

PEDIATRICS

Pediatric Patients: Pediatric patients are individuals younger than 18 years of age.

They are classified according to age:

Age Group	Definition	Physiological Characteristics
Premature Infants	Babies born before 37 weeks of gestation	Immature liver, kidneys, lungs, and GI tract Poor drug metabolism and excretion Increased sensitivity to medications
Neonates	1 day to 1 month of age	Immature liver enzymes Reduced kidney function Slow gastric emptying Increased permeability of the blood-brain barrier
Infants	1 month to 1 year of age	Rapid maturation of liver and kidney function Increasing drug metabolism Rapid growth with doubling/tripling of body weight during the first year
Children	1 to 11 years of age	Liver enzyme activity may be higher than in adults Faster metabolism of some drugs Improved immune function and steady growth
Adolescents	12 to 16 years of age	Hormonal changes associated with puberty Changes in body composition (fat and muscle mass) Drug handling gradually approaches that of adults

Physiological changes at each developmental stage influence drug absorption, distribution, metabolism, and excretion (ADME). Therefore, pediatric drug therapy must be individualized according to the patient's age and developmental stage.

INFANT MORTALITY AND IT'S IMPROVEMENT

Infant mortality refers to the number of infants who die before reaching one year of age per 1,000 live births. Historically:

- During the 19th century, nearly 200 infants died for every 1,000 births.
- By 1925, this number decreased to approximately 75 per 1,000 births.
- By 2013, infant mortality further declined to about 6 deaths per 1,000 births.

This remarkable improvement did not happen by chance.

It was made possible through several advances in healthcare, including:

1. Better prenatal and maternal care
2. Safer delivery practices
3. Vaccination programs
4. Improved nutrition
5. Early diagnosis of diseases
6. Availability of antibiotics
7. Better neonatal intensive care units (NICUs)
8. Improved sanitation and hygiene

These developments have significantly increased the survival of newborns and infants.

Drug Therapy in Children

- Although children frequently require medications, surprisingly, most medicines available today were originally developed and tested in adults.
- Only about one-fourth (25%) of drugs approved by the U.S. Food and Drug Administration (FDA) have specific pediatric indications.

- This means that many medications prescribed for children are used off-label, where physicians rely on available scientific evidence and clinical experience rather than formal pediatric approval.

Why is Pediatric Pharmacotherapy Challenging?

One of the biggest challenges in pediatric medicine is the lack of sufficient clinical data. For many drugs, there is limited information regarding:

1. **Pharmacokinetics** : This refers to *what the body does to the drug*, including: ADME Parameters of drugs
2. **Pharmacodynamics**: This refers to *what the drug does to the body*, including: Therapeutic effects, Adverse effects
3. **Drug Efficacy**: A drug that is effective in adults may not produce the same effect in newborns or infants because receptor sensitivity and organ function differ.
4. **Drug Safety**: Children are much more susceptible to adverse drug reactions because many of their organs are still developing.

Therefore, medications must always be prescribed with extreme caution.

Historical Drug Disasters in Pediatrics

Because of insufficient knowledge of pediatric pharmacology, several serious drug-related tragedies occurred.

Drug/Condition	Cause/Mechanism	Clinical Features/Effects	Lesson Learned
Gray Baby Syndrome (Chloramphenicol) 	High doses of chloramphenicol (100–300 mg/kg/day) administered to neonates. Immature liver enzymes (deficient glucuronidation) and reduced renal excretion cause drug accumulation, leading to toxic serum concentrations.	Abdominal distension Vomiting, Diarrhea, Refusal to feed, Gray discoloration of the skin, Respiratory distress, Hypotension, Progressive circulatory shock, Death if untreated	Neonates are not small adults. Drug doses must be individualized according to developmental stage because immature organs cannot metabolize and eliminate drugs efficiently.
Thalidomide Tragedy	Thalidomide was prescribed to pregnant women for morning sickness during the late 1950s and early 1960s. The drug crossed the placenta and caused severe fetal malformations (teratogenicity).	Phocomelia (shortened or absent limbs), Ear defects, Eye defects, Heart defects, Nerve damage, Mental retardation	This tragedy led to stricter drug approval regulations and mandatory evaluation of drug safety during pregnancy before marketing.
Isotretinoin Teratogenicity	Isotretinoin, used to treat severe acne, is highly teratogenic. Exposure during pregnancy causes severe congenital abnormalities.	Birth defects involving the: Brain, Heart, Face, Ears	Patient education and pregnancy prevention are essential before prescribing isotretinoin to females of reproductive age.
Kernicterus (Sulfonamides)	Sulfonamides displace bilirubin from albumin, increasing free bilirubin levels. In neonates, the immature blood-brain barrier allows bilirubin to enter the	Jaundice, Poor feeding, High-pitched cry, Muscle rigidity, Seizures, Permanent brain damage, Hearing	Drugs that are safe in adults may cause life-threatening toxicity in neonates because of immature liver

 Jaundice Kernicterus Yellowing of eyes Yellowing of skin Excess bilirubin in blood Bilirubin moves from bloodstream into brain tissue Kernicterus	brain, causing bilirubin encephalopathy (kernicterus).	loss, Cerebral palsy, Death in severe cases	function, reduced protein binding, and an underdeveloped blood-brain barrier.
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Special Considerations in Pediatric Drug Therapy

1. Dosage Regimen

1. Children are not small adults.
2. Pediatric doses should not be calculated by simply reducing the adult dose based on body weight (mg/kg) or body surface area (mg/m²).
3. Drug dosing should also consider age, organ maturity, developmental stage, and disease condition.
4. Individualized dosing helps achieve effective treatment and prevents toxicity.

