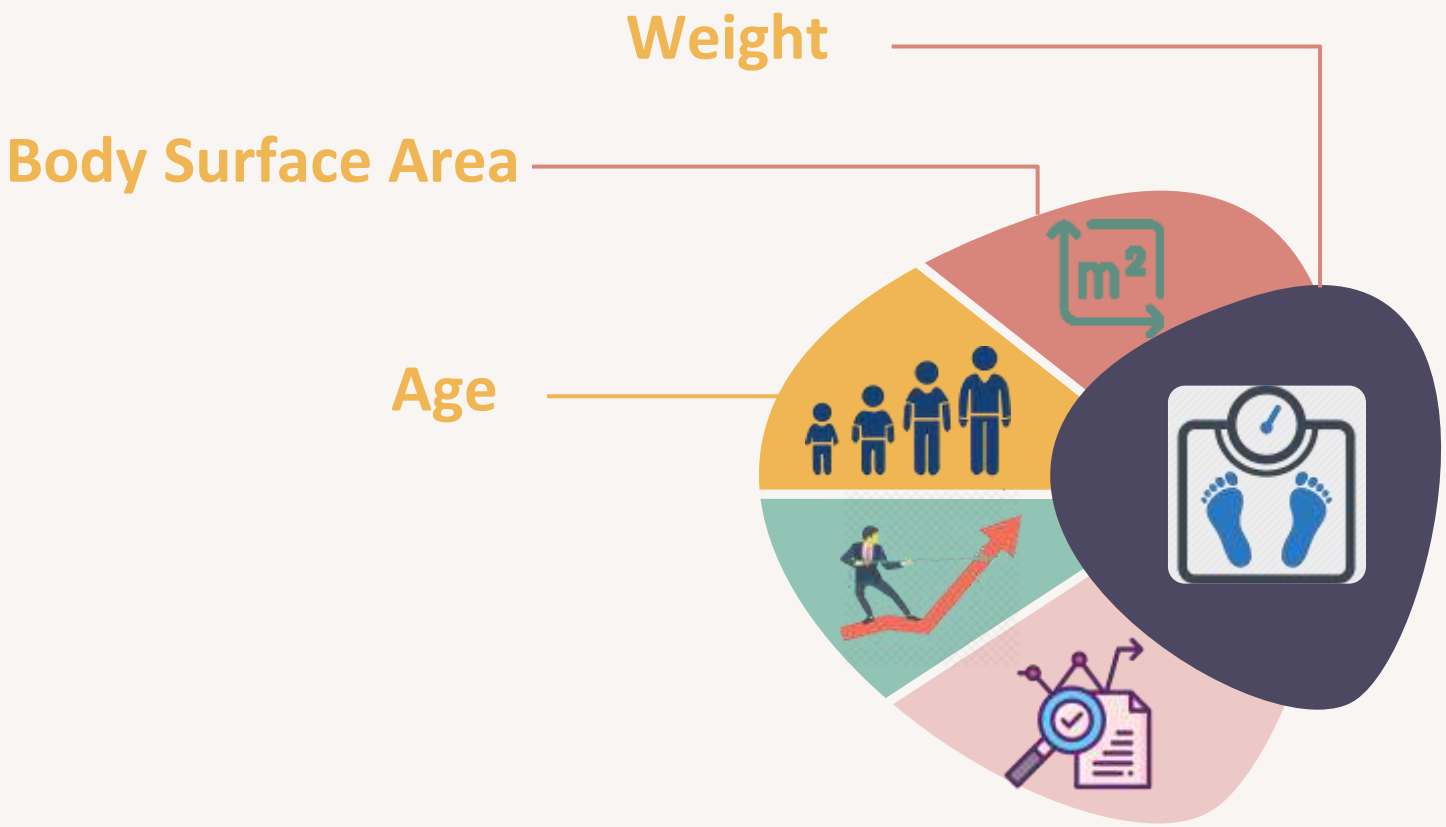
Nonsteroidal anti-inflammatory drugs, such as ibuprofen, are not recommended for use in infants younger than age 6 months because of unknown effects on the developing kidney.

INTRODUCTION

This requires knowledge of the pharmacokinetic and pharmacodynamic differences between children and adults and how these differences impact both therapeutic and adverse drug effects.

Premature	Birth before 37 completed weeks gestation
Neonate	0-4 weeks
Infant	1month-1 year
Toddler	1-3 years
Child	4-12 years
Adolescent	13-18 years
Adult	>18 years

Medication Dosing in Children



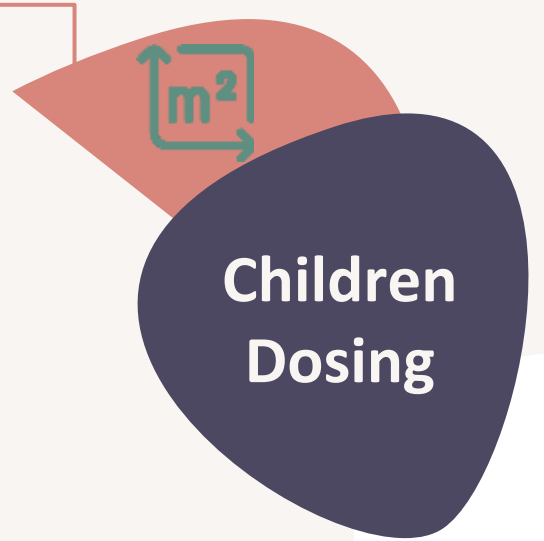
Medication Dosing in Children

Weight

- Most pediatric drug dosages are calculated using **mg/kg/day** to account for differences in **metabolism and excretion**.
- **Example: Antibiotics, analgesics, and antihypertensives** require **weight-based adjustments**.

