CHAPTER 10

PEDIATRIC TOXICOLOGY

Author

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Abstract

Pediatric toxicology addresses the unique physiological, developmental, and exposure characteristics that differentiate children from adults in toxic emergencies. Age-specific concerns include altered toxicokinetics with greater absorption through immature gastrointestinal tracts and skin, different distribution patterns due to higher body water proportions, underdeveloped hepatic enzyme systems affecting metabolism, and variable elimination capabilities. These factors often increase vulnerability to toxins while producing different clinical manifestations than seen in adults. Exposure patterns change dramatically with development: infants primarily experience caregiver medication errors; toddlers and preschoolers suffer exploratory ingestions of household products, medications, and plants; school-age children face increasing risk from recreational substances and intentional misuse; and adolescents demonstrate adult-pattern exposures including self-harm attempts. Treatment modifications necessitate weight-based dosing calculations, careful fluid management, adjusted decontamination approaches, and antidote adaptations. Children's smaller airways, decreased glycogen reserves, and immature thermoregulation require special consideration during supportive care. Prevention strategies target developmental stage-specific risks through proper storage practices, child-resistant packaging, supervision appropriate to developmental capabilities, and age-appropriate education. Effective management requires understanding these distinctive aspects while recognizing red flags suggesting non-accidental poisoning requiring child protection involvement.

Keywords: *Pediatric Poisoning, Developmental Toxicology, Accidental Ingestion, Weight-Based Dosing, Child-Resistant Packaging, Toxicokinetic Differences*

Learning Objectives

After completion of the chapter, the learners should be able to:

- Explain how developmental differences in absorption, distribution, metabolism, and excretion affect toxic responses in pediatric patients across different age groups.
- Identify common toxic exposures specific to different developmental stages from infancy through adolescence.
- Calculate appropriate pediatric doses for decontamination methods, antidotes, and supportive medications based on weight, body surface area, and age-specific factors.
- Modify treatment approaches for pediatric toxic exposures with consideration for airway differences, fluid requirements, glucose homeostasis, and thermoregulation.
- Implement age-appropriate prevention strategies including safe storage practices, caregiver education, and recognition of household hazards.
- Differentiate between accidental and non-accidental poisonings using history, clinical presentation, and exposure patterns, and initiate appropriate interventions when malicious intent is suspected

AGE-SPECIFIC CONCERNS

Pediatric toxicology involves distinct developmental, physiological, and behavioral factors creating unique challenges in exposure assessment, management, and prevention.

Developmental Toxicodynamics

Developmental toxicodynamics addresses how age-related differences in physiological systems affect responses to toxic exposures across pediatric developmental stages. The immature blood-brain barrier, particularly in neonates and young infants, demonstrates increased permeability to numerous compounds that would be excluded in mature systems. This heightened central nervous system vulnerability results from both incomplete tight junction formation between capillary endothelial cells and reduced expression of efflux transporters including P-glycoprotein that actively remove potentially toxic substances. Specific agents demonstrating enhanced central nervous system effects in young children due to this mechanism include certain antibiotics, opioids, and antihistamines, which may produce unexpected neurological manifestations at doses well-tolerated by older children and adults.

Receptor expression and sensitivity fluctuate throughout development, creating variable responses to receptor-mediated toxicants across age groups. Alpha-adrenergic receptors demonstrate both decreased density and reduced coupling efficiency to downstream signaling pathways in neonates and infants, potentially diminishing responses to both therapeutic and toxic sympathomimetic effects. Conversely, gamma-aminobutyric acid (GABA) receptors show enhanced sensitivity in young children, particularly to benzodiazepines and other GABA-potentiating agents, explaining the increased risk for respiratory depression with these medications compared to older age groups. Cholinergic systems undergo significant maturation during early development, with variable muscarinic and nicotinic receptor expression across brain regions creating potentially unpredictable responses to both anticholinergic and cholinergic toxicants.

Metabolic enzyme ontogeny significantly affects both activation and detoxification pathways for numerous toxic substances. Cytochrome P450 isoforms demonstrate distinct developmental trajectories: CYP3A7 predominates in fetal liver but rapidly declines after birth as CYP3A4 expression increases; CYP2D6 and CYP2C9 remain significantly below adult activity until several months of age; while CYP1A2 may not reach mature activity until early childhood. These patterns create specific vulnerabilities, such as reduced capacity to metabolize caffeine (a CYP1A2 substrate) in infants, explaining their prolonged half-life for this common dietary constituent. Phase II conjugation pathways similarly show developmental patterns, with glucuronidation particularly deficient in neonates due to immature uridine diphosphate glucuronosyltransferase expression, creating risk for both reduced clearance of certain toxicants and potential alternative metabolism through more toxic pathways.