2. Bioavailability

1. Bioavailability is the amount of drug that reaches the bloodstream after administration.
2. In children, bioavailability differs because the gastrointestinal tract is still developing.
3. Drug absorption may be higher or lower than in adults.
4. These differences can alter the therapeutic effect of the drug.

3. Pharmacokinetics (PK)

1. Pharmacokinetics includes Absorption, Distribution, Metabolism, and Elimination (ADME).
2. These processes vary between premature infants, neonates, infants, children, and adults.
3. Drug dose, dosing interval, and route of administration should be adjusted according to age.
4. Individualization improves drug efficacy and safety.

4. Pharmacodynamics (PD)

1. Pharmacodynamics refers to how the drug affects the body.
2. Children's receptors and organs may respond differently to drugs than those of adults.
3. The same drug concentration may produce different therapeutic or adverse effects.
4. Drug response should be monitored carefully.

5. Efficacy and Safety

1. Drug effectiveness may vary with age.
2. The risk of adverse drug reactions also differs because children's organs are still developing.
3. Therapeutic response and toxicity should be monitored regularly.
4. Safe and effective therapy requires age-appropriate dosing.

6. Limited Clinical Data

1. Many drugs have not been adequately studied in children.
2. Pediatric dosing recommendations are often based on limited evidence or extrapolated from adult studies.
3. More pediatric clinical research is needed.
4. Careful monitoring is essential when using such medicines.

7. Pediatric Dosage Forms

1. Many medicines are not available in child-friendly dosage forms.
2. Pharmacists often prepare liquid formulations (extemporaneous preparations) from adult tablets or capsules.
3. Examples include amiodarone, baclofen, captopril, ursodiol, and spironolactone.

4. These preparations help infants and young children take medicines more easily.

8. Modification of Adult Formulations

1. Adult injectable medicines are often diluted to provide small pediatric doses.
2. Examples include aminophylline, methylprednisolone, morphine, and phenobarbital.
3. Improper dilution may affect drug stability, compatibility, and bioavailability.
4. Accurate preparation is essential for safe treatment.

9. Intravenous (IV) Drug Administration

1. Infants have small and fragile veins.
2. They can tolerate only small volumes of IV fluids.
3. Accurate infusion pumps and dosing devices should be used.
4. Careful administration reduces medication errors.

10. Oral Drug Administration

1. Young children often have difficulty swallowing tablets or capsules.
2. Poor taste may lead to refusal of medication.
3. Liquid formulations or taste-masking techniques may improve acceptance.
4. Proper administration techniques improve treatment success.

11. Medication Adherence

1. Children depend on parents or caregivers to receive medicines correctly.
2. Missed doses or incorrect administration can reduce treatment effectiveness.
3. Parents and caregivers should receive proper counseling.
4. Good adherence improves therapeutic outcomes.

12. Ethical Considerations

1. Children cannot legally provide informed consent for research.
2. Parents or legal guardians provide consent on their behalf.
3. Pediatric clinical studies require strict ethical review.
4. The benefits of research must outweigh the risks.

13. Advances in Pediatric Pharmacokinetics

1. Improved analytical techniques have increased knowledge of pediatric drug therapy.
2. Better understanding of drug disposition helps optimize dosing.
3. These advances improve treatment effectiveness.
4. They also reduce the risk of adverse drug reactions.

<https://whimsical.com/ayesha964/pharmacokinetics-absorption-in-pediatric-patients-T3dGc3uvy25K5DWxboniUY>

PHARMACOKINETICS

Absorption of Drugs in Pediatric Patients

Absorption is the movement of a drug from its site of administration into the systemic circulation. In children, absorption differs from adults because organs are still developing. The greatest differences are seen in premature infants and neonates.

Drug absorption in children differs significantly from adults because the organs responsible for drug absorption continue to mature after birth. Drug absorption changes continuously from birth to adolescence.

- Age-related physiological changes affect:

Gastric pH

Gastric emptying

Intestinal motility

Blood flow

Skin permeability

Pulmonary function

- These developmental changes alter:

- Rate of absorption Extent of absorption (bioavailability)
- Drug therapy should therefore always be individualized according to:
 - Age
 - Weight
 - Gestational age
 - Organ maturity
 - Disease condition

1. Oral (Gastrointestinal) Absorption

Oral administration is the most common route in children. However, gastrointestinal physiology changes markedly during infancy, making drug absorption unpredictable.

A. Gastric pH

Developmental Changes

1. Full-term newborn: Gastric pH = **6–8 (nearly neutral)**
2. Within 24 hours: Gastric pH falls to **1–3**
3. Premature infants maintain higher gastric pH longer because acid secretion is immature.
4. Adult acid secretion develops by approximately **2 years of age**.

Effect on Drug Absorption

Higher gastric pH means:

1. Acid-labile drugs are protected from acid degradation.
2. Weak acidic drugs remain less ionized and are absorbed less efficiently.

Clinical Examples

Increased absorption

- Penicillin, Ampicillin, Nafcillin
- These antibiotics are destroyed by gastric acid in adults but survive better in neonates.