Medication Dosing in Children

Body Surface Area



•Chemotherapeutic agents, which are dosed by body surface area, incorporating height as an additional variable.

Medication Dosing in Children

<30 WEEKS' GESTATION
0-28 days: 2.5 mg/kg/day IV/IM
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>36 WEEKS' GESTATION
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Age-Dependent Variations

- Some drugs require **modified doses** based on **postnatal and gestational age**.
- **Example: Neonatal gentamicin dosing** considers both **postconceptional and postnatal age** due to **renal immaturity**.

Preventing Medication Errors in Children

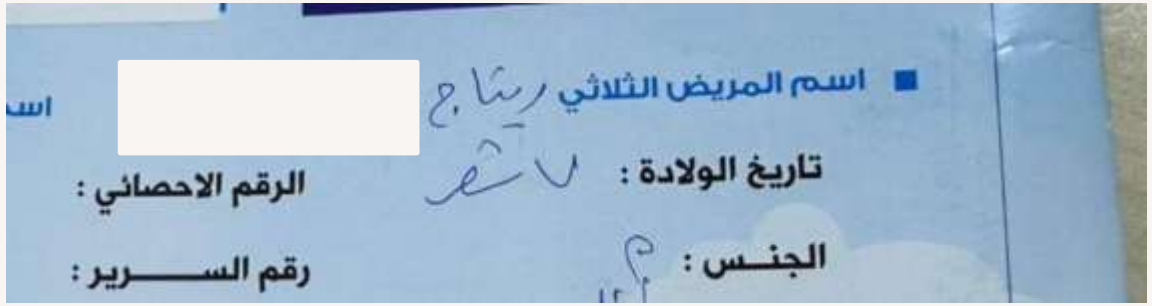
Common Causes of Pediatric Medication Errors

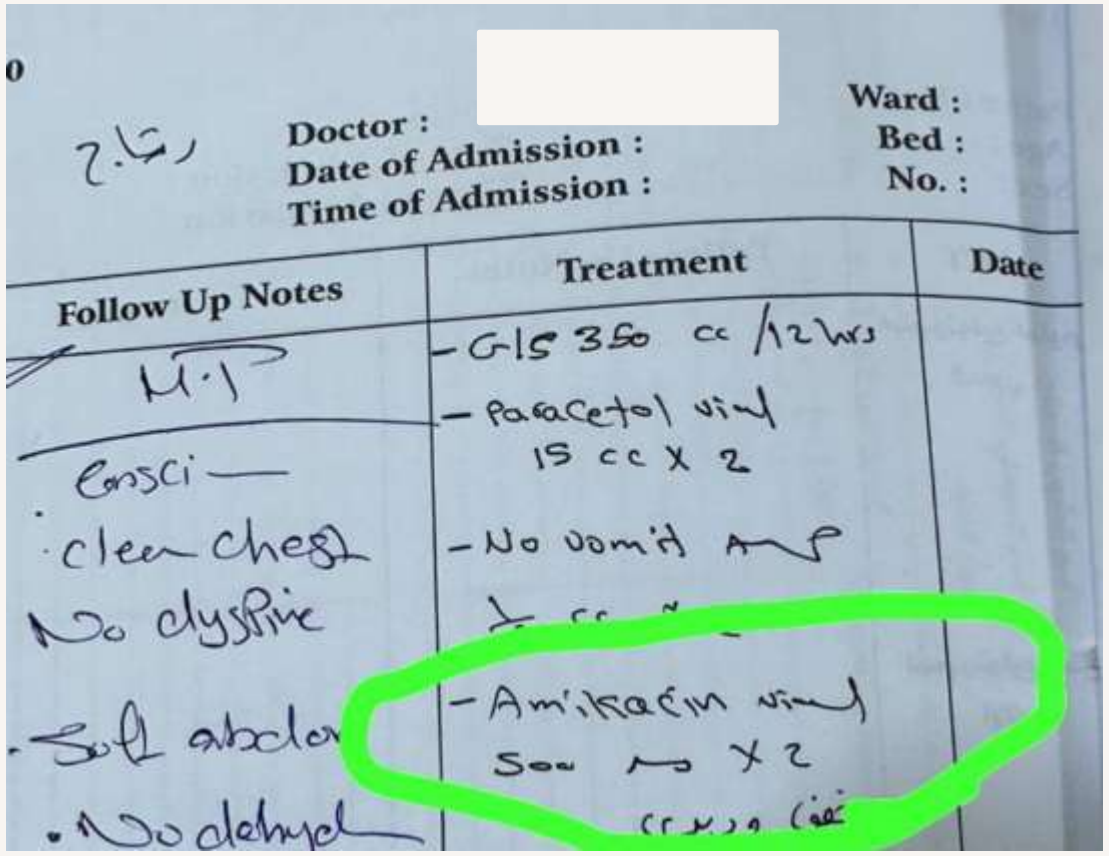
- Errors in **weight-based dosing calculations**.
- Misinterpretation of **pediatric drug formulations and concentrations**.
- **Decimal point errors** leading to **overdoses or underdoses**.

Strategies to Reduce Errors

- **Standardization** of pediatric drug concentrations and dosing guidelines.
- **Implementation of smart-pump technology**.
- **Enhanced caregiver education** on accurate dosing techniques.
- **Pharmacist review** of pediatric prescriptions to ensure safety.