Organ system maturation affects functional reserve capacity and compensatory responses to toxic insults. The developing kidney demonstrates both reduced glomerular filtration rate and incomplete tubular function in neonates and young infants, limiting toxicant elimination and potentially enhancing nephrotoxicity from agents excreted through renal mechanisms. Cardiovascular compensatory mechanisms, including baroreceptor sensitivity and adrenergic responsiveness, develop progressively throughout infancy and early childhood, creating potential for more rapid decompensation in young children exposed to cardiotoxic substances. Thermoregulatory capacity remains limited in infants due to both physiological factors (higher surface area to volume ratio, reduced subcutaneous fat, immature sweating mechanisms) and behavioral limitations restricting autonomous temperature regulation responses, creating enhanced vulnerability to toxicants affecting thermoregulatory processes.

Long-term developmental consequences may result from exposures during critical windows of susceptibility, particularly affecting brain development, reproductive system maturation, and immune function. The concept of the developmental origins of health and disease recognizes that exposures during these sensitive periods may program lifelong alterations in physiological systems through epigenetic modifications, altered cell differentiation pathways, or permanent structural changes.

Table 10.1: Developmental Factors Affecting Toxicity in Pediatric Patients

Age Group	Physiological Differences	Toxicokinetic Impact
Neonates (0-1 month)	Immature blood-brain barrier, reduced GFR, higher body water %	Enhanced CNS penetration, reduced elimination, larger Vd for water-soluble drugs
Infants (1-12 months)	Higher gastric pH, developing CYP450 enzymes, reduced plasma protein	Enhanced absorption of basic compounds, altered metabolism, higher free drug fraction
Toddlers (1-3 years)	Higher metabolic rate, ongoing organ development, higher BSA:weight ratio	Faster metabolism of some toxins, target organ sensitivity, increased absorption/elimination rates
Children (4-12 years)	Maturing enzyme systems, smaller fat stores than adults	Approach adult patterns but with quantitative differences
Adolescents (13-18 years)	Hormonal changes, approaching adult physiology	Similar to adults for most toxicokinetic parameters

Neurodevelopmental toxicants, including lead, methylmercury, and certain pesticides, may produce subtle cognitive or behavioral effects at exposure levels below those causing obvious acute toxicity, with manifestations potentially delayed until developmental demands reveal functional deficits years after the exposure. This temporal disconnect between exposure and manifest effects creates particular assessment

challenges, as causative relationships may remain unrecognized without specific investigation.

Pediatric Toxicokinetics

Pediatric toxicokinetics addresses how developmental differences in absorption, distribution, metabolism, and elimination processes affect the disposition of toxic substances across age groups. Gastrointestinal absorption demonstrates several age-dependent variations potentially affecting toxic exposures. Gastric pH remains relatively neutral (compared to adult acidic environments) until approximately 2 years of age, enhancing absorption of basic compounds while potentially reducing acidic substance uptake. Gastrointestinal transit time shows greater variability in infants and young children, creating unpredictable absorption patterns, particularly for extended-release formulations designed assuming adult physiology. Enhanced permeability of the immature intestinal mucosa potentially increases absorption of compounds normally limited by the mature intestinal barrier, though this effect generally resolves within the first months of life as tight junction formation completes.

Remember

Children differ from adults toxicologically due to developmental variations in absorption, distribution, metabolism, and excretion, with factors including higher body surface-to-weight ratio, lower plasma protein levels, immature hepatic enzymes, and variable renal function.

Distribution patterns reflect significant body composition differences across pediatric age groups. Total body water constitutes approximately 75-80% of body weight in neonates compared to 55-60% in adults, with particularly expanded extracellular compartments creating larger distribution volumes for water-soluble compounds and potentially lower peak plasma concentrations after fixed mg/kg dosing. Adipose tissue percentage increases during infancy, then fluctuates throughout childhood with characteristic patterns including the adiposity rebound during early childhood, affecting distribution of lipophilic compounds. Plasma protein binding capacity demonstrates quantitative and qualitative differences, with reduced albumin concentrations and altered binding characteristics in neonates and young infants, potentially increasing free fractions of highly protein-bound toxicants. Additionally, endogenous substances including bilirubin and free fatty acids may compete for binding sites, further displacing toxicants from protein binding in neonates.

Hepatic metabolism undergoes profound maturation throughout pediatric development, affecting both detoxification and bioactivation processes for numerous xenobiotics. Phase I oxidative metabolism through cytochrome P450 enzymes follows isoform-specific developmental trajectories, creating age-dependent vulnerability or resistance to specific toxicants based on their metabolic pathways. Phase II conjugation demonstrates similar developmental patterns with clinical significance: glucuronidation, catalyzed by uridine diphosphate glucuronosyltransferases, remains markedly reduced in neonates and young infants, necessitating alternative metabolic pathways for certain compounds and potentially creating increased toxicity risk when these alternative pathways generate reactive metabolites. Paradoxically, some metabolic pathways may actually show enhanced activity during certain developmental windows, creating potential for increased toxicity from metabolite-mediated mechanisms compared to adults exposed to the same xenobiotics.