Decreased absorption

- Phenobarbital
- Other weak acidic drugs

B. Gastric Acid Secretion

Development

- Immature at birth
- Gradually increases
- Adult secretion reached by about **2 years**

Clinical Importance

Gastric acid determines:

- Drug dissolution
- Drug ionization
- Stability
- Bioavailability

Some drugs require acidic environments for optimal absorption.

C. Gastric Emptying

Development

Neonates have:

- Delayed gastric emptying
- Particularly prolonged in premature infants

Adult values reached around **6 months**.

Effect

Delayed gastric emptying causes:

- Delayed drug absorption

- Delayed onset of action
 - Longer contact time with intestinal mucosa
- Sometimes poorly absorbed drugs may actually show improved absorption because they remain longer in the intestine.

Clinical Significance

- Oral medications may act more slowly.
- Time to peak concentration is prolonged.

D. Gastric Transit Time

Development

Food and drugs remain longer in the stomach.

Effect

- Delays movement into small intestine.

E. Intestinal Transit Time

Development

Intestinal motility is slower during infancy.

- Slower onset of absorption.

Clinical Importance

Emergency medications given orally may act later than expected

Effect

Drugs remain longer in the intestine, leading to:

- Slower absorption
- Sometimes greater total absorption

F. Gastrointestinal pH

The pH differs throughout infancy.

This influences:

- Drug ionization
- Drug dissolution
- Drug stability

The effect depends entirely on the drug.

G. Passive Diffusion and Active Transport

Passive Diffusion

Develops early.

Most drugs cross intestinal membranes by passive diffusion.

Active Transport

Carrier-mediated transport matures around 4 months.

Examples include:

- Vitamins
- Amino acids
- Certain antibiotics

Clinical Significance

Drug absorption becomes more predictable after infancy.

H. Effect of Food

Milk

Formula

Breastfeeding

Solid food

can all alter absorption.

Mechanisms

Food may:

- Delay gastric emptying
- Bind drugs
- Alter gastric pH

Examples

Some antibiotics should not be taken with milk because calcium binds the drug and reduces absorption.

I. Posture

Infants lying flat may have slower gastric emptying.

This may alter drug absorption slightly.

Especially important in hospitalized neonates.

J. Disease States

Conditions affecting GI absorption include:

- Vomiting
- Diarrhea

- Malabsorption
- Intestinal infections

Effect

Drug absorption becomes:

- Reduced

K. Therapeutic Interventions

Examples include:

- Nasogastric suction
- Continuous feeding
- Acid-suppressing drugs

These interfere with oral drug absorption.

2. Intramuscular (IM) Absorption

IM absorption is highly variable in newborns.

Developmental Factors

Premature infants have:

- Less muscle mass
- Poor muscle perfusion
- Weak muscle contractions
- Vasomotor instability

Effect

Drug reaches circulation slowly and unpredictably.

Drug Examples**Phenobarbital**

Rapidly absorbed.

Diazepam

Poorly absorbed from muscle.

Demonstrates that IM absorption is drug dependent.

3. Intraosseous (IO) Absorption**Principle**

When IV access cannot be established during emergencies:

A needle is inserted into the bone marrow cavity (usually proximal tibia).

Bone marrow has:

- Rich vascular supply
- Venous sinusoids

Drug rapidly enters systemic circulation.

4. Skin (Topical/Percutaneous) Absorption

Infant skin is much more permeable than adult skin.

- Delayed
- Highly unpredictable

Dose adjustment may be necessary.

Clinical Importance

As infants grow:

- Muscle mass increases.
- Blood flow improves.
- IM absorption approaches adult values.

Limitations

IM injections are:

- Painful
- Stressful
- Difficult in small infants

Therefore:

- Avoid IM injections whenever possible.
- Reserve IM administration for emergencies or when IV access is unavailable.

Clinical Uses

Preferred during:

- Pediatric cardiac arrest
- Shock
- Severe dehydration
- Trauma

Almost all emergency medications can be administered by the IO route.

A. Thin Stratum Corneum

The outer skin barrier is immature.
Drug passes through more easily.

B. Increased Skin Hydration

Infant skin contains more water.
Hydrated skin absorbs drugs faster.

C. High Body Surface Area (BSA)

Infants have:

- Larger BSA relative to body weight.

Therefore:

A small amount of topical drug may produce significant systemic exposure.

D. Underdeveloped Epidermal Barrier

Drug penetrates deeper layers more easily.
Higher risk of toxicity.

Clinical Examples

Systemic toxicity has occurred with:

- Hexachlorophene
- Salicylic acid
- Rubbing alcohol

Topical Corticosteroids

Infants absorb more steroid.

May develop:

- Growth suppression
- Adrenal suppression
- Cushing syndrome

- Bathing
- Swimming
- Exercise

Hyoscine Patch

Used for:

- Excessive drooling

Avoid in premature infants because excess prilocaine absorption may cause **methemoglobinemia**.

Topical Theophylline

Used experimentally in premature infants for neonatal apnea.
Can produce therapeutic blood concentrations.

Fentanyl Patch

Provides:

- Continuous opioid analgesia
- Used only for chronic pain in opioid-tolerant patients (not opioid-naïve children)

Needle-Free Jet Injectors

Deliver drugs subcutaneously without needles.

Used for:

- Growth hormone
- Insulin
- Vaccines
- Sedation

Transdermal Patches

Methylphenidate

Approved in children aged **6–12 years**.

Patch remains effective during:

EMLA Cream

Contains:

- Lidocaine
- Prilocaine

Advantages:

- Reduced needle phobia
- Comparable absorption to SC injection

5. Ophthalmic Absorption

Eye drops are not purely local.