Preventing Medication Errors in Children





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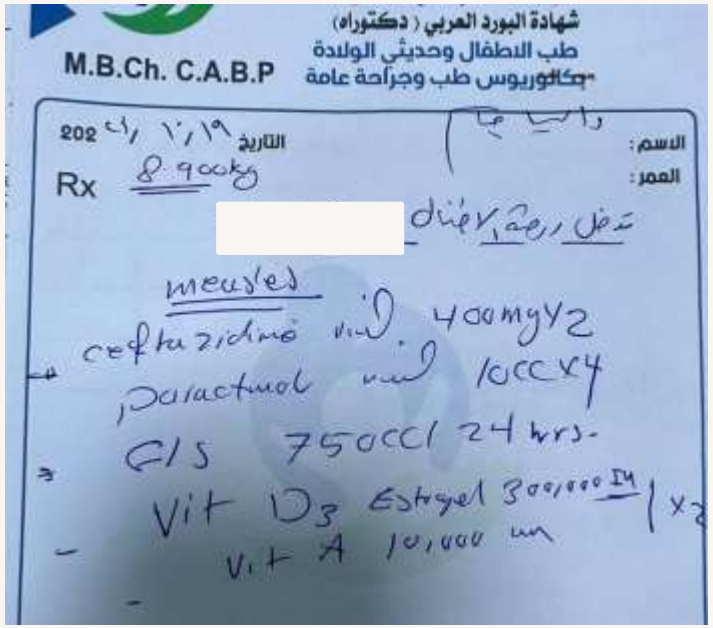

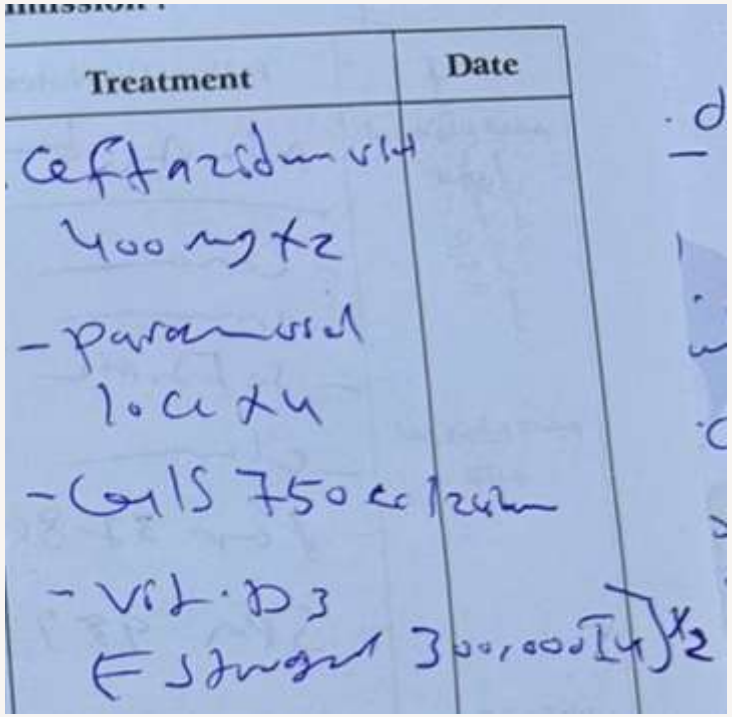

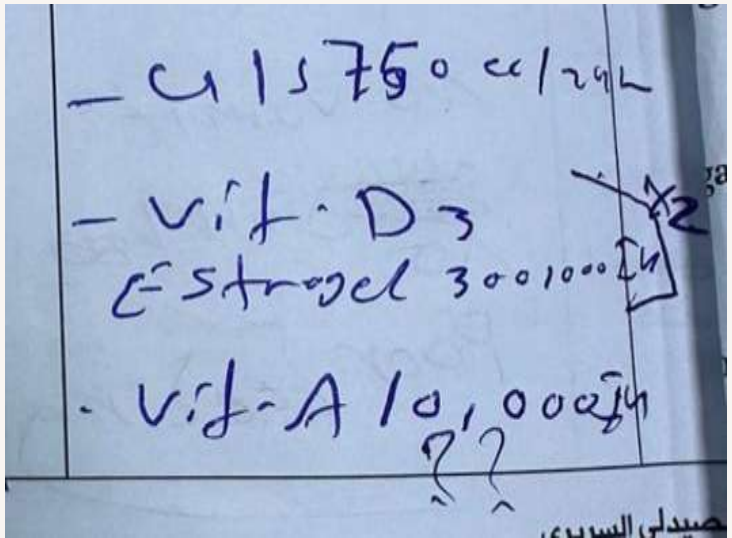

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CASE STUDY

A 3-month-old infant (5 kg) was brought to the pediatric clinic with a fever of 38.5°C (101.3°F). The physician prescribed Acetaminophen (Paracetamol) for fever management.

Correct dose: 10–15 mg/kg per dose every 4–6 hours

Total daily dose limit: 75 mg/kg/day

Intended dose: 12 mg/kg per dose → 12 mg × 5 kg = 60 mg per dose

CASE STUDY

The Error: The physician mistakenly calculated the dose as mg/kg/day instead of mg/kg/dose, leading to a prescription of 12 mg/kg/day instead of per dose.
Total daily dose prescribed: 12 mg × 5 kg = 60 mg/day
divided over 4 doses: 60 mg ÷ 4 = 15 mg per dose