Renal elimination capacity demonstrates substantial postnatal development affecting toxicant clearance. Glomerular filtration rate approaches adult values (when adjusted for body surface area) by approximately 6-12 months of age, though remains significantly reduced in neonates, creating prolonged elimination of renally excreted toxicants during this period. Tubular secretion and reabsorption processes mature more gradually, with some transport mechanisms not reaching adult capacity until later childhood. This differential maturation of filtration versus tubular functions potentially alters the clearance patterns of toxicants compared to adult predictions, particularly for compounds where tubular secretion represents a significant elimination mechanism. For toxicants undergoing enterohepatic circulation, age-related differences in biliary transport and intestinal microbiota composition potentially affect reabsorption patterns and overall elimination kinetics.

Collectively, these toxicokinetic factors necessitate specific consideration when evaluating potential toxicity and determining appropriate interventions across pediatric age groups. Dosage calculations based solely on weight or body surface area may inadequately account for developmental differences in absorption, distribution, metabolism, and elimination processes. Age-appropriate pharmacokinetic models incorporating these developmental changes provide more accurate predictions of toxicant disposition, though remain incompletely developed for many substances. Clinical vigilance regarding potentially unexpected toxicokinetic patterns remains essential when managing pediatric exposures, particularly for substances whose properties have been primarily characterized in adult populations.

Behavioral Development

Behavioral development profoundly influences exposure risk patterns throughout childhood, with characteristic age-specific behaviors creating distinctive vulnerability periods for particular toxicants. Oral exploration represents a fundamental developmental behavior beginning in early infancy, intensifying during the 6-24 month period when hand-to-mouth activity peaks as part of normal sensory development and object exploration. This natural exploratory behavior creates significant ingestion risk for accessible household substances, medications, and small objects, particularly as mobility develops allowing access to previously unreachable areas. Compounding this risk, genuine taste discrimination remains undeveloped in young children, who may willingly consume bitter or unpleasant substances that would trigger rejection in adults, including harmful chemicals in attractive containers or medications designed without consideration of taste aversion as a protective factor.

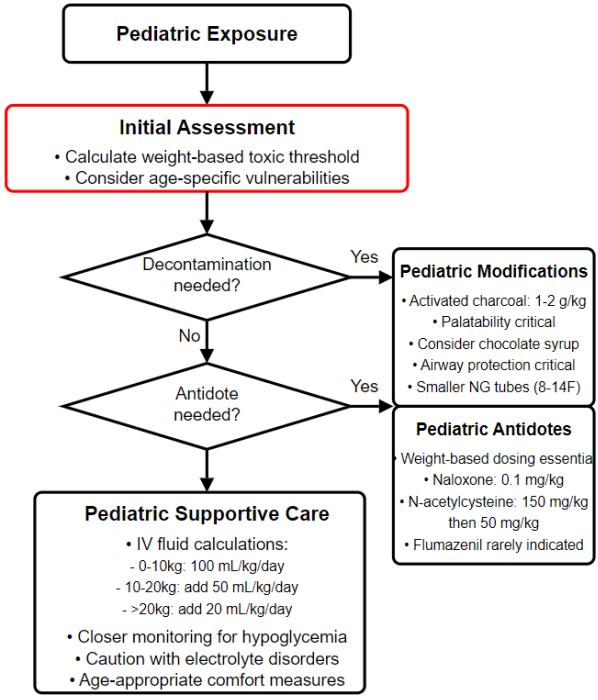

Figure 10.1 Modifications in Pediatric Treatment

Expanding environmental interaction characterizes the developmental progression from infancy through early childhood. Crawling emergence (typically 7-10 months) dramatically expands the accessible environment, providing access to low-lying hazards including houseplants, pest control products, fallen medications, and spilled household chemicals. Walking development further extends this environmental exploration, with vertical reach progressively increasing through climbing behaviors emerging around 12-18 months. These mobility developments occur before corresponding cognitive abilities to recognize and avoid hazards, creating a high-risk period where physical capabilities outpace safety awareness. This developmental mismatch necessitates environmental modification rather than reliance on educational approaches during this stage.

Remember

Developmental stage significantly influences exposure risk, with exploratory ingestions peaking in toddlers (especially household products and medications), while adolescents exhibit intentional exposures including recreational substance use and self-harm attempts

Cognitive development follows predictable patterns affecting risk recognition and safety behavior implementation throughout childhood. Preoperational thinking (approximately 2-7 years) includes several characteristics increasing poisoning vulnerability: egocentrism limiting perspective-taking and understanding of others' safety warnings; magical thinking potentially creating misconceptions about substance properties; concrete interpretation of information without abstract understanding of harm concepts; and limited cause-effect reasoning affecting comprehension of delayed toxicity. During this period, safety rules may be followed concretely without underlying comprehension, requiring consistent external monitoring rather than reliance on independent judgment. School-age children (approximately 7-11 years) develop increased capacity for logical operations and cause-effect reasoning, enabling more effective safety education, though still benefit from environmental protections for high-risk substances.

Adolescent development introduces distinct risk patterns reflecting both neurodevelopmental changes and social-environmental factors. Risk-taking behaviors increase during adolescence, influenced by normative neurodevelopmental processes including heightened reward sensitivity, sensation-seeking tendencies, and still-developing executive function capabilities affecting impulse control and consequence evaluation. These developmental characteristics, combined with increased independence from adult supervision and peer influence