Excess drug drains through the nasolacrimal duct into systemic circulation.

Clinical Example

Phenylephrine eye drops may cause:

- Hypertension
- Tachycardia

Especially in infants.

Clinical Tip

Gentle pressure over the nasolacrimal duct for **1–2 minutes** after instilling eye drops can reduce systemic absorption.

6. Rectal Absorption

Useful when oral administration is impossible.

Indications

- Vomiting
- Unconsciousness
- Seizures
- Refusal to swallow

Characteristics

Absorption is:

- Variable

- Drug dependent
- Sometimes rapid

Example

Rectal diazepam:

- Rapidly terminates seizures
- Can be administered by parents at home during emergencies

7. Buccal Absorption

The buccal mucosa is:

- Thin
- Highly vascular

Drugs absorbed here enter systemic circulation directly, bypassing much of the first-pass hepatic metabolism.

Advantages

- Rapid onset
- No swallowing required
- Useful in postoperative patients
- Useful in nausea and vomiting

Highly Lipophilic Drugs

Absorbed rapidly:

- Fentanyl
- Midazolam

Buccal Midazolam

Preferred over rectal diazepam for:

- Acute seizures

Reasons:

- Faster
- Easier administration
- More socially acceptable

Fentanyl Lozenges

Used for:

- Painful procedures
- Breakthrough cancer pain

Not licensed for routine pediatric use.

Melt/Wafer Formulations

Examples:

- Ondansetron
- Piroxicam

Although they dissolve in the mouth, they are swallowed and absorbed from the GI tract rather than the buccal mucosa.

Buccal Desmopressin

Higher bioavailability than tablets.

120 µg buccal ≈ 200 µg oral

8. Intranasal Absorption

The nasal mucosa has an extensive blood supply, allowing rapid systemic drug absorption.

Uses

Local Therapy

Examples:

- Nasal decongestants
- Corticosteroid nasal sprays

Systemic Therapy

Examples:

- Desmopressin for diabetes insipidus
- Midazolam for seizures and procedural sedation
- Fentanyl for rapid analgesia

- Diamorphine for acute pain relief

Advantages

- Rapid onset
- Non-invasive
- Useful when IV access is difficult
- Avoids first-pass metabolism

Limitations

Absorption decreases with:

- Nasal congestion
- Excess mucus

- Mucociliary clearance

Adverse Effects

Excessive absorption of intranasal corticosteroids may lead to:

- Adrenal suppression
- Growth retardation
- Cushingoid features

9. Inhalational Absorption

Drugs are delivered directly into the lungs, providing a rapid onset of action because of the lungs' large surface area and rich blood supply.

Advantages

- High drug concentration at the site of action (lungs)
- Reduced systemic exposure
- Rapid onset
- Lower doses required than systemic therapy

- Airway size
- Lung maturity
- Pulmonary blood flow
- Breathing pattern
- Correct inhaler technique
- Appropriate spacer use in young children

Clinical Uses

- Mainstay of asthma management
- Bronchodilators (e.g., salbutamol)
- Inhaled corticosteroids for long-term control

Systemic Absorption

Long-term use of high-dose inhaled corticosteroids may result in:

- Adrenal suppression
- Growth retardation
- Reduced bone mineral density (rare)

Therefore, the **lowest effective dose** should be used and growth should be monitored.

Factors Affecting Pulmonary Absorption

Drug absorption depends on:

Distribution

Distribution is the reversible movement of a drug from the bloodstream to body tissues and organs after absorption.

In children, especially premature infants and neonates, drug distribution differs significantly from adults because of developmental changes in body composition and physiology.

Premature infants, neonates, infants, children, and adolescents all have different distribution patterns.

The differences occur because of developmental changes in:

1. Body water
2. Body fat
3. Plasma protein binding
4. Organ blood flow
5. Tissue composition

Therefore, pediatric drug doses cannot simply be calculated by reducing the adult dose; age-related physiological differences must be considered.

Factors Affecting Drug Distribution

Drug distribution depends on two major factors:

1. Physicochemical Properties of the Drug: These are characteristics of the drug itself and do not change with age.

a. pKa (Degree of Ionization)

Determines whether a drug is ionized or non-ionized.

Non-ionized drugs cross cell membranes more easily.

Influences tissue penetration.

b. Molecular Weight

Small molecules distribute more rapidly.

Large molecules remain mainly within the vascular compartment.

c. Lipid Solubility (Partition Coefficient)

Lipid-soluble drugs easily cross cell membranes.

Water-soluble drugs remain mainly in extracellular fluid.

Important Clinical Point

2. Patient-Specific Physiological Factors

These undergo significant maturation after birth and are the major determinants of pediatric drug distribution.

They include:

1. Organ blood flow (vascular perfusion)
2. Body composition
3. Plasma protein binding
4. Tissue binding
5. Disease states

A. Vascular Perfusion: Vascular perfusion refers to the amount of blood reaching various organs.

Developmental Changes

Immediately after birth: Blood flow distribution differs from adults.

Organ perfusion gradually matures during infancy.

Highly perfused organs

include: Brain, Heart, Liver, Kidneys

These organs receive drugs first.

Effect on Drug Distribution

Initially: Drug rapidly reaches highly perfused organs.

Later: Drug redistributes into: Muscle, Fat, Skin

As circulation matures, distribution becomes similar to adults.