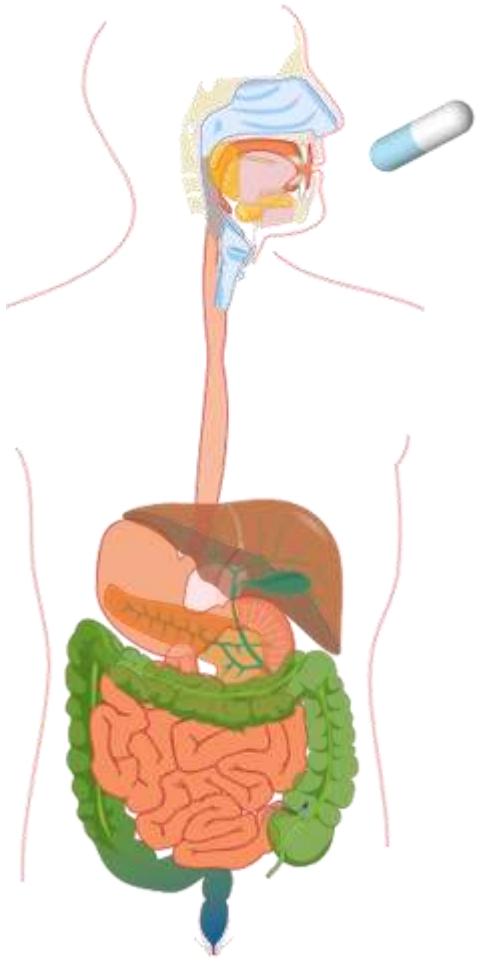
GROWTH & DEVELOPMENT

Children undergo considerable physiologic changes between birth and adulthood. Although many changes are easily observed, such as the ability to walk or the development of language, and others are less evident.

PHARMACOKINETICS

All aspects of pharmacokinetics are affected by growth and physical maturation, beginning during gestation and ending in adulthood. These changes are complex, and their timing can vary widely from patient to patient.

DRUG ABSORPTION



ORAL DRUG ABSORPTION

Enteral absorption of drugs is altered at birth and does not approximate adult patterns for several months.

Gastric acid production is decreased, giving the neonate a higher pH in the stomach.

This results in a greater absorption of acid-labile drugs such as some forms of penicillins, but reduced absorption of weakly acidic drugs such as phenobarbital.

ORAL DRUG ABSORPTION

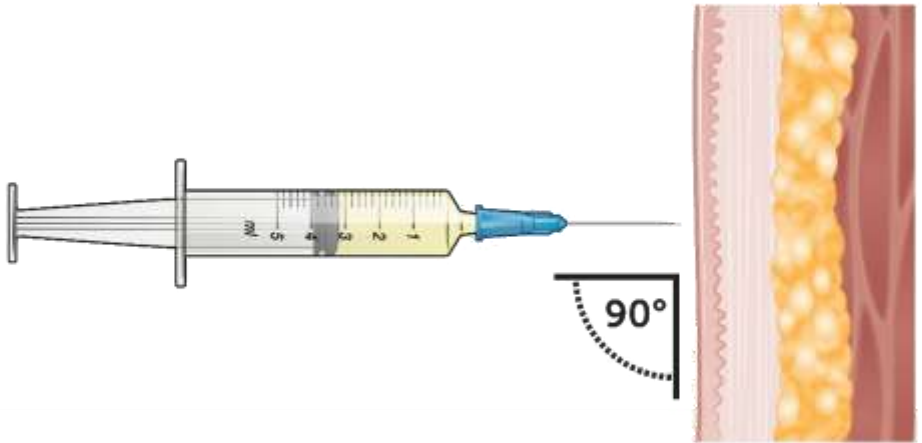
Gastric emptying time is delayed, and intestinal transit time is prolonged at birth, but both quickly increase within the first few days of life.

Premature infants have delayed development of normal gastric emptying and intestinal transit.

Adult values for gastric emptying and intestinal transit time are generally reached by age 4 to 8 months.

INTRAMUSCULAR DRUG ABSORPTION

Drug administration by IM injection typically results in a delay in time to reach peak serum concentrations in neonates. This delay is related to reduced muscle size, weaker muscle contractions, and an immature vasculature resulting in more erratic blood flow to and from the muscle



INTRAMUSCULAR DRUG ABSORPTION

The delay is considered a disadvantage when rapid absorption is needed, such as with antibiotic administration.

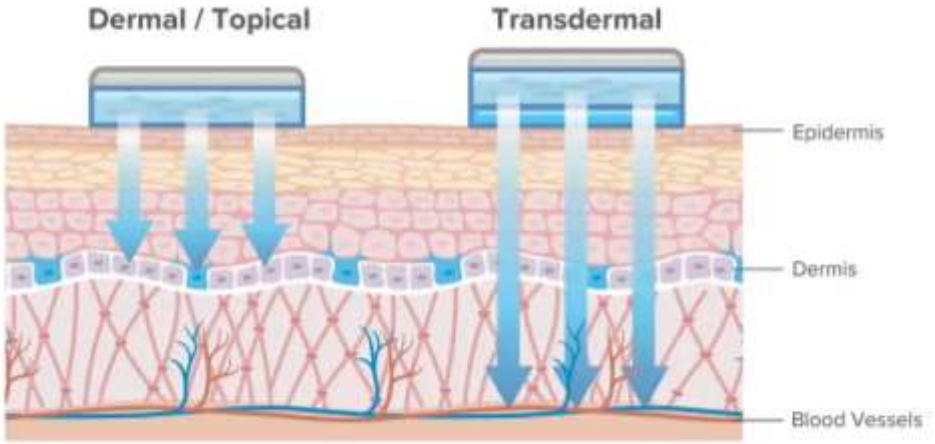
It’s considered an advantage in other cases, such as for the administration of phytonadione after birth.

The delayed absorption from muscle results in a depot-like effect, providing a slow release of the drug into the systemic circulation and ensuring prolonged effectiveness, particularly in exclusively breastfed infants who may not get enough vitamin K from milk.

TRANSDERMAL DRUG ABSORPTION

Transdermal or percutaneous administration results in greater drug absorption in neonates than it does in older children and adults.

Enhanced absorption results from a greater skin to body surface area ratio, approximately three times that of adults, as well as a thinner stratum corneum, better epidermis hydration, and greater perfusion.



TRANSDERMAL DRUG ABSORPTION

The greater degree of percutaneous absorption in infants has resulted in significant toxicity.

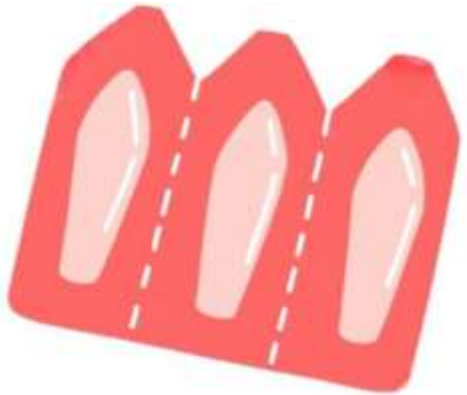
Hexachlorophene, when used routinely to bathe infants, has resulted in seizures and is now considered contraindicated in this age range.

Application of povidone–iodine as a topical disinfectant before surgery has been linked to neonatal thyroid dysfunction and, as a result, is now used only briefly in limited quantities to limit percutaneous iodine absorption.

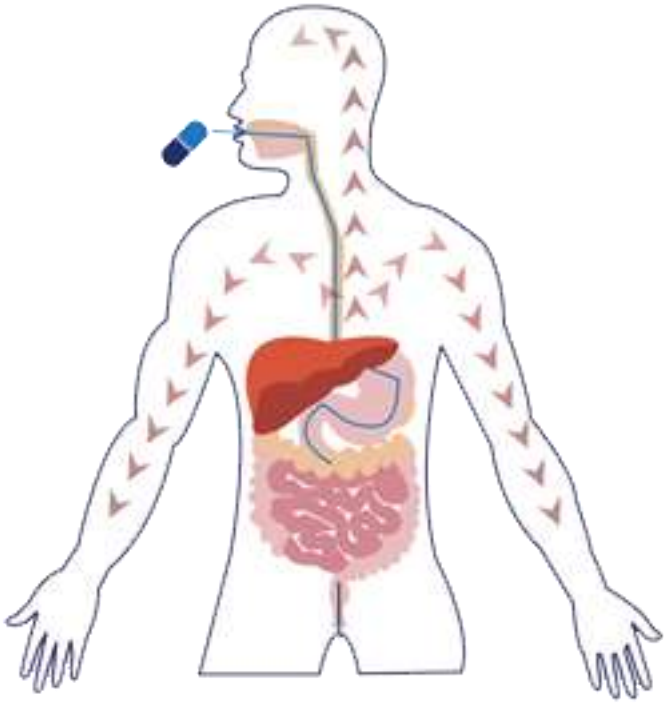
RECTAL DRUG ABSORPTION

Most drugs are well absorbed by this route in children, but the strong rectal contractions in infants can result in an inability to retain suppositories for the length of time needed to achieve optimal absorption.

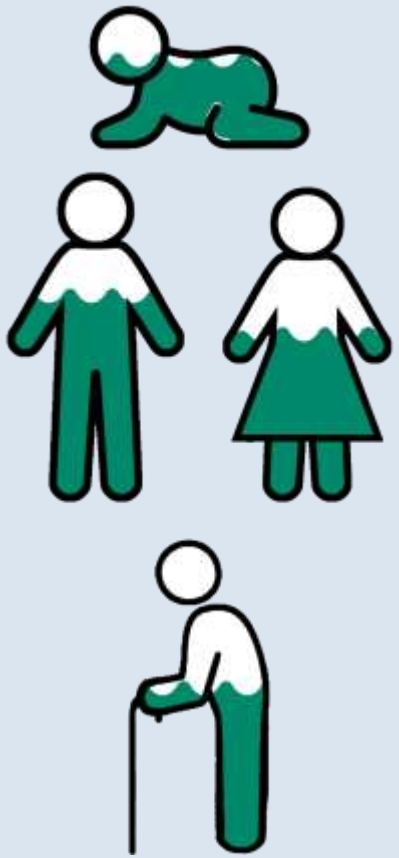
Gels and liquid (rectal diazepam gel) dosage preparations that do not require an extended time for dissolution are better options.



DRUG DISTRIBUTION



BODY WATER



Total body water content decreases with increasing age.

Approximately 85% of a premature newborn's weight and 70%-80% of a term newborn's weight are body water, compared with only 60%-65% in a 1-year-old.

These changes result in a much greater distribution of highly water-soluble drugs, such as the **aminoglycosides** or **linezolid**, and a reduced accumulation of highly lipid-soluble drugs, such as amiodarone, benzodiazepines, or digoxin.

BODY WATER

The volume of distribution of gentamicin in premature neonates ranges from 0.5 to 0.7 L/kg.

This value falls to 0.4 L/kg by the end of the first year of life and further declines to 0.2 to 0.3 L/kg by adulthood.

As a result, the weight-based dose for an infant (4 mg/kg) is often much higher than a comparable dose in an adult.

BODY FAT

Body fat increases throughout gestation and infancy.

A premature neonate may have as little as 1%-2% body fat, whereas a term neonate will have closer to 10%-15% body fat. A 1-year-old will have a body fat of 20%-25%, similar to that of an adult.