Clinical Significance: Rapid CNS drug delivery may occur in neonates because: Brain receives a larger proportion of cardiac output. Blood–brain barrier is relatively immature.

B. Body Composition: One of the most important determinants of pediatric drug distribution.

Body composition changes dramatically with age.

These include changes in:

- | | |
|------------------------|------------------------|
| 1. Total body water | 3. Intracellular fluid |
| 2. Extracellular fluid | 4. Fat content |

Total Body Water (TBW): Developmental Changes

Age	Total Body Water	Full-term infant	78%
Fetus	94%	Adult	60%
Premature infant	85%		

- ✓ Water-soluble drugs distribute mainly into body water.
- ✓ Since neonates have much more body water: They have a larger volume of distribution (Vd).
- ✓ Clinical Consequence: After giving the same mg/kg dose: Drug becomes diluted into a larger volume. Therefore: Plasma concentration becomes lower.
- ✓ To reach therapeutic concentrations: Higher loading doses (mg/kg) are often required.
- ✓ Examples: Water-soluble drugs include: Aminoglycoside, Vancomycin, Beta-lactam antibiotics

Extracellular Fluid (ECF): Development

Age Extracellular Fluid

Premature infant 50%

4–6 months 35%

1 year 25%

Adult 19%

Effect

- ✓ Many water-soluble drugs remain primarily in extracellular fluid.
- ✓ Since neonates possess a much larger extracellular compartment:
- ✓ Drug distributes more extensively.
- ✓ Clinical Significance: Larger loading doses are required.
- ✓ Water-Soluble Drugs Examples: Gentamicin, Tobramycin, Amikacin

Distribution volume is: Highest in Extremely premature infants

Gradually decreases as: Gestational age increase, Birth weight increases

C. Plasma Protein Binding

Many drugs circulate bound to plasma proteins. Only free (unbound) drug is pharmacologically active.

Developmental Changes

Neonates have:

1. Lower albumin concentration
2. Lower globulin concentration
3. Reduced protein-binding capacity
4. Reduced protein-binding affinity

5. Higher concentrations of: Bilirubin, Free fatty acids → compete for protein-binding sites.

Effect

Less drug binds to plasma proteins.
More drug remains free.

Clinical Consequences Free drug: efficacy and toxicity increase

1. Produces therapeutic effects
2. Produces adverse effects
3. Crosses membranes
4. Is filtered by kidneys

Albumin

Albumin mainly binds: Acidic drugs.

Examples:

Phenytoin

Phenobarbital

Salicylates

Warfarin

Because albumin concentration is reduced: More free drug circulates.

Globulins

Basic drugs bind more to globulins.

Globulin concentration is also lower in neonates.

Result: Higher free concentrations.

Age-Related Maturation

1. Acidic drugs: Adult protein binding develops around 3 years.
2. Basic drugs: Adult protein binding develops between 7–12 years.
3. Protein binding changes throughout childhood.

Tissue Binding Characteristics

1. Some drugs bind to: Muscle, bone, fat, other tissues
2. The extent of tissue binding changes with age because these tissues continue to develop after birth.

3. Clinical Importance As children grow:

- Tissue composition changes.
- Drug storage and release become more predictable.
- Distribution patterns gradually resemble those of adults.

Disease States: Disease may have a greater impact on drug distribution than normal developmental changes.

Examples include:

- | | | |
|---------------------|-----------------|-----------|
| 1. Renal impairment | 4. Severe burns | 7. Sepsis |
| 2. Liver disease | 5. Edema | |
| 3. Hypoalbuminemia | 6. Dehydration | |

Disease may:

- | | | |
|---------------------------|-----------------------------------|--|
| 1. Reduce protein binding | 3. Change body water distribution | 4. Increase or decrease volume of distribution |
| 2. Alter tissue perfusion | | |

Clinical Significance: Drug doses often need adjustment based on the child's clinical condition, not just age.

Distribution into Breast Milk

Many medications taken by lactating mothers pass into breast milk.

Drug transfer depends on:

1. Lipid solubility
2. Molecular weight
3. Protein binding
4. Ionization
5. Maternal plasma concentration

Clinical Importance: Breastfed infants may receive clinically significant drug exposure.

The risk is greatest in

1. Premature infants
2. Neonates
3. Infants with renal or hepatic impairment

Metabolism

1. Drug metabolism (biotransformation) is the **enzymatic conversion of drugs into more water-soluble compounds**, making them easier to eliminate from the body.
2. The **liver** is the principal organ responsible for drug metabolism, although metabolism also occurs in the intestines, kidneys, lungs, and plasma.
3. Drug metabolism in children is **not constant throughout childhood**.
4. The capacity to metabolize drugs changes dramatically with age because **hepatic enzyme systems mature gradually after birth** → Different enzyme systems mature at **different rates**.
5. Premature infants and neonates have **immature liver enzymes**.
6. As a result:
 - Drug metabolism is slower.
 - Drug clearance is reduced.
 - Drug half-life is prolonged.
7. drug metabolism depends on: Age , Developmental stage , Hepatic enzyme maturation , Genetic polymorphisms

Clinical Significance

- Premature infants require lower maintenance doses or longer dosing intervals.

- Older children often metabolize drugs faster than adults.
- Pediatric doses should be individualized according to age and developmental stage.

Development of Hepatic Drug Metabolism

The metabolic capacity of the liver changes throughout childhood.