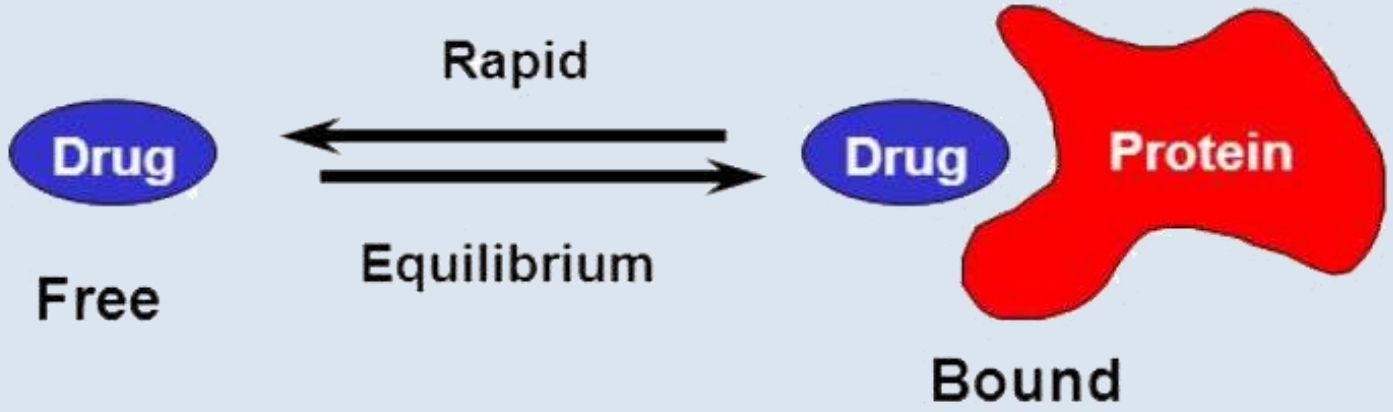
BODY FAT

The increasing rate of childhood obesity has generated concern about the efficacy and safety of current weight-based dosing strategies.

The need to make dosage adjustments in these children remains controversial, and only limited research is available.

PROTEIN BINDING

Plasma protein binding is reduced in neonates as a result of decreased circulating levels of both albumin and α1 acid glycoprotein, as well as decreased binding affinity.



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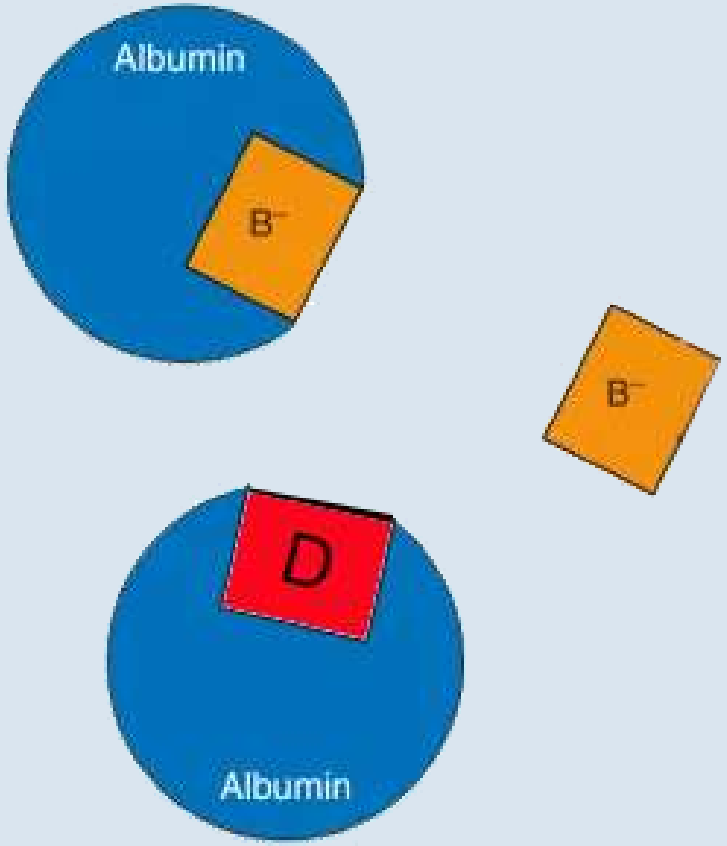
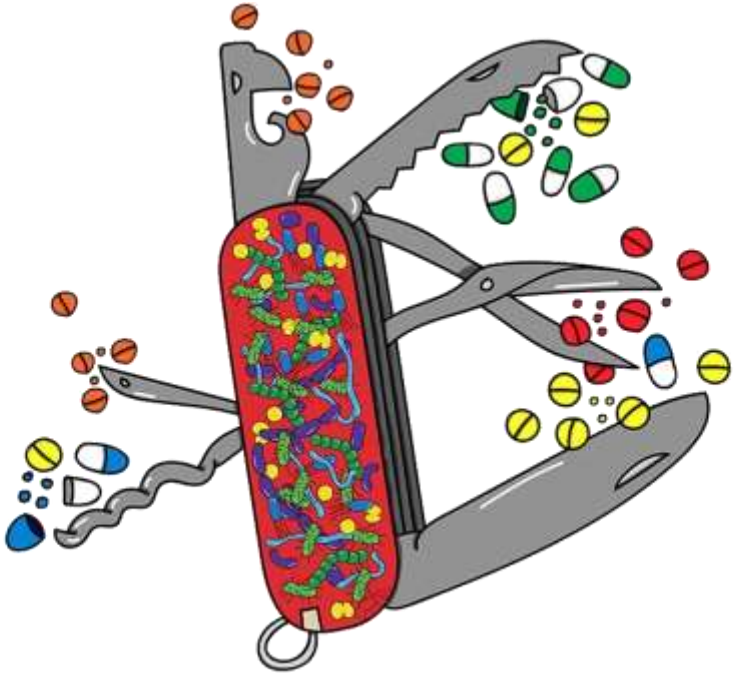


Administration of drugs with a high binding affinity for albumin, such as the **sulfonamides**, during the neonatal period can result in competition with bilirubin for binding sites.

The resulting increase in unbound bilirubin can lead to kernicterus due to deposition of bilirubin in the brain.

For this reason, **sulfonamides** are not recommended for neonates and are not approved by the FDA for use in infants younger than age 2 months.

DRUG METABOLISM



PHASE I DRUG METABOLISM

Phase I reactions, which include oxidation, reduction, hydroxylation, and hydrolysis, develop at varying rates during childhood, resulting in the wide range of half-lives reported for many drugs.