Age	Metabolic Capacity
Premature infant	Very low
Neonate	Low
Infant	Rapidly increasing
Young child (1–9 years)	Higher than adults
Adolescent	Similar to adults

Clinical Importance

Drug clearance changes with age.

Therefore:

- Neonates often require **lower maintenance doses**.
- Young children may require **higher mg/kg doses**.
- Adolescents generally receive adult-equivalent doses.

Phases of Drug Metabolism

Drug metabolism occurs in **two phases**.

Phase I Reactions (Functionalization)/ Cytochrome P450 System)

These reactions introduce or expose functional groups on the drug molecule.

Types

- Oxidation (most common)
- Reduction
- Hydrolysis

Most Phase I reactions are catalyzed by the **Cytochrome P450 (CYP450) enzyme system**.

Development

Most CYP enzymes are:

- Immature at birth.
- Increase rapidly after birth.

- Reach or exceed adult activity during childhood.
- Decline to adult levels during adolescence.

Effect

Reduced CYP activity causes:

- Slow drug metabolism.
- Drug accumulation.
- Longer elimination half-life.

Example: Phenobarbital

Phenobarbital undergoes oxidative metabolism.

Neonates

Oxidative metabolism is poor.

Drug clearance is reduced.

Half-life is prolonged.

Clinical Significance

- Lower daily doses are required in premature infants.
- Clearance increases rapidly after birth.
- Older children may require relatively higher weight-based doses.

Phase II Reactions (Conjugation)

Phase II reactions attach endogenous substances to drugs, making them highly water-soluble for excretion.

Common conjugation pathways include:

- Glucuronidation
- Sulfation
- Acetylation

- Methylation
- Glutathione conjugation

Phase II Metabolism – Sulfation

Development

Unlike glucuronidation:
The sulfation pathway is **well developed even in premature infants and newborns**.

Importance

Sulfation acts as an **alternative metabolic pathway** when glucuronidation is immature.

Clinical Significance

Neonates can metabolize several drugs adequately through sulfation despite immature liver function.

Phase II Metabolism – Glucuronidation

Development

Glucuronidation is:

- Poorly developed at birth.
- Gradually matures over the first **several months to approximately 1 year** of life.

The enzyme responsible is **UDP-glucuronosyltransferase (UGT)**.

Effect

Reduced glucuronidation causes:

- Slower metabolism
- Drug accumulation

- Longer half-life
- Increased toxicity

Clinical Importance

Many drugs depend on glucuronidation for elimination.

Neonates metabolize these drugs much more slowly than adults.

Example: Paracetamol (Acetaminophen)

Adults

Approximately **70%** of paracetamol is metabolized by **glucuronidation**.

Newborns

Less than **20%** undergoes glucuronidation.

Instead,

Most metabolism occurs through **sulfation**.

Clinical Significance

Children are generally **less susceptible to paracetamol toxicity** than adults because:

- Sulfation is efficient.
- Less drug is converted to the toxic metabolite **NAPQI**.

However, overdose can still cause severe hepatotoxicity.

Example: Chloramphenicol

Chloramphenicol requires glucuronidation for detoxification.

Neonates

Deficiency of **glucuronyltransferase** prevents metabolism.
Drug accumulates rapidly.

Clinical Consequence

Development of **Gray Baby Syndrome**.

Features

- Abdominal distension
- Vomiting
- Cyanosis
- Hypothermia
- Hypotension
- Gray discoloration of the skin

- Cardiovascular collapse

Clinical Recommendation

Avoid chloramphenicol in premature infants and neonates unless no safer alternative is available.

Drugs Requiring Lower Daily Doses in Premature Infants

Because hepatic metabolism is reduced:

The following drugs often require lower maintenance doses or longer dosing intervals:

- Theophylline
- Phenobarbital
- Phenytoin
- Diazepam

Compensatory Metabolic Pathways

Children may rely on alternative metabolic pathways when a major pathway is immature.

Example

Paracetamol:

Adults: Main pathway: Glucuronidation

↓

Neonates: Main pathway: Sulfation

Compensatory sulfation prevents excessive accumulation of paracetamol.

Pharmacogenetics and Pharmacogenomics

Not all children metabolize drugs at the same rate. Inherited genetic variations influence:

- Drug metabolism
- Drug efficacy
- Drug toxicity

Genetic testing helps individualize drug therapy and improve safety, especially for drugs with a narrow therapeutic index.

Elimination

1. Drug elimination is the process by which a drug and its metabolites are removed from the body, primarily through the kidneys (urine) and, to a lesser extent, through the bile, feces, lungs, sweat, saliva, and breast milk.
2. In pediatric patients, **renal excretion is the major factor affecting elimination of many drugs**, and renal function changes dramatically during infancy.
3. The kidneys are the primary organs responsible for eliminating many drugs and their metabolites.
4. Renal function is **immature at birth**, especially in premature infants → Drug elimination is therefore **much slower** in premature infants and neonates than in older children and adults → Slower elimination leads to: Drug accumulation, Prolonged half-life, increased risk of toxicity
5. As the kidneys mature, drug clearance gradually increases.

Kidney Maturation The kidneys are anatomically and functionally immature at birth
→ Renal function improves rapidly during infancy.

Developmental Changes

At birth:

1. Kidneys are smaller and incompletely developed.
2. Nephrons are present but not fully functional.

3. Renal blood flow is reduced.

4. Tubular function is immature.

Effect on Drug Elimination

Because of immature kidneys:

- Drug filtration is reduced.
- Drug secretion is reduced.