The cytochrome P-450 (CYP) 3A enzymes, which play a major role in drug metabolism, including that of erythromycin, develop early in life.

PHASE I DRUG METABOLISM

The earliest isozyme in this group to show activity is CYP3A7, the primary metabolic enzyme present in utero.

Enzymatic activity of CYP3A7 declines rapidly after birth, continues to decline, and is typically undetectable after age 1 year.

As levels of CYP3A7 decline, CYP3A4 and CYP3A5 levels rise.

Drugs like **erythromycin** are metabolized at a slower rate as a result of lower levels of CYP3A4 activity, so a more conservative approach to dosing is often used.

PHASE II DRUG METABOLISM

Phase II reactions include sulfation, acetylation, and glucuronidation, the latter involves uridine 5′- diphosphate glucuronosyltransferase (UGT) enzymes, which are present at low levels in fetal hepatic and renal tissues

A gradual increase in UGT expression occurs in the first 6 months of life, but still remains lower than that of adults for the first 2 to 3 years of life.

The reduced ability of infants to perform glucuronidation has been known for many years as a result of the **chloramphenicol** "gray baby syndrome".

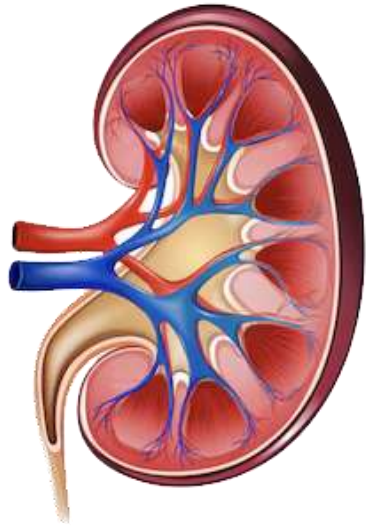
PHASE II DRUG METABOLISM

In the sulfation pathway, sulfotransferases (SULTs) develop extensively in utero, reaching levels of enzyme activity similar to that of adults at birth.

The reliance on sulfation during infancy is found with several drugs including **morphine**, **thyroid hormones**, and **acetaminophen**.

Glucuronidation of acetaminophen via UGTs is decreased in infants, and as a result, the primary route of acetaminophen metabolism is the formation of sulfate conjugates for the first year of life.

DRUG ELIMINATION



GLOMERULAR FILTRATION

The kidneys are not fully developed at birth, the ability to filter, excrete, and reabsorb substances is not maximized until age 1 year.

At birth, full-term neonates have an average glomerular filtration rate (GFR) of only 2-4 mL/min/1.73 m^2.

There is a rapid rise in GFR during the first 2 weeks of life, reaching 40 mL/min/1.73 m^2 as a result of increased renal blood flow, increased function of the existing nephrons, and the appearance of additional nephrons.

By 1 year of age, GFR value approaches adult values of 100-120 mL/min/1.73 m^2.

GLOMERULAR FILTRATION

The impact of these GFR changes can be seen in many renally eliminated drugs, including the aminoglycosides and vancomycin.

To account for reduced renal function, most pediatric references use a combination of patient weight and age to determine gentamicin dosing in neonates.

<30 WEEKS' GESTATION

0-28 days: 2.5 mg/kg/day IV/IM

>28 days: 3 mg/kg/day IV/IM

30-36 WEEKS' GESTATION

0-14 days: 3 mg/kg/day IV/IM

>14 days: 5 mg/kg/day IV/IM divided q12hr

>36 WEEKS' GESTATION

0-7 days: 5 mg/kg/day IV/IM divided q12hr

>7 days: 7.5 mg/kg/day IV/IM divided q8hr

TUBULAR SECRETION

Tubular secretion is reduced immediately after birth, but gradually increases during the first year of life.

A reduction in tubular secretion results in a prolonged elimination half-life for **penicillins**, **cephalosporins**, **furosemide**, and **digoxin**.

The half-life of digoxin decreases from ~30–40 hours in a term neonate to 20–25 hours in a 1-year-old as renal function matures.

TUBULAR SECRETION

In the first days after birth, serum creatinine values reflect maternal creatinine transferred through the placenta and may appear falsely elevated.

After the first week, serum creatinine values are typically low as a result of less muscle mass, especially in premature neonates, and may not accurately represent renal function.

Urine output is often used as an additional measure of renal function in this population.

TUBULAR SECRETION

After infancy, serum creatinine may be used to estimate clearance.

There are several equations designed for pediatric use; guidelines recommend the bedside isotope dilution mass spectroscopy (IDMS) Schwartz equation:

$$\mathbf{CL_{cr}=(0.413XHt)/S_{cr}}$$

where CL_{Cr} is creatinine clearance (mL/min/1.73 m^2), Ht is height (cm), and S_{Cr} is serum creatinine (mg/dL).

TUBULAR SECRETION

H.G. is a 10-year-old male admitted with osteomyelitis in his left ankle. The team plans to treat H.G. with vancomycin for 6 weeks. He is 55.11 inches (140 cm) tall and weighs 70.55 pounds (32 kg). His serum creatinine is 0.5 mg/dL (normal for age 0.5–1.0 mg/dL). What is H.G.'s creatinine clearance?

CL_{cr}=(0.413X140)/0.5

Using this method, H.G. has a calculated creatinine clearance of 116 mL/min/1.73 m^2

Pediatric Pharmacodynamic Differences

•**Receptor Maturation and Sensitivity:** Neonates and infants may have reduced receptor density, affinity, or function.

•Signal Transduction Changes: Immature second messenger systems

Pediatric Pharmacodynamic Considerations by System

- Central Nervous System (CNS)

- Immature neurotransmitter pathways can **enhance or diminish** drug effects.
- Increased blood-brain barrier **permeability** results in **greater drug penetration** and **CNS side effects**.