- Drug excretion is slower.

- Drug half-life is prolonged.

Clinical Significance

Neonates require:

- Lower maintenance doses, or
- Longer dosing intervals to prevent drug accumulation.

Glomerular Filtration Rate (GFR): Glomerular filtration is the **passive filtration of plasma and drugs from the glomerular capillaries into the renal tubules.**

Only: Free (unbound) and Small molecular weight drugs are filtered.

Developmental Changes

Approximate GFR:

Age	GFR (mL/min/1.73 m ²)
Preterm infant	0.6–0.8
Full-term infant	2–4
Adult	120–130

Thus, neonatal GFR is only a small fraction of adult values.

Effect

Low GFR causes:

- Reduced filtration
- Reduced renal clearance
- Prolonged elimination
- Longer drug half-life

Clinical Significance

Drugs eliminated primarily by filtration require:

- Lower doses
- Longer dosing intervals

Examples:

- Gentamicin
- Tobramycin
- Vancomycin

Three Processes of Renal Drug Elimination → All three are immature at birth

Renal elimination depends on **three physiological processes**:

1. Glomerular filtration
2. Tubular secretion
3. Tubular reabsorption

1. Glomerular Filtration

Development

- Significantly reduced at birth.
- Increases rapidly after birth.
- Remains below adult levels until

approximately **3–6 months** of age.

Effect

Reduced filtration delays elimination of drugs cleared mainly by the glomerulus.

Clinical Examples

Examples of drugs cleared mainly by glomerular filtration include:

- Aminoglycosides
- Vancomycin
- Digoxin (partially)

2. Tubular Secretion

Definition

Tubular secretion is an **active transport process** that moves drugs from the blood into the renal tubules.

Development

At birth:

- Tubular secretion is poorly developed.
- Transport systems mature gradually during infancy.

Effect

Reduced secretion causes:

- Slower elimination
- Drug accumulation
- Longer elimination half-life

Clinical Importance

Many antibiotics and organic acids are eliminated by tubular secretion. Immaturity delays their excretion.

3. Tubular Reabsorption

Definition

Tubular reabsorption returns drugs from the renal tubules back into the bloodstream.

Development

Tubular reabsorption is:

- Relatively reduced in infants.
- Matures later than glomerular filtration.

Effect

Reduced reabsorption allows more drug to remain in the urine.

This partially compensates for the reduced GFR.

However, because filtration and secretion are also immature, **overall renal elimination remains reduced.**

Maturation of Renal Function

Both glomerular and tubular functions mature progressively after birth.

- Rapid improvement during the first weeks and months of life.
- Most renal functions reach near-adult levels by approximately **6–8 months of age.**

Clinical Significance

As renal function matures:

- Drug clearance increases.
- Drug half-life decreases.
- Dose requirements increase.

Frequent dose adjustments are necessary during infancy.

Combined Effect of Immature Metabolism and Elimination

Premature infants have:

- Poor glucuronidation (hepatic metabolism)
- Poor renal elimination

Both processes contribute to chloramphenicol accumulation.

Clinical Outcome

Development of **Gray Baby Syndrome.**

This illustrates how impaired metabolism and impaired elimination can together produce severe toxicity.

Dose Adjustment

Because renal clearance changes rapidly during infancy:

Drug doses should always be adjusted according to:

- Gestational age
- Postnatal age
- Current renal function
- Clinical response

Other Factors Affecting Drug Elimination

Besides age, several additional factors influence renal drug elimination.

Nutritional Status

Malnutrition may alter:

- Renal function
- Plasma protein concentrations

- Drug handling

Clinical Significance

Dose modification may be necessary in malnourished

children to avoid underdosing or toxicity.

Disease States

Certain diseases alter renal elimination independently of age.

Examples include:

- Renal disease

- Hepatic disease
- Cystic fibrosis
- Nephrotic syndrome
- Congestive heart failure

Pharmacodynamics

In pediatric patients, pharmacodynamic responses differ from adults because of:

1. Developing organs
2. Immature receptors
3. Ongoing growth
4. Disease-specific physiological changes
5. Developmental changes in body systems

Therefore, the same drug may produce:

1. Different therapeutic effects
2. Different adverse effects
3. Different dose requirements in children compared to adults.

While prescribing drugs for children, physician should consider:

1. Drug efficacy
2. Drug toxicity
3. Developmental physiology
4. Disease-specific changes
5. Organ maturity
6. Long-term safety
7. Age-related adverse effects

Failure to consider these factors may result in:

1. Therapeutic failure
2. Drug toxicity
3. Permanent developmental abnormalities
4. Growth impairment
5. Increased morbidity and mortality

Physiological differences alter drug response.

1. Immature receptor systems
2. Different receptor sensitivity
3. Different receptor number
4. Immature nervous system
5. Immature endocrine system
6. Developing immune system
7. Rapid growth
8. Organ maturation
9. Disease-specific physiological differences

Pathophysiological Differences Affect Drug Response

Certain diseases behave differently in children than adults.

These disease-specific differences alter:

1. Drug efficacy
2. Drug selection
3. Drug dosage
4. Therapeutic outcome

Example 1: Asthma

Children	Adults
Mostly reversible extrinsic (allergic) asthma	Non-specific intrinsic bronchial hyperreactivity
Respond well to allergen control	Less benefit from allergen control
Hyposensitization therapy is useful	Limited role

Clinical significance

Because childhood asthma is usually allergic in origin:

- Adjunctive hyposensitization therapy is beneficial.
- Treatment differs from adult asthma.

Example 2: Digoxin

Infants require a **higher maintenance dose** of digoxin than adults.

1. Lower receptor binding affinity in myocardial tissue
2. Increased digoxin-binding sites on neonatal erythrocytes
3. Different receptor sensitivity

Although infants are smaller, they require **relatively higher maintenance doses** than adults.

Example 3: Insulin

Insulin requirements are highest during adolescence.

1. Rapid body growth
2. Puberty
3. Increased growth hormone
4. Increased insulin resistance during adolescence

Clinical significance

Insulin doses should be adjusted frequently during puberty.

Drug Toxicity in Pediatric Patients

Drug toxicity varies according to age.

Some adverse effects:

- Occur only in newborns
- Occur only in infants
- Appear many years later
- Affect growth and development

Therefore,

Long-term medication safety must always be considered in pediatric patients.

Drug	Pediatric Toxicity	Reason
Promethazine	Severe respiratory depression	Immature respiratory center
Chloramphenicol	Increased toxicity (Gray baby syndrome risk)	Immature hepatic metabolism
Codeine	Respiratory depression and death	CYP2D6 ultra-rapid metabolism
Propylene glycol	Hyperosmolality	Poor metabolism in infants
Benzyl alcohol	Gasping syndrome	Immature detoxification
Ethanol-containing formulations	CNS depression	Immature metabolism
Sorbitol	GI disturbances	Osmotic effects
Cold medications	Serious toxicity	Lack of proven efficacy
Tetracyclines	Teeth staining and bone growth inhibition	Calcium chelation

Toxicity of Pharmaceutical Excipients

Inactive ingredients may produce toxicity in children.

Excipient	Toxic Effect
Propylene glycol	Hyperosmolality
Benzyl alcohol	Gasping syndrome
Ethanol	CNS depression
Sorbitol	Osmotic diarrhea

Factors Affecting Pediatric Drug Therapy

Factor	Effect on Drug Therapy	Examples
Hepatic (Liver) Disease	Decreases drug metabolism and increases toxicity	Morphine, Propranolol, Theophylline
Renal (Kidney) Disease	Decreases drug excretion, causing drug accumulation	Gentamicin, Vancomycin
Cystic Fibrosis	Increases drug clearance, requiring higher doses	Tobramycin, Amikacin
Obesity	Alters drug distribution and dosing	Vancomycin, Chemotherapy drugs
Gastrointestinal Disease	Reduces drug absorption	Oral medications
Hypoxemia	Slows elimination of some drugs	Amikacin
Critical Illness	Changes drug metabolism and clearance	Phenytoin

DRUG THERAPY IN CHILDREN (DOSAGE AND DOSE REGIMEN SELECTION)

Drug therapy in children is more complex than in adults because children are continuously growing and developing.

Drug doses must be individualized based on physiological factors such as age, body weight, body surface area (BSA), organ maturity, and disease state. Extrapolating adult doses to children can lead to underdosing or toxicity.

1. DRUG THERAPY IN CHILDREN

General Principles of Pediatric Drug Therapy

- Children are not small adults.
- Drug doses should never be extrapolated directly from adult doses.
- Pediatric dosing recommendations should always be obtained from a pediatric dosage handbook or pediatric formulary (e.g., BNF-C).
- Pediatric formularies include:
 - Licensed drug use
 - Unlicensed drug use
 - Off-label drug use
 - Prescribing guidelines
 - Drug monographs

METHODS OF PEDIATRIC DOSE CALCULATION (PPT of calculation)

2. DOSE REGIMEN SELECTION

Selecting the correct dose involves more than calculating mg/kg.

The clinician must determine:

- Correct dose
- Correct dosing interval
- Correct dosage form
- Correct route
- Appropriate monitoring

Factors Affecting Dose Regimen Selection

Factor	Key Points
Age/Weight/BSA	Confirm accuracy, calculate dose appropriately, recalculate as the child grows
Appropriate Dose	Depends on age, organ maturity, pharmacokinetics, and disease state

Dosing Interval	Consider clearance, disease, and the child's waking schedule
Route/Formulation	Choose the safest and most practical route; avoid unsuitable excipients
Monitoring	Assess efficacy, toxicity, growth, and therapeutic drug levels where indicated
Drug Interactions	Evaluate drug–drug and drug–food (especially milk) interactions
Legal Considerations	Check licensed, off-label, or unlicensed use and ensure evidence supports therapy

ISSUES IN PEDIATRIC DRUG THERAPY

Issue	Key Points
Pain Management	Assess and treat pain using medicines and non-drug methods.
Drug Administration	Accurate dose measurement and safe administration are essential.
Alteration of Dosage Forms	Child-friendly formulations may require preparation or modification.
Medication Adherence	Ensure children and caregivers follow the prescribed treatment correctly.
Dose Requirements	Calculate doses based on weight or body surface area; avoid using adult doses directly.
Drug Interactions	Consider interactions with drugs, food, milk, and herbal products.
Complementary Medicine	Herbal medicines may interact with prescribed drugs; inform healthcare providers.
Medication Safety	Prevent errors through careful calculation, monitoring, and use of pediatric formulations.
Adverse Drug Reactions	Monitor for age-specific side effects and report suspected ADRs.
Medication Errors	Prevent errors through proper calculations, verification, and standardized procedures.