NERVOUS SYSTEM

Example: Opioids have an **exaggerated depressant effect** in neonates.

- Cardiovascular System

Immature adrenergic response **affects drug action** on **blood pressure and heart rate**.

Cardiovascular system

Example: Beta- adrenergic receptors in neonates are less responsive, reducing the effect of drugs like dopamine and epinephrine.

Case Studies in Pediatric Pharmacodynamics

Neonatal Hypotension

- **Patient:** 24-week gestational age neonate with severe hypotension.
- **Issue:** Lack of response to dopamine infusion at 20 µg/kg/min due to reduced adrenergic receptor density.
- **Solution:**
  - Increase dopamine dose up to 40 µg/kg/min while monitoring for peripheral vasoconstriction.
- **Clinical Insight:** Premature neonates may require higher catecholamine doses due to immature receptor function.

Pediatric Pharmacodynamic Considerations by System

- Respiratory System

Underdeveloped chemoreceptors alter the **response to respiratory stimulants**.

Example: Caffeine is used in neonates to stimulate immature respiratory centers.

- Immune System

Altered immune function affects **vaccine responses** and **drug-induced hypersensitivity reactions**.

Example: Children have an **increased risk of drug-induced skin reactions**.

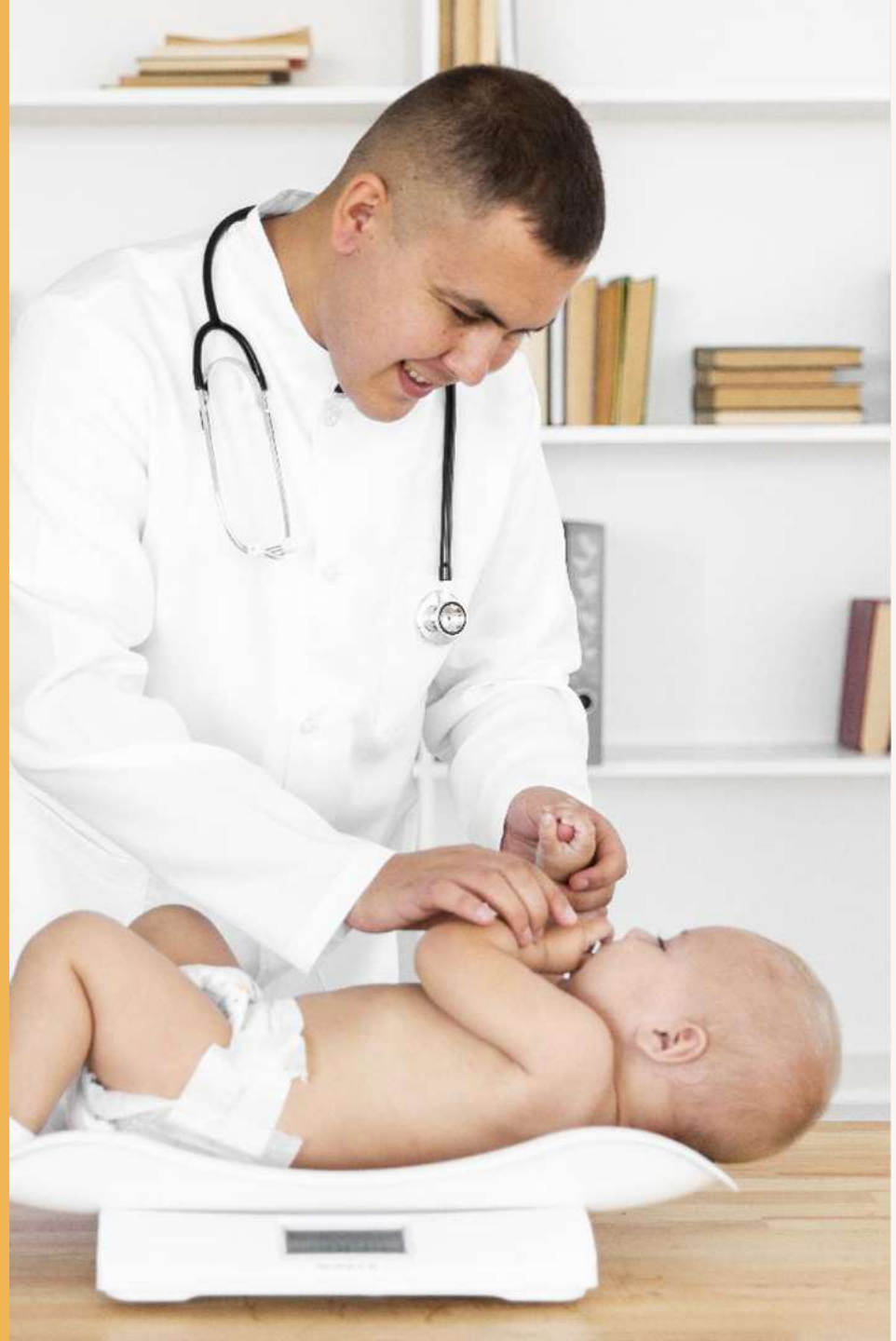
Increasing Availability of Pediatric Medication Information

Challenges in Pediatric Drug Research

•Limited clinical trials due to **ethical and logistical concerns**.
•**Off-label drug use** is common due to a lack of **pediatric-specific guidelines**.

FDA Initiatives to Improve Pediatric Drug Research

•**Pediatric Exclusivity Program:** Provides pharmaceutical companies with a **6-month patent extension** for conducting pediatric studies.
•**Best Pharmaceuticals for Children Act (BPCA):** Funds research on **off-patent medications** commonly used in children.
•**Pediatric Research Equity Act (PREA):** Requires drug manufacturers to **conduct pediatric studies** for drugs likely to be used in children.



Thanks!

Do you have any